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Anticoagulant-associated adverse drug reactions in 2013–15

ORIGINAL ARTICLE

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BACKGROUND

The aim of this study was to obtain a better insight into the adverse drug reaction profiles of the new direct-acting oral anticoagulants (DOACs).

MATERIAL AND METHOD

A review was undertaken of all reports of adverse drug reactions for warfarin, dabigatran, rivaroxaban and apixaban received by the Norwegian regional medicines information and pharmacovigilance centres (RELIS) in the period June 2013–May 2015.

RESULTS

Approximately 65 000 persons used direct-acting oral anticoagulants and 80 000 used warfarin in the study period. A total of 409 reports of adverse drug reactions were included in the study. Altogether 55 % of the reports related to men. The patients were over 70 years of age in 76 % of the reports for direct-acting oral anticoagulants and in 85 % for warfarin. The most common adverse drug reactions were haemorrhages (48 % for direct-acting oral anticoagulants and 75 % for warfarin). Most of them were cerebral haemorrhages (91 for direct-acting oral anticoagulants and 92 for warfarin). Blood clots (therapeutic failure), cognitive impairment, headache and hair loss were among the other adverse drug reactions. The highest levels of comorbidity were seen in patients who died. The number of reported deaths was highest for rivaroxaban (1.1 deaths/1 000 users) with a declining incidence for apixaban (0.9 ‰), dabigatran (0.7 ‰) and warfarin (0.6 ‰). The degree of reporting differed for

the different drugs, and therefore the spontaneous reporting system cannot be used to compare the incidence of adverse drug reactions associated with different medications.

INTERPRETATION

Adverse drug reactions, including serious adverse reactions, may occur with the use of any anticoagulant. Factors that may increase the risk of adverse reactions are advanced age, high comorbidity, impaired renal function, and polypharmacy.

Main points

Adverse drug reactions, including serious adverse reactions, occurred upon use of both warfarin and the new direct-acting oral anticoagulants (dabigatran, rivaroxaban and apixaban)

Patients with comorbidities, advanced age or concurrent use of other medications that may cause haemorrhaging were at increased risk of serious adverse events and death

All treatment with anticoagulants requires thorough and regular follow-up

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For many years, warfarin was the oral medication of choice in Norway for anticoagulation. Since 2012, however, several new drugs have become available: dabigatran, rivaroxaban, apixaban and edoxaban. After these new anticoagulants – direct-acting oral anticoagulants (DOACs) – were approved for reimbursement on the Norwegian 'blue prescription' scheme, their use has increased steadily. These drugs have gradually replaced warfarin (Figure 1a). Dabigatran is a direct thrombin inhibitor, whereas rivaroxaban, apixaban and edoxaban are factor Xa inhibitors. Edoxaban entered the market after data collection and is therefore not included in the analysis.

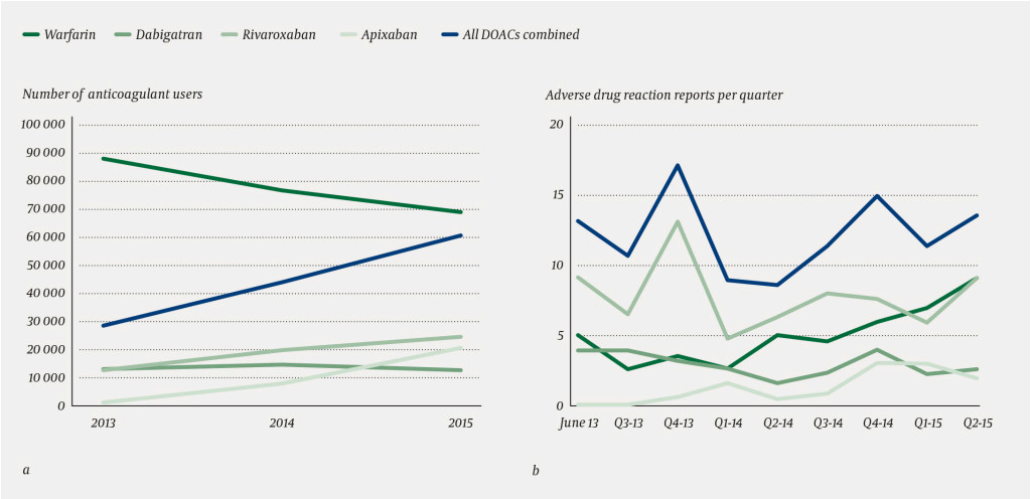

Figure 1 a) Number of unique users of direct-acting oral anticoagulants (DOACs) per year for the period 2013–15. Source: Norwegian Prescription Database. b) Number of adverse drug reaction reports per quarter (Q). Number shown is monthly average per quarter. Source: Norwegian Pharmacovigilance Database

