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ORIGINAL RESEARCH ARTICLE

Using the Symmetry Analysis Design to Screen for Adverse Effects of Non-vitamin K Antagonist Oral Anticoagulants

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Abstract

Introduction Knowledge on adverse effects (AEs) related to non-vitamin K antagonist oral anticoagulants (NOACs) in real-world populations is sparse.

Objective Our objective was to identify signals of potential AEs in patients with atrial fibrillation (AF) initiating NOAC treatment using a hypothesis-free screening approach.

Methods Using the nationwide Danish registries, we identified patients with AF initiating dabigatran, rivaroxaban, or apixaban between 2011 and 2015 ($n = 50{,}627$). Applying a symmetry analysis design, we screened for AEs of NOAC, as reflected by new drug treatments, incident diagnoses, or procedures. For signals with the lowest number needed for one additional patient to be harmed (NNTH), we evaluated whether they likely represented genuine AEs or other types of associations. Signals assessed as potential AEs were grouped into five categories for analysis of effect modification according to patient and drug characteristics.

Results Of the identified signals, 61 were classified as potential AEs. Most signals could be categorized as the following types of AEs: bleedings, non-bleeding gastrointestinal symptoms, mental disease, urinary tract disorders, and musculoskeletal symptoms. Older age and first-ever use of anticoagulants was associated with strengthening of all "NOAC-adverse effect" associations. Conversely, use of low-dose NOAC and apixaban led to attenuation of most associations.

Conclusion Through a symmetry analysis-based hypothesis-free screening of large-scale healthcare databases, we were able to confirm well-established AEs of NOAC therapy in clinical practice as well as potential AEs that deserve further investigation.

Key Points

A hypothesis-free screening of automated healthcare databases generated signals of potential adverse effects to non-vitamin K antagonist oral anticoagulant (NOAC) therapy. The vast majority of signals could be categorized as bleedings, non-bleeding gastrointestinal adverse effects, mental disease, urinary tract disorders, or musculoskeletal symptoms.

The risk of experiencing adverse effects seems to vary according to patient and drug characteristics such as age and NOAC dose.

Our study generated several specific signals of potential adverse effects of NOAC therapy. These signals should be evaluated in future studies.

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1 Introduction

Non-vitamin K antagonist oral anticoagulants (NOACs; dