1.1. Overview of reports on novel oral anticoagulants (NOACs)

Introduction

Lareb published overviews of reports concerning the novel anticoagulants (NOACs) apixaban (Eliquis®), dabigatran (Pradaxa®) and rivaroxaban (Xarelto®) in 2014 and 2015 [1,2]. With the current overview, Lareb provides a short update of the reports received for these NOACs.
For this overview, data from both the national ADR database, 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 April 29, 2016 the Netherlands Pharmacovigilance Centre Lareb had received 1112 reports (with 1941 ADRs) in the national reporting database. Compared to the previous overview this is an increase of 432 reports (63%). Figure 1 shows different trends for the number of reports received through the years depending on the source, with increasing numbers for reports directly received by Lareb and decreasing numbers for reports from Marketing Authorisation Holders (MAHs).
In our prospective LIM cohort, 1393 patients were included, of which 477 (35%) reported at least 1 ADR. In total 825 ADRs were reported in LIM for the NOACs.

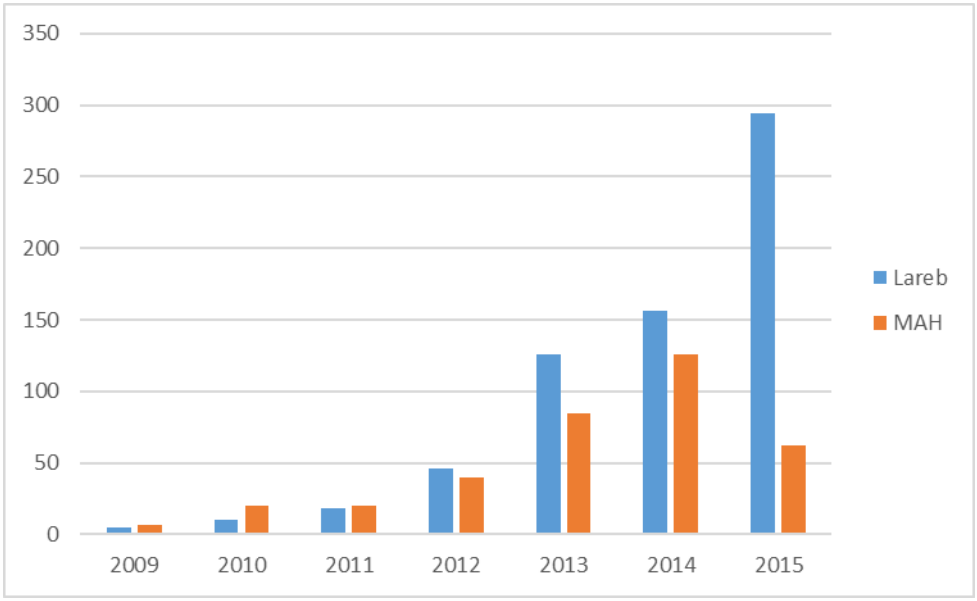

Figure 1. Number of spontaneous reports received by Lareb for the NOACs per year for different sources

There were 554 reports with a serious outcome, including 15* reports originating from LIM that were exported to the national ADR database.
In 66 reports a fatal outcome was reported (compared to 45 reports in the previous overview), 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 for the NOACs

	Dabigatran	Rivaroxaban	Apixaban	Total
Total number of reports	484	528	100	1112
Number of serious reports	250 (52%)	269 (51%)	35 (35%)	554 (50%)
Total number of ADRs*	784	997	160	1941
Reports with a fatal outcome#	30	29	7	66

* 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 novel oral 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	188	2* (1%)	186 (99%)	0
Rivaroxaban	209	2* (1%)	207 (99%)	0
Apixaban	80	3* (4%)	77 (96%)	1[#]

* Eight additional reports were reported as serious by the patient, but deemed non-serious according to the CIOMS criteria by the Lareb assessor.
*[#] 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