Prior to marketing authorisation being granted, large multicentre studies (1–3) known as RE-LY (dabigatran), ROCKET AF (rivaroxaban) and ARISTOTLE (apixaban), had shown the new drugs to be as effective as warfarin in preventing stroke. The drugs also resulted in a lower incidence of intracranial haemorrhage when compared to warfarin. In addition, they were shown to protect against deep vein thrombosis and pulmonary embolism (4). The drugs should be easier to dose than warfarin, give rise to fewer drug-drug interactions, and eliminate the need for regular monitoring with blood tests.

The Norwegian Directorate of Health and the Norwegian Medicines Agency have issued guidelines for use of the new anticoagulants (5).

Spontaneous reporting of adverse drug reactions

Patients that participate in clinical trials differ in many ways from patients receiving treatment in normal clinical practice. It is therefore important to monitor the effectiveness and safety of drugs even after they have received marketing authorisation. One component of the regulatory authorities' pharmacovigilance strategy is the spontaneous reporting system, in which healthcare personnel and patients can report suspected adverse drug reactions occurring upon normal clinical use of drugs. The advantage of this method is that it can detect signals of serious, unusual and/or unknown drug reactions. These can then be investigated and potentially confirmed. One disadvantage is that many notifiable events, including serious events, are not reported. (Adverse drug reactions are defined as serious if they are fatal, life-threatening, necessitate/prolong hospitalisation, cause persistent/significant disability/inability to work or a congenital anomaly/birth defect. In addition, the reaction itself may result in an adverse event being classified as serious (6)).

Owing to underreporting, spontaneous reporting cannot be used in isolation to calculate the frequency of a given adverse reaction. Furthermore, reporting rates differ between drugs. Adverse reactions are reported more frequently for new drugs than for older ones, for example. The spontaneous reporting system cannot therefore be used to compare the incidence of adverse reactions for different drugs (7, 8).

Experience with warfarin

In Norway, warfarin is the drug with most reported serious and fatal adverse drug reactions (9). Treatment with warfarin can be complicated, in part because of the narrow therapeutic window. Adverse reactions reported for warfarin are typically haemorrhages. A Norwegian study examined 713 cases of haemorrhage associated with the use of warfarin, and found that haemorrhages were related to high INR and occurred at the start of treatment. More than half of the cases were cerebral haemorrhages, followed by gastrointestinal haemorrhages and all other haemorrhages combined. Altogether, 53 % of the

events were fatal. To reduce the number of haemorrhagic adverse events, the authors advised lower initial doses, more frequent follow-up, and INR values at the lower end of the recommended range (10).

Experience with the new drugs

Rare adverse reactions are often not captured in the clinical trials conducted prior to approval of new drugs. Sometimes the frequency of adverse reactions is incorrectly estimated owing to the relatively small number of individuals exposed to the drug or the use of a highly selected patient population (7).

Following the marketing of dabigatran, rivaroxaban and apixaban, the Norwegian Medicines Agency and RELIS (the medicines information and pharmacovigilance centre network) wished to obtain additional information about adverse reactions associated with the new drugs. Healthcare personnel were encouraged to report all events related to suspected adverse reactions upon use of anticoagulants, and to report information on medical history and other medication use in a supplementary form.

The purpose of this study was to obtain a better insight into the safety profile of the new anticoagulants.

Material and methods

Dataset

Data were collected from all reports in the Norwegian Pharmacovigilance Database for warfarin, dabigatran, rivaroxaban and apixaban in the project period (1 June 2013–31 May 2015). A form for obtaining supplementary information on medical history and medication use was sent to all those who submitted reports in the same period. No follow-up to increase the response rate was attempted. Information from these forms was included in the dataset. Only reports from healthcare personnel to the RELIS centres were included. The reporting and recording of adverse reactions was based on the common European criteria for adverse reactions (6), but the vast majority of the reports also fulfilled the narrower criteria used by the World Health Organisation (WHO) (11).

Adverse reaction reports are only available in the database in anonymised form; although the reports do contain information about patients' age and gender, it is not possible to identify individual patients on this basis. Data for the number of users of relevant drugs in the study period, together with certain patient characteristics (age range and gender), were retrieved from the Norwegian Prescription Database. These data cannot be used to identify individual patients.

