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Safety profile of non-vitamin K oral anticoagulants (NOACs) from a patient perspective: a web-based cohort event monitoring study

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ORIGINAL RESEARCH

Safety profile of non-vitamin K oral anticoagulants (NOACs) from a patient perspective: a web-based cohort event monitoring study

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ABSTRACT

Objectives: Non-vitamin K oral anticoagulants (NOACs) are a relatively new group of anticoagulants. Characteristics of adverse drug reactions (ADRs) as experienced by patients in everyday use have not yet been fully clarified. The aim was to gain insight into the safety profile of NOACs from a patient's perspective.

Methods: This was a prospective, observational web-based cohort event monitoring study among first-time users of NOACs. Patients were recruited between July 2012 and April 2017. They were invited to complete four web-based questionnaires 2 weeks, 5 weeks, 3 months and 6 months after starting treatment. Information was collected about patient characteristics, drug use, and characteristics of ADRs.

Results: 1748 NOAC users were included. 661 (38%) experienced at least one ADR. The reported ADRs were comparable with the information described in the Summary of Product Characteristics and generally occurred within 1 week after the start. In 59% of ADRs the patients recovered. These ADRs had no impact on the use and dosage of the NOAC in 68%. In total, 9% of the patients discontinued the NOAC because of ADRs.

Conclusion: Overall NOACs were well tolerated by the participants. Most reported ADRs occurred within 1 week after the start. Patients recovered from most ADRs without changes to the use of the NOAC.

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Adverse drug reaction; adverse events; cohort event monitoring; NOAC; non-vitamin K oral anticoagulants; patient reported outcomes; pharmacovigilance

1. Introduction

Apixaban, dabigatran, edoxaban, and rivaroxaban belong to the group of non-vitamin K oral anticoagulants (NOACs). Dabigatran and rivaroxaban were the first NOACs marketed in Europe in 2008, followed by apixaban in 2011 and edoxaban in 2015. NOACs are an alternative for vitamin K antagonists in the treatment of atrial fibrillation, and also have a place in the treatment of venous thromboembolism (VTE) and prevention of VTE after orthopedic surgery. Over the past years, NOACs have emerged as the preferred choice, particularly for patients that newly started on anticoagulation [1]. NOACs are administered orally, have a decreased need for monitoring and show fewer food and drug interactions compared to vitamin K antagonists [2].

The safety profile of the NOACs has been compared with the vitamin K antagonists in several randomized controlled trials (RCT). There is however a lack in information about whether the safety profile of the NOACs as observed in RCTs is comparable with that experienced by patients in daily practice [3]. RCTs are conducted in ideal settings with strict inclusion and exclusion criteria and may not be fully comparable with the circumstances in real-world clinical practice where these drugs are used by heterogeneous populations in less controlled situations. As a consequence, the type and frequency of adverse drug reactions (ADRs) mentioned in the Summary of Product Characteristics (SPC) do not fully match with the conditions in real life. Moreover, information on the

time course of the reported ADRs as experienced by patients and their possible influence of adherence is not known, but of vital importance for the success of the treatment.

The primary aim of this study is to gain insight into the safety profile of NOACs from a patient's perspective. The secondary aim was to compare the occurrence and incidence of the ADRs with the information described in the SPC and to describe their characteristics, such as the time to onset and outcome.

2. Method

2.1. Study design

This was a prospective, observational web-based cohort event monitoring (CEM) study, in which patient-reported outcomes were used to gain insight into the safety profile of the NOACs in daily practice. Data were collected over time through web-based questionnaires, sent automatically to the patient four times during the study period using the Lareb Intensive Monitoring (LIM) system [4]. Patients were asked if they experienced any 'adverse drug reaction' during the use of a specific drug.

2.2. Study population

This study included patients who are first time users of the NOACs apixaban, dabigatran, edoxaban, or rivaroxaban. Patients were invited to participate in this study by their

pharmacist. Although patients are free to obtain their medication from any pharmacy, the majority of patients in the Netherlands is associated with only one pharmacy. Eligible patients were identified from pharmacy records if they received a NOAC prescription for the first time between July 2012 and April 2017. Patients over 18 years of age were able to participate. It was the pharmacist's role to invite the patient into the study. The patient was informed about the purpose, method of data collection, and provided a leaflet with further study information. Patients who were willing to participate could register online.

