Overview of reports on direct oral anticoagulants (DOACs)

Introduction

The group of novel anticoagulants consists of the oral anticoagulants apixaban, (Eliquis®) argatroban (Arganova®), dabigatran (Pradaxa®), rivaroxaban (Xarelto®) and the non-oral anticoagulants bivalirudine (Angiox®) and fondaparinux (Arixtra®). The introduction of these drugs as a replacement for low molecular weight heparins (LMWH) and vitamin K antagonists (VKA) has raised questions regarding their safety [1,2]. Lareb has published overviews of reports concerning novel anticoagulants in Quarterly Reports 2014-1 [3-5]. With this overview, Lareb provides a short update of the reports received on the novel oral anticoagulants dabigatran, rivaroxaban and apixaban for the current Quarterly Report. Because these coagulants have been marketed for a while now, for the oral coagulants the term direct oral anticoagulants (DOACs) is used,

For this overview, data from both the national ADR database, including spontaneous- and study reports, and the Lareb Intensive Monitoring System (LIM) were used. Dabigatran, rivaroxaban and apixaban have been monitored with the LIM methodology since September 2012.

Reports

On January 26, 2015 the Netherlands Pharmacovigilance Centre Lareb had received 680 reports in the national reporting database (spontaneous and study reports), consisting of 1248 ADRs.

There were 267 patients in the LIM system who had reported at least 1 ADR. In total 383 ADRs were reported in LIM for the DOACs. The total number of patients in the study was 800, this includes the patients who did not report an ADR.

There were 413 reports of serious ADRs, including 8* reports originating from LIM that were exported to the national ADR database.
In 45 reports a fatal outcome was reported, including 1 report from LIM. Additional information is provided in table 1 and 2.

Table 1. Numbers of reports received by Lareb in the national reporting database

	Dabigatran	Rivaroxaban	Apixaban	Total
Total number of reports	334	309	37	680
Number of serious reports	201 (60%)	196 (63%)	16 (43%)	413 (61%)
Total number of ADRs#	552	632	64	1248
Number of serious ADRs	336	432	24	792
Reports with a fatal outcome$	22	20	3	45

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 2. Number of patients using direct anticoagulants who reported at least one ADR in Lareb Intensive Monitoring (LIM)

Active substance	Number of reports			Reports with fatal outcome
	Total	Serious (%)	Non-serious (%)	
Dabigatran	131	4* (3%)	127 (97%)	0
Rivaroxaban	107	2 (2%)	105 (98%)	0
Apixaban	29	2 (7%)	27 (93%)	1**

** Serious ADRs (including reports with a fatal outcome) reported in LIM are also exported to the Lareb reporting database, which means that they are counted in both datasets
* Two of these reports were reported as serious by the patient, but deemed non-serious according to the CIOMS criteria by the Lareb assessor

In order to provide more insight into the spectrum of ADRs reported to Lareb, the ADRs were grouped into MedDRA® System Organ Classes (SOCs). Only the oral anticoagulants were taken into account, similarly to the overview in the Lareb Quarterly Report 2014-1.

Table 3: Overview of reported ADRs in the Lareb database of the oral direct anticoagulants per MedDRA® System Organ Class

System Organ Class (SOC)	APIXABAN		DABIGATRAN		RIVAROXABAN	
	N	%	N	%	N	%
Blood and lymphatic system disorders			13	2,4	15	2,4
Cardiac disorders	1	1,6	16	2,9	23	3,6
Congenital, familial and genetic disorders			1	0,2		
Ear and labyrinth disorders			1	0,2	2	0,3
Eye disorders	1	1,6	10	1,8	18	2,8
Gastrointestinal disorders	15	23,4	136	24,6	108	17,1
General disorders and administration site conditions	9	14,1	55	10,0	69	10,9
Hepatobiliary disorders	1	1,6	5	0,9	4	0,6
Immune system disorders	1	1,6			2	0,3
Infections and infestations			6	1,1	11	1,7
Injury, poisoning and procedural complications	1	1,6	11	2,0	37	5,9
Investigations	8	12,5	10	1,8	29	4,6
Metabolism and nutrition disorders	1	1,6	14	2,5	4	0,6
Musculoskeletal and connective tissue disorders			11	2,0	23	3,6
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1	1,6	10	1,8	3	0,5
Nervous system disorders	8	12,5	87	15,8	67	10,6
Psychiatric disorders	4	6,3	17	3,1	11	1,7
Renal and urinary disorders			24	4,3	35	5,5
Reproductive system and breast disorders			6	1,1	12	1,9
Respiratory, thoracic and mediastinal disorders	1	1,6	24	4,3	44	7,0
Skin and subcutaneous tissue disorders	9	14,1	22	4,0	31	4,9
Social circumstances					1	0,2
Surgical and medical procedures			10	1,8	6	0,9
Vascular disorders	3	4,7	63	11,4	77	12,2
Total	64	100,0	552	100,0	632	100,0