Recording of reports of adverse drug reactions

Background data for all identified reports were reviewed by at least one of the authors. Demographic parameters (age, gender) were recorded, along with the severity of the reported reaction, medication use, suspected adverse reactions, and possible risk factors for adverse reactions to anticoagulants (Tables 1–4, see also Appendix for complete list of variables). The Norwegian Pharmacovigilance Database has functionality for managing duplicates, and these were removed prior to the analysis.

Usage data

The number of users of the four drugs was retrieved from the Prescription Database for the study period together with certain patient characteristics (age range and gender). The usage figures are presented as the total number of users of each drug in 2013, 2014 and 2015, respectively.

Analysis

Information from the recorded reports was compiled in an Excel spreadsheet and analysed descriptively with respect to age and gender, polypharmacy, adverse events and risk factors for adverse events. Since data from spontaneous reports of adverse reactions are not representative of all adverse reactions that occur, and because reporting rates differ between drugs, only descriptive statistics were used and not inferential statistics.

Results

Number of users and adverse drug reactions

Data extracted from the Prescription Database for the study period showed that there were 65 000 users of direct-acting oral anticoagulants, and 80 000 users of warfarin. Gender and age distribution are shown in Table 1. The number of patients prescribed direct-acting oral anticoagulants increased over the period, while the number of warfarin users fell (Figure 1a).

Table 1

Descriptive data for patient population and adverse drug reaction reports. The interval between drug initiation and an adverse event was calculated only for the group for which the time of drug initiation was known. DOACs = direct-acting oral anticoagulants. Source: Prescription Database and Norwegian Pharmacovigilance Database

	Dabigatran	Rivaroxaban	Apixaban	Warfarin
Total number of anticoagulant users[1]	19 164	28 243	15 290	81 097
Number of reports	73	184	34	118

	Dabigatran	Rivaroxaban	Apixaban	Warfarin
Number of reports/1 000 anticoagulant users[1]	3.8	6.5	2.2	1.3
Male users of each anticoagulant (%)	60	55	53	60
Reports related to men (%)	57	48	53	66
Reports with supplementary form (%)	48	53	44	33
Adverse reaction occurred in first month (%)	24	34	20	2
Adverse reaction occurred in first 6 months (%)	55	73	75	11
Proportion of patients aged 70 years and above:		**DOAC**		**Warfarin**
In adverse reaction reports (%)		76		85
In entire population of anticoagulant users (%)		58		65

[1]Data were obtained from the Prescription Database; all other data were obtained from the Norwegian Pharmacovigilance Database

The total number of adverse reaction reports was 409 (291 for direct-acting oral anticoagulants and 118 for warfarin). Reporting increased for both types of anticoagulants over the study period (Figure 1b). The number of adverse reaction reports per 1 000 anticoagulant users was highest for rivaroxaban (6.5 reports/1 000 users), somewhat lower for dabigatran (3.8 %) and apixaban (2.2 %), and markedly lower for warfarin (1.3 %) (Table 1).

The most frequently reported adverse reactions were cerebral haemorrhage, haemorrhage in skin/muscle/joint/mucous membranes and gastrointestinal haemorrhage. All reported adverse reactions are listed in Table 2. A minority of patients experienced adverse reactions in the first month of treatment, while most of the events occurred in the first six months (Table 1).

Table 2

Number and type of adverse reactions reported to RELIS for each of the drugs in the period 1 June 2013–31 May 2015. The numbers presented are absolute, and are not adjusted for the number of users. Source: Norwegian Pharmacovigilance Database

	Dabigatran	Rivaroxaban	Apixaban	Warfarin	Total
Cerebral haemorrhage	14	63	14	92	183
Skin/muscle/joint/mucosal haemorrhage	13	41	2	7	63
Gastrointestinal haemorrhage	16	18	5	10	49
Fall in haemoglobin/anaemia	11	19	3	5	38
Fall/trauma	1	10	3	11	25
Therapeutic failure	5	15	2	1	23
Ulcer, epigastric pain	12	4	0	1	17
Thrombosis	2	11	2	1	16
Rash/itching	3	9	2	2	16
Cerebral infarction	4	6	2	2	14
Cognitive impairment	2	10	0	1	13
Hepatic impairment	5	4	1	0	10
Headache	1	6	2	0	9
INR increase	0	0	0	9	9
Dizziness	1	7	0	1	9
Rectal bleeding	3	3	1	1	8
Postoperative bleeding	0	5	1	0	6
Dyspnoea	0	5	0	0	5
Impaired renal function	2	2	1	0	5
Hair loss	1	2	0	1	4
Peripheral neuropathy	2	2	0	0	4
Interstitial lung disease	1	2	0	0	3
Triggered arrhythmia	1	2	0	0	3
Renal haemorrhage	1	0	0	0	1

The indication for anticoagulation was atrial fibrillation in 304 (74 %) of the adverse reaction reports, and deep vein thrombosis or pulmonary embolism in 69 (17 %). This ratio is consistent with the usage pattern for anticoagulants in Norway (12). In the remaining reports, other indications were stated.