2.3. Questionnaire

Upon online registration, information was gathered about patient characteristics (gender, date of birth, e-mail address, pharmacist), type of NOAC (start date and indication), and use of concomitant drugs. Finally, they were asked to sign the declaration of consent.

After registration, patients who were included in the study were invited to complete four questionnaires which were sent by e-mail after 2 weeks, 5 weeks, 3 months and 6 months after the reported start date of the drug. A reminder was sent if the questionnaire was not completed within 5 days after the first invitation. If the questionnaire was still not completed 4 weeks after the reminder, the patient was considered as lost to follow-up. Patients could also actively indicate if they wanted to stop participation; these patients were also coded as lost to follow-up.

Questions were asked about the patient's experiences with the NOAC and possible ADRs that occurred during treatment. A translation of the Dutch questionnaire can be found in Electronic Supplementary Material 1. The patient could describe the experienced ADRs in an open text field. In case of an ADR, additional questions were asked, including date of onset, management, outcome, and seriousness of the reaction. A single patient may experience multiple ADRs at the same time. A reaction was defined as serious according to the criteria of the Council for International Organizations of Medical Sciences (CIOMS) Working Party [5], i.e. those ADRs leading to (prolongation of) hospitalization, life-threatening events, reactions leading to death, disabling events, congenital abnormalities, and other medically significant reactions. More than one reason for seriousness could be given in the questionnaire. The questionnaire was in Dutch and designed in such a way that given answers about the ADRs were automatically pre-filled in the follow-up questionnaires in order to make it more efficient for patients to complete these questionnaires.

2.4. Data management and analysis

All data were stored in an Oracle database. Reported ADRs and indications were coded by an experienced pharmacovigilance assessor using the Medical Dictionary for Regulatory Activities (MedDRA®) terminology 21.0 [6]. The total number of patients who completed the first questionnaire was used to calculate the frequency of each ADR. This calculated frequency was compared with information about the incidence rate as is described in the drug's SPC, section 4.8 'Adverse drug reactions' [7–10]. The ADR characteristics 'outcome' (recovered/not recovered), 'action with the NOAC' (discontinued/no change), and 'time to onset of the ADR' (in days) were analyzed descriptively. Differences in experienced ADRs between men and women were analyzed using a Pearson's Chi-square (χ^2) test. A p-value <0.05 was considered statistically significant. Data extraction and analysis were performed using Microsoft SQL Server® 2012, Microsoft Excel® 2013, and SPSS Statistics® 22.

3. Results

3.1. Patient characteristics

A total of 1748 patients using a NOAC participated in this study, of which 365 used apixaban, 550 used dabigatran, 45 used edoxaban and 788 used rivaroxaban (Table 1). The response for completing all four questionnaires was 77%. Participants had a median age of 66 years at the time of registration. There were 582 (33%) females and 1166 (67%) males.

3.2. ADRs experienced by patients

In total, 661 (38%) participants experienced at least one ADR during the study period. Edoxaban users experienced the highest percentage of ADRs (56%, $n = 25$) followed by dabigatran (41%, $n = 225$), rivaroxaban (37%, $n = 289$), and apixaban (33%, $n = 122$). The total number of reported ADRs was 192 for apixaban, 399 for dabigatran, 46 for edoxaban, and 526 for rivaroxaban. The median number of ADRs reported per patient was 2, with interquartile range (Q1–Q3) 1 to 5.

The top 10 most reported ADRs are presented in Table 2. The top 7 most reported ADRs were comparable between apixaban and rivaroxaban. The ADR profile for dabigatran has similarities with the other NOACs, but seems to have more gastrointestinal-related ADRs in its top 10.

Fourteen (2%) participants experienced a serious ADR (a total of 15 ADRs). These serious ADRs included: arrhythmia, arthralgia, cerebral hemorrhage, cerebrovascular accident,

Table 1. Patient characteristics.

	apixaban	dabigatran	edoxaban	rivaroxaban
Cohort size, no. patients	365	550	45	788
Median age in years, (interquartile range)	67 (61–71)	67 (61–72)	69 (61–72)	66 (59–71)
No. females (%)	142 (39%)	157 (29%)	11 (24%)	272 (35%)
Most reported indications, no. patients (%)*				
Atrial fibrillation	70 (19%)	88 (16%)	3 (7%)	86 (11%)
Arrhythmia	27 (7%)	38 (7%)	3 (7%)	54 (7%)
Pulmonary embolism	7 (5%)	2 (0.4%)	3 (7%)	22 (3%)
Thrombosis prophylaxis	20 (2%)	17 (3%)	0	52 (7%)

*This question was not mandatory.