Due to the substantial number of reports with a fatal outcome, the individual cases will not be described. Instead, the most frequently reported ADRs in these reports are presented in table 3. These data show that haemorrhages are the most frequently reported ADRs followed by pulmonary embolism. Additionally, nine reports, mainly form MAHs, mention the MedDRA term 'Death' as an ADR since no other ADR was present in the report. 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 3. Most frequently reported ADRs* (with a minimum of two) in reports with a fatal outcome

Dabigatran		Rivaroxaban		Apixaban	
Death[#]	9	Pulmonary embolism	6	Haemorrhage intracranial	2
Haemorrhage intracranial	3	Cerebral haemorrhage	6	-	
Haemorrhage	3	Haemorrhage intracranial	3	-	

* Several ADRs can originate from a single report
[#] The majority of cases (8 of 9) with 'death' coded as an ADR represent reports from MAHs

Since reports of haemorrhages and thrombo-embolic events associated with the use of NOACs 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 haemorrhages and thrombo-embolic events are presented in table 4 and 5.

Table 4. Number and percentages (of total number of reported ADRs) related to thrombo-embolic events

Drug	Thrombo-embolic events			
	Arterial	Venous	Mixed / unspecified	Total
Apixaban	3 (1.9%)	0 (0%)	2 (1.3%)	5 (3.1%)
Dabigatran	49 (6.3%)	6 (0.8%)	42 (5.4%)	97 (12.4%)
Rivaroxaban	13 (1.3%)	32 (3.2%)	16 (1.6%)	61 (6.1%)

Table 5. Number and percentages (of total number of reported ADRs) related to haemorrhages*

Drug	Haemorrhages		
	CNS	Gastrointestinal	Total
Apixaban	8 (5.0%)	4 (2.5%)	30 (18.8%)
Dabigatran	57 (7.3%)	55 (7.0%)	189 (24.1%)
Rivaroxaban	33 (3.3%)	68 (6.8%)	184 (28.5%)

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

Recent associations analysed by Lareb regarding NOAC reports

Since the previous report in the first quarter of 2015, several drug – ADR associations with NOACs as suspect drugs were analysed by Lareb based on case-by-case signal detection. The analysed associations were *dabigatran and headache (n=23, March 2016), dabigatran / rivaroxaban and myalgia (both n=8, April 2015), dabigatran and peripheral coldness (n=9, April 2015), dabigatran and renal insufficiency (n=7, April 2015), dabigatran and tinnitus (n=6, May 2016), rivaroxaban and dyspnoea (n=9, May 2015), rivaroxaban and insomnia (n=5, February 2016), rivaroxaban and paraesthesia (n=8, April 2015).* For each of these analyses, there was not enough evidence to support a signal at the moment. In case of new reports, the association will be re-evaluated.

In addition to the associations above, a database search for dabigatran / rivaroxaban associated pulmonary alveolar haemorrhage was performed based on the PRAC minutes (January 2016). No reports were found for this association in the Lareb database.

Other sources of information

Literature

As mentioned in our previous overview, a large amount of studies looking at the bleeding risk profiles of the novel oral anticoagulants (mainly in comparison with warfarin) has been published in recent years. And although several meta-analyses have been performed, the results on bleeding risks do not seem conclusive so far. In a recent meta-analysis evaluating the risk of major bleeding with the use of NOACs, fifty 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 [3].
Two additional meta-analyses investigating the risk of bleeding in patients with atrial fibrillation were of interest. A meta-analyses of the three major phase III clinical trials for rivaroxaban, dabigatran and apixaban investigated the risk of different types of bleedings [4]. Pooled analysis showed that the use of NOACs showed no significant difference in the risk of overall major bleedings between the NOACs and warfarin (risk ratio [RR] 0.86, 95% CI 0.70 – 1.05). However, the use of NOACs was associated with a significantly lower risk of intracranial bleedings (RR 0.46, 95% CI 0.33 – 0.65). Additionally, no significant difference was found for the risk of major gastrointestinal bleedings showed (RR 1.20, 95% CI 0.92 – 1.56). A second meta-analysis of clinical trials for rivaroxaban, dabigatran, apixaban and edoxaban focused on major bleedings for the European subpopulation [5]. The results show that the risk of major bleeding for the Western Europe region was significantly lower for the NOACs than for warfarin (RR 0.83, 95% CI 0.71 – 0.97).