The supplementary forms were completed for 33 % of warfarin-related reports and 51 % of DOAC-related reports (187 forms in total).

Gender and age

More of the reports concerned male patients than female, except for rivaroxaban, where 48 % of the reports concerned men. In the DOAC group, 76 % of patients in the adverse reaction reports were aged 70 and above, while the corresponding figure for warfarin was 85 %. In the entire treated population, 58 % of the DOAC group were aged 70 and above, compared with 65 % of the warfarin group. The average age of all patients in the adverse reaction reports was 75–80 years, while the average age of those who died was 79–81 years (Table 3).

Table 3

Description of fatal events. The interval between drug initiation and an adverse event was calculated only for the group for which the time of drug initiation was known. The numbers presented are absolute, and are not adjusted

	Dabigatran	Rivaroxaban	Apixaban	Warfarin
Average age in reports	76	75	80	79
Average age of deceased patients in reports	79	81	81	80
Number of deaths/1 000 anticoagulant users	0.7	1.1	0.9	0.6
Most common causes of death, in numbers:				
Cerebral haemorrhage	5	21	8	56
Gastrointestinal haemorrhage	4	3	0	6
Cerebral infarction	2	3	1	0
Time of death:				
Death within first month (%)	0	21	22	0
Death within first 6 months (%)	29	53	78	13

[1]Data were obtained from the Prescription Database; all other data were obtained from the Norwegian Pharmacovigilance Database

The percentage of adverse reaction reports classified as serious was 97 % for warfarin, 82 % for apixaban, 76 % for rivaroxaban and 74 % for dabigatran. Initially, both serious and less serious adverse events were reported for direct-acting oral anticoagulants. Gradually, however, only serious events were reported. For warfarin, reports over the entire period mainly concerned serious adverse reactions.

Fatal outcomes

The percentage of adverse reaction reports with fatal outcomes was 50 % for warfarin, 38 % for apixaban, 19 % for dabigatran and 17 % for rivaroxaban. The number of deaths per 1 000 anticoagulant users was highest for rivaroxaban, with successively declining numbers for apixaban, dabigatran and warfarin. The most common causes of death stated in the reports were cerebral haemorrhage, gastrointestinal haemorrhage and cerebral infarction. The numbers have not been adjusted for the number of users. Most deaths occurred within the first six months of treatment initiation. A smaller proportion of patients died in the first month of treatment (Table 3).

Comorbidity

The patients that died had greater comorbidity, including hypertension, cardiovascular disease and renal failure, than those who survived. This applied to users of both direct-acting oral anticoagulants and warfarin (Table 4).

Table 4

Percentage of patients with reported hypertension, cardiovascular disease and impaired renal function among those receiving direct-acting oral anticoagulants (DOACs) and those receiving warfarin. The figures in parentheses are the absolute numbers that survived and that died. Source: Norwegian Pharmacovigilance Database

	Hypertension	Cardiovascular disease	Renal failure
DOAC, survivors (%) (n = 231)	34 (78)	16 (36)	8 (18)
DOAC, deceased (%) (n = 58)	40 (23)	28 (16)	19 (11)
Warfarin, survivors (%) (n = 59)	29 (17)	25 (15)	5 (3)
Warfarin, deceased (%) (n = 59)	34 (20)	32 (19)	8 (5)

Discussion

The increase in the number of adverse reactions reported over the study period for direct-acting oral anticoagulants and warfarin probably reflects both increased prescribing of these drugs and the fact that the Norwegian Medicines Agency/RELIS particularly encouraged reporting of adverse reactions associated with the use of anticoagulants (13).

It is known that many adverse reactions are not reported and that the reporting of adverse reactions is not random. In our dataset, there were more reports for direct-acting oral anticoagulants (relative to the number of users) than for warfarin. However, this does not mean that direct-acting oral anticoagulants give rise to more adverse reactions than warfarin. It may be that there is more interest in reporting adverse reactions for new drugs. When a drug is well-known, less serious adverse reactions are reported less often (14, 15). In a Swedish study of warfarin, only 14 % of serious haemorrhages were reported (16).