Table 2. Top 10 reported ADRs.

NOAC	Ranking	ADR	Number	Calculated frequency* (95% CI)	SPC (incidence)
apixaban	1	Headache	21	5.6% (4.5–8.2)	-
	2	Fatigue	12	3.3% (2.4–5.2)	-
	3	Dizziness	11	3.0% (2.1–4.8)	-
	4	Nausea	9	2.5% (1.7–4.1)	1–10%
	5	Epistaxis	7	2.0% (1.2–3.4)	0.1–1% to 1–10% [#]
	6	Abdominal pain	6	1.6% (1.0–3.0)	-
	7	Diarrhoea	6	1.6% (1.0–3.0)	-
	8	Heart rate irregular	5	1.4% (0.8–2.6)	-
	9	Pollakiuria	5	1.4% (0.8–2.6)	-
	10	Haematoma	4	1.1% (0.6–2.2)	1–10%
dabigatran	1	Diarrhoea	43	7.8% (5.5–10.1)	0.1–1%
	2	Dyspepsia	20	3.6% (2.0–5.2)	0.01–0.1%
	3	Fatigue	20	3.6% (2.0–5.2)	-
	4	Abdominal discomfort	19	3.5% (1.9–5.0)	-
	5	Dizziness	19	3.5% (1.9–5.0)	-
	6	Nausea	19	3.5% (1.9–5.0)	0.1–1%
	7	Abdominal pain	18	3.3% (1.8–4.8)	0.01–0.1%
	8	Headache	18	3.3% (1.8–4.8)	-
	9	Pruritus	10	1.8% (0.7–3.0)	0.01–0.1%
	10	Flatulence	9	1.6% (0.6–2.7)	-
edoxaban	1	Abdominal pain	3	6.7% (0–14.1)	1–10%
	2	Blood urine present	3	6.7% (0–14.1)	1–10%
	3	Dizziness	3	6.7% (0–14.1)	1–10%
	4	Headache	3	6.7% (0–14.1)	1–10%
	5	Fatigue	2	4.4% (0–10.6)	-
	6	Malaise	2	4.4% (0–10.6)	-
	7	Nausea	2	4.4% (0–10.6)	1–10%
	8	Pruritus	2	4.4% (0–10.6)	1–10%
	9	Taste disorder	2	4.4% (0–10.6)	-
	10	[§]			
rivaroxaban	1	Dizziness	53	6.7% (4.9–8.5)	1–10%
	2	Headache	34	4.3% (2.9–5.8)	1–10%
	3	Fatigue	27	3.4% (2.1–4.7)	1–10%
	4	Nausea	26	3.3% (2.0–4.5)	1–10%
	5	Epistaxis	18	2.3% (1.2–3.3)	1–10%
	6	Diarrhoea	17	2.1% (1.1–3.2)	1–10%
	7	Abdominal pain	15	1.9% (0.9–2.9)	1–10%
	8	Oedema	15	1.9% (0.9–2.0)	1–10%
	9	Myalgia	14	1.8% (0.8–2.7)	-
	10	Dry mouth	12	1.5% (0.7–2.4)	0.1–1%

* Incidence calculated based on the number of participants that completed the first questionnaire.

[#] Incidence dependent on the indication for which the NOAC is used.

[§] Other ADRs are reported only once.

epistaxis, genital hemorrhage, haematuria, headache, menorrhagia, palpitations, pericarditis, post-procedural hemorrhage, retinal vein thrombosis, and thyroid disorder. Except for arrhythmia, which was reported twice, the other ADRs were all reported only once. Reasons for seriousness were: hospitalization (n = 13), death (n = 2), and disabling events (n = 1).