Prescription data

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

Table 6. Number of patients using novel oral anticoagulants in the Netherlands between 2010 and 2014 [6].

Drug	2010	2011	2012	2013	2014
Dabigatran	1,048	2,066	4,678	13,065	19,092
Rivaroxaban	6,244	7,035	9,850	12,730	20,659
Apixaban	.	.	3	730	4,811

According to the Stichting Farmaceutische Kengetallen (SFK) the number of dispensed daily defined doses (DDD) of the NOACs by community pharmacies has doubled in 2015 compared to 2014 [7]. Figure 2 shows the number of dispensed DDDs for these drugs from 2011 – 2015.

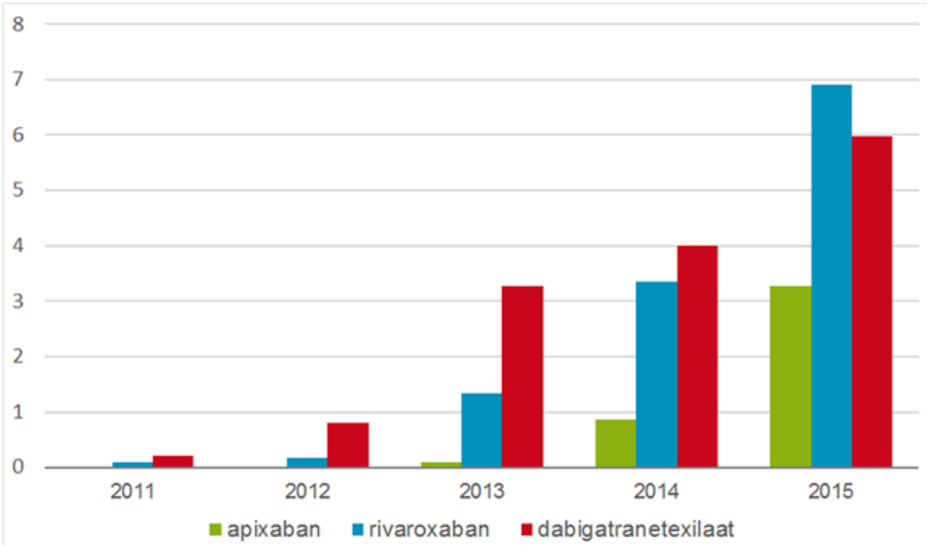

Figure 2. Number of dispensed daily defined doses (DDD) for each of the NOACs from 2011 - 2015

Discussion and conclusion

Previously, Lareb published overviews of the novel anticoagulants in their Quarterly Reports 2014-1 and 2015-1. The aim of this report was to give an update on the number of reports of ADRs associated with the use of the novel oral anticoagulants.

Since the previous overview, the total number of spontaneous reports for NOACs received by Lareb has increased with more than 60%. This increase was mainly due to an increase in cases reported directly to Lareb, which accounts for approximately 80% of the total number of NOAC reports in both 2015 and 2016.

The increased total number of reports resulted in the analysis of several drug – ADR associations, which did not reveal a new safety concern. Several of these associations will be closely monitored and will be re-analysed in the case of additional reports.

Due to the nature of spontaneous reporting, no direct comparisons between drugs can be made in terms of reporting frequencies for any ADR. Therefore, the occurrence of thrombo-embolic events and / or bleedings cannot be compared between the three NOACs. Nevertheless, it is striking that for dabigatran 12.4% of all ADRs reported represents a thrombo-embolic event. Although no specific explanation for this observation could be found, it should be noted that the majority of reports of thrombo-embolic events are MAH reports, and based on their internal pharmacovigilance activities, selective reporting of thromboembolic events may explain this observation.

In conclusion, the ongoing pharmacovigilance activities for the NOACs did not reveal any new safety concerns.

References

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