Incidence of adverse reactions for each drug

The most frequently reported adverse reactions in our study (Table 2) are consistent with those seen in other studies (17, 18). The adverse reactions are presented in absolute numbers. Since these have not been adjusted for the number of users and for underreporting, they cannot be used to estimate the frequency of adverse reactions. The number of reported adverse reactions varies for the different direct-acting oral anticoagulants in the study. Rivaroxaban has the highest incidence, also after correction for the number of users. In a recently published Norwegian study, rivaroxaban appeared to present a greater risk of haemorrhage than dabigatran or apixaban (19). This was also observed in a Swedish study (17). Our study also captured some potential adverse reactions, such as hair loss and various adverse effects related to the central nervous system, which were not specified in the Summaries of Product Characteristics, but which have subsequently been investigated by the pharmaceutical regulatory authorities.

Time preceding first adverse reaction

The majority of adverse reactions to direct-acting oral anticoagulants occurred in the first six months of treatment, while a smaller number occurred in the first month. The corresponding figures for warfarin are small because there were few new warfarin users in our dataset. Since an earlier Norwegian study had shown that most warfarin-related haemorrhages occurred shortly after treatment initiation (in the course of the first month) (10), it had been suggested that this may also be the case for anticoagulants in general. However, our dataset appears to suggest that adverse reactions to direct-acting oral anticoagulants may occur to a greater degree when the patient has been taking the drugs for a somewhat longer period of time. It is important to consider this during the treatment and follow-up of patients prescribed anticoagulants, especially now that patients are increasingly treated with direct-acting oral anticoagulants rather than warfarin (19).

Age and gender

There was in general a higher proportion of men than women in the adverse reaction reports. This may be because more men than women have atrial fibrillation and receive treatment with anticoagulants (Table 1) (20), and this is reflected in a greater number of adverse reactions. The somewhat lower proportion of men in rivaroxaban-related reports appears to reflect random variation. Most patients in the adverse reaction reports were over 70 years of age (Table 3). Older patients are often more severely ill and therefore at greater risk of adverse reactions, including during treatment with anticoagulants (21).

Proportion of serious adverse drug reactions

Over the course of the study period, the proportion of serious adverse reactions reported for rivaroxaban increased. This can be explained by clinicians becoming increasingly familiar with the drug, and therefore no longer reporting less serious adverse reactions. The reporting pattern for rivaroxaban increasingly resembled that for warfarin, for which reports almost exclusively concern serious adverse effects.

Adverse drug reactions with fatal outcomes

The majority of deaths in our dataset were caused by cerebral haemorrhage. This is consistent with the findings of the pivotal studies (1–3) and a subsequent epidemiological study (17). Most of the patients that died had been using anticoagulants for more than a month, and this is important to bear in mind when following-up such patients.

Comorbidity

Greater comorbidity (including hypertension, cardiovascular disease and renal failure) was seen in the patients who died than in those who survived. One study reported that low body weight, altered body composition of fat and muscle, renal insufficiency, high comorbidity, dementia and risk of falls were predisposing factors for adverse reactions upon use of direct-acting oral anticoagulants (21). Another study showed that factors including renal impairment predicted a high risk of haemorrhage (17). Dabigatran is contraindicated in patients with severe renal impairment (creatinine clearance < 30 ml/min), because such patients will have high serum drug concentrations, resulting in a high risk of haemorrhage (22). It is also important to assess the renal function of patients treated with apixaban and rivaroxaban, which are not recommended for those with creatinine clearance below 15 ml/min (5).

Study limitations

Underreporting is known to be a problem in the spontaneous reporting of adverse drug reactions, and our dataset is relatively small. The study findings are therefore not suitable for comparing the incidence of adverse drug reactions with warfarin versus direct-acting oral anticoagulants, or for drawing conclusions regarding the frequency and types of adverse reactions associated with the various drugs.

Conclusion

The adverse drug reaction profile of direct-acting oral anticoagulants has yet to be fully characterised. All treatment with anticoagulants should be preceded by a thorough assessment of the individual patient. The elderly in particular should be treated on the basis of strict indication and any adverse reactions closely monitored. Dose reduction may be considered in the event of impaired renal function, comorbidity and where there is a risk of interaction with other drugs. It is also important to pay attention to any reports from patients of discomfort or possible adverse effects after initiation of treatment. In our dataset, many of the adverse reactions – including those that were fatal – occurred after several months of treatment with the drugs.

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