Table 4: Overview of ADRs of the oral direct anticoagulants per MedDRA® System Organ Class in LIM*

System Organ Class (SOC)	APIXABAN		DABIGATRAN		RIVAROXABAN	
	N	%	N	%	N	%
Blood and lymphatic system disorders					1	0,7
Cardiac disorders	1	2,6	7	3,6	5	3,3
Congenital, familial and genetic disorders						
Ear and labyrinth disorders			3	1,6	1	0,7
Eye disorders	2	5,3	5	2,6		
Gastrointestinal disorders	11	28,9	81	42,2	45	29,4
General disorders and administration site conditions	4	10,5	16	8,3	22	14,4
Hepatobiliary disorders						

Immune system disorders			1	0,5	1	0,7
Infections and infestations			2	1,0		
Injury, poisoning and procedural complications	1	2,6			1	0,7
Investigations	1	2,6	3	1,6	4	2,6
Metabolism and nutrition disorders			1	0,5		
Musculoskeletal and connective tissue disorders	2	5,3	10	5,2	8	5,2
Neoplasms benign, malignant and unspecified (incl cysts and polyps)						
Nervous system disorders	10	26,3	23	12,0	29	19,0
Psychiatric disorders					5	3,3
Renal and urinary disorders	1	2,6	6	3,1	1	0,7
Reproductive system and breast disorders					2	1,3
Respiratory, thoracic and mediastinal disorders	2	5,3	7	3,6	5	3,3
Skin and subcutaneous tissue disorders	3	7,9	17	8,9	16	10,5
Social circumstances						
Surgical and medical procedures						
Vascular disorders			10	5,2	7	4,6
Total	**38**	**100**	**192**	**100**	**153**	**100**

* If the same patient reported the same ADR in multiple questionnaires, the ADR is only counted once

Reports considering haemorrhages are present in multiple MedDRA® System Organ Classes. Therefor Lareb grouped all reported MedDRA® Preferred Terms that are associated with bleeding (both serious and non-serious according to CIOMS criteria) in the different SOCs in order to give insight in the number of ADRs per active substance where haemorrhage was reported.
In addition, the number of ADRs considering (venous or arterial) thrombo-embolism is given, since this might be an indicator of lack of efficacy of the treatment in a patient. See table 5.

Table 5. Number of ADRs considering haemorrhage or (venous or arterial) thrombo-embolism

Active substance	ADRs considering hemorrhage in all SOCs	% of total number of ADRs	ADRs considering thrombosis-embolism	% of total number of ADRs	Total number of ADRs
Apixaban	12	18.6%	1	1.6%	64
Dabigatran	137	24.8%	45	8.2%	552
Rivaroxaban	208	32.9%	46	7.3%	632

Other sources of information

Literature

There's a great amount of studies looking at the risk profiles of the direct anticoagulants, also comparing them to older anticoagulants such as warfarin. Results on bleeding risks do not seem conclusive so far. Below some studies were selected to give insight into publications on bleeding risk for the direct oral coagulants. In a recent retrospective cohort study published in JAMA, dabigatran was associated with a higher risk of bleeding relative to warfarin, with hazard ratios of 1.30 (95% CI, 1.20-1.41) for any bleeding event, 1.58 (95% CI, 1.36-1.83) for major bleeding, and 1.85 (95% CI, 1.64-2.07) for gastrointestinal bleeding. The risk of intracranial hemorrhage was higher among warfarin users, with a hazard ratio of 0.32 (95% CI, 0.20-0.50) for dabigatran compared with warfarin. Dabigatran was consistently associated with an increased risk of major bleeding and gastrointestinal hemorrhage for all subgroups analyzed. The risk of major bleeding among dabigatran users was especially high for African Americans and patients with chronic kidney disease [6].
Another recent meta-analysis was performed to evaluate the risk of major bleeding with the use of New Oral Anticoagulants (NOACs). Fifty trials randomized controlled trials (RCTs) comparing NOACs (rivaroxaban, dabigatran, apixaban, edoxaban and darexaban) with