3.3. Description of ADRs in SPC

For apixaban, only nausea, epistaxis, and hematoma are described in the SPC (Table 2). The frequency of occurrence of these ADRs in this study corresponds to the incidences described in the SPC. For dabigatran, diarrhea, dyspepsia, nausea, abdominal pain, and pruritus are described in the SPC. The incidence described in the SPC was 0.1–1%, while the frequency in this study was 7.8%. For rivaroxaban, all ADRs, with the exception of myalgia, are described in the SPC. Incidence rates were comparable to the frequency as calculated in this study. For edoxaban, the numbers were low. Nevertheless, it shows that the calculated frequencies were comparable to the incidence described in the SPC.

3.4. Gender differences

No gender differences were found in the top 10 most reported ADRs, except for nausea. Nausea was reported more often by women than men (5.5% versus 2.1%, $p < 0.001$).

3.5. Characteristics of ADRs

3.5.1. Time to onset of ADR

The time to onset of the reported ADRs was comparable for all NOACs. The ADRs occurred with a median of 1 week after the start of the NOAC. The reported median time to onset (with interquartile range) was 7 days (1–28), 5 days (2–20), 5 days (10–50), and 6 days (2–22) for apixaban, dabigatran, edoxaban, and rivaroxaban, respectively.

We explored in-depth the time to onset of abdominal pain, diarrhea, dizziness, epistaxis, fatigue, headache and nausea for apixaban, dabigatran and rivaroxaban (Figure 1). We chose these ADRs as they are in the top 10 ADRs for all three drugs, with the exception of epistaxis for dabigatran. Edoxaban was not included given the low number of reports

Figure 1. Boxplots demonstrating time to onset.

Boxplot only shows outlines with time to onset of maximal 44 days. Number of included reports for respectively apixaban, dabigatran, and rivaroxaban:

- abdominal: 6, 18, 15
- diarrhoea: 8, 43, 17
- dizziness: 11, 19, 55
- epistaxis: 8, 3, 19
- fatigue: 13, 21, 28
- headache: 22, 19, 35
- nausea: 9, 19, 29

for these ADRs. Most ADRs had a median time to onset of less than 1 week. For epistaxis with rivaroxaban and abdominal pain with rivaroxaban and dabigatran, the median time to onset was less than 2 weeks. Abdominal pain with apixaban had the longest median time to onset with 28 days.

3.5.2. Outcome of the ADR and discontinuation of the NOAC

The patients recovered in over half of the ADRs (59%, $n = 682$). Of these, for 68% of ADRs the patients recovered without any changes in the use of the NOAC. For 6% of ADRs it was reported that the NOAC was discontinued after which the patients recovered from the ADR. In general, a total of 165 (9%) participants discontinued the NOAC due to an ADR during the first 6 months of treatment.

4. Discussion

This study provides insight into the safety profile of NOACs in everyday use as reported by patients. Besides information about the occurrence of ADRs and its frequencies, this study gives insight into the characteristics of ADRs as experienced by patients. Six hundred and sixty-one (38%) participants experienced at least one ADR during the study period. Of these, 14 participants experienced a serious ADR. Some of the reported ADRs do not necessarily have to be biologically or

pharmacologically related to the NOAC, but may also be caused by the underlying disease, for example, 'arrhythmia' or 'palpitations'. For the most reported ADRs, the profile is largely comparable for apixaban and rivaroxaban, which are both factor Xa inhibitors. Although edoxaban also belongs to this drug group, the low number of participants does not allow a comparison with the other factor Xa inhibitors users.

Dabigatran, a direct thrombin inhibitor, shows a slightly different ADR profile. For dabigatran diarrhea is the most often reported ADR with a frequency of 8%. For apixaban and rivaroxaban, the frequency of diarrhea was lower with 1.2% and 2.1%, respectively. Headache was most often reported by patients using apixaban (5.6%) and dizziness by patients using rivaroxaban (6.7%). These ADRs were also reported by patients using dabigatran; however, the frequency was lower; 3.5% for both ADRs.

We compared calculated frequency with information about the incidence of the ADRs in the drug's SPC. For apixaban, edoxaban, and rivaroxaban these two were comparable. For dabigatran, the calculated frequencies were slightly higher in this study compared to incidences in the drug's SPC.

Health-care professionals and patients use the SPC, patient information leaflet, and secondary sources to obtain information about the safety of drugs. Almost all top 10 reported ADRs for rivaroxaban are also described in the SPC; however, for apixaban, which has a similar mechanism of action as rivaroxaban, this was the case for only three ADRs. There is no clear explanation for these differences. In addition, with the

exception of epistaxis, most reported ADRs were not related to bleeding. In the SPC of apixaban, edoxaban, and rivaroxaban, for several bleeding-related ADRs, an incidence of 1–10% is reported. For this reason, we expected a higher number of patients with bleeding-related ADRs. For health-care professionals, it is important to be aware of nonbleeding-related ADRs with NOACs as these ADRs might not always be considered relevant but may indeed influence the patient's drug adherence and daily life.

A total of 165 (9%) participants discontinued the NOAC due to an ADR during the first 6 months of treatment. This is comparable with a study of *Vedovati et al.*, in which 9.8% (128 patients) discontinued the use of a NOAC during the first 6 months of treatment [11]. In their prospective cohort study, they included 1305 consecutive non-valvular atrial fibrillation patients prescribed with NOACs and investigated any permanent discontinuation of the NOAC after 1-year. Discontinuation of the NOAC was 15.4% ($n = 201$) after 1 year of treatment, meaning that more than 60% of the discontinuations occurred within the first 6 months. Of all ADRs for which a recovery was reported, 68% recovered without any changes to the use of the NOAC. This indicated that discontinuation of the NOAC is not always needed in order for the patient to recover from the ADR.

4.1. Strengths and limitations

The strength of the web-based CEM method is that it can provide insight into the safety of drugs in daily practice; both the occurrence of ADRs and its characteristics. The approach can easily be implemented and allows for the inclusion of large numbers of participants over a short time span. The response rate for completing all four questionnaires was 77%. Similar response rates were also seen for other CEM studies, for example, in a study about the antidiabetic drug metformin by our center, the response rate for completing all six questionnaires of the study was 62% (1042/1667 participants) [12]. In a study about varenicline, a drug indicated for smoke cessation therapy, the response rate for completing all five questionnaires was lower with 37% (249/665 participants) [13].

Patients were invited to participate in this study by the pharmacist. We do not know what proportion of potentially eligible patients actually registered to participate in this study. In addition, we do not know to what extent the pharmacist made a selection whether or not to invite a patient for participation. This may have introduced selection bias.

Another point of attention is lost to follow-up. It is unknown why patients dropped out of the study; this may have been because of lack of interest, but it may also be due to the occurrence of a (serious) ADR. In future studies, the reasons for drop out should be analyzed in more detail. In order to participate in a CEM study, patients must have enough reading and writing skills to fill in the questionnaire and have access to the internet. This may have introduced some selection bias. In respect to access to the internet, Statistics Netherlands reports that 97.1% of the Dutch households had Internet access in 2017. For people aged 25–45 years old this is 99.8% and for people aged over 65 this was 88.3% [14].

NOACs are used for several different indications. In this study, the most reported indications for NOAC use were atrial fibrillation, arrhythmia, thrombosis (prophylaxis), and pulmonary

embolism. It was not explored to what extent the patient's indication would influence the occurrence of ADRs.

When the male-female ratio is compared to prescription data from the Dutch Foundation for Pharmaceutical Statistics (SFK) 2017, it is shown that our study population included more men; 67% versus 51% as compared to the general population of NOAC users. As we found little differences for the occurrence of different types of ADRs between men and women, we believe the difference in the male-female ratio would have little impact when generalizing the results.

5. Conclusion

Most reported ADRs were comparable with the information described in the SPC. ADRs that were most often reported by patients were not related to bleedings, with the exception of epistaxis. Generally, the ADRs occurred within 1 week after start and were overall well tolerated by the participants. In 59% of ADRs the patient recovered. ADRs may resolve spontaneously under continuation of the use of the NOAC; the majority of patients recovered without changes to the use of the NOAC.

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Author contributions

L Rolfes and C Ekhart were responsible for data analysis and drafting of the manuscript. J Hendriks was responsible for development of the questionnaire. J Hendriks and P van der Horst were responsible for coding of the reported adverse drug reactions. E van Puijenbroek was responsible for the study design and critical revision of the manuscript.

Declaration of interest

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

Reviewer disclosures

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