comparators (vitamin K antagonists) were selected, including 155,537 patients. Pooled analysis of all NOACs for all indications together demonstrated no significant difference between NOACs and comparators for risk of major bleeding (odds ratio [OR] 0.93, 95% CI 0.79-1.09). Pooled analysis also showed that NOACs caused significantly less major bleeding compared to vitamin K antagonists (VKA) (0.77, 0.64-0.91). Risk of major bleeding with new oral anticoagulants varied with their indication for use. NOACs may increase the risk of major bleeding after hip surgery, acute coronary syndrome and acute medically ill patients; but may be associated with less bleeding in treatment of acute VTE/PE [7]. AIM: A network meta-analysis was performed from three trials comparing dabigatran, rivaroxaban and apixaban with warfarin in patients with atrial fibrillation. Data were extracted of the RE-LY study of dabigatran 110 mg bid and dabigatran 150 mg bid, the ROCKET AF trial of rivaroxaban and the ARISTOTLE trial of apixaban for the composite outcome of ischemic stroke and systemic embolism, for major bleeding, intracerebral bleeding, mortality and myocardial infarction. Apixaban was safer (less major bleeding) than dabigatran (150 mg bid, P=0.036) or rivaroxaban (P=0.0002). Intracerebral hemorrhage occurred with equal frequency for all agents except for rivaroxaban (higher risk than dabigatran 110 mg bid, P=0.0070) [8].

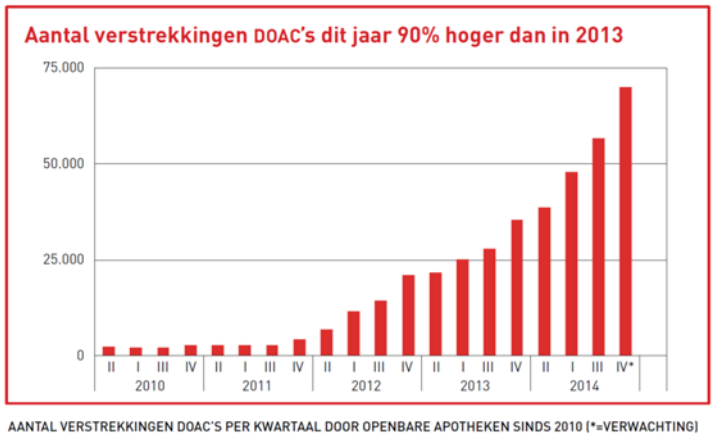
Prescription data

The number of patients using oral direct anticoagulants in the Netherlands [3] is shown in table 6.

Table 6. Number of patients using direct anticoagulants in the Netherlands between 2009 and 2013 [9].

Drug	2009	2010	2011	2012	2013
Dabigatran	1,026	1,048	2,066	4,686	13,304
Rivaroxaban	1,960	6,244	7,035	9,866	12,902
Apixaban	.	.	.	3	729

According to the Stichting Farmaceutische Kengetallen (SFK) the number of long-term users of direct oral anticoagulants (DOACs) will be 33,000 in 2014, double the number from a year earlier [10].
The SFK Figure [10] below, shows the number of times the DOACs have been dispenses in the community pharmacy from 2010-2014.



AANTAL VERSTREKKINGEN DOAC'S PER KWARTAAL DOOR OPENBARE APOTHEKEN SINDS 2010 (*=VERWACHTING)

Discussion and conclusion

Earlier this year, Lareb published an overview of the novel anticoagulants in their Quarterly Report 2014-1. The aim of this report was to give an update on the number of the ADRs associated with the use of direct anticoagulants.
Since the previous analysis dating back to October 21, 2013 (Quartely Report 2014-1 [3]) the number of reports sent to Lareb regarding direct anticoagulants has increased with more than 70%. Many of these cases were reported through the Marketing Authorization Holders.
The percentage of serious reports is 61%, based on the reports in the national reporting database.
In general, the distribution of ADRs over the different SOCs is still rather similar between both groups.
The current overview did not give rise to a new signal of adverse drug reactions related to the use of direct anticoagulants.

References

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This overview was published in March 2015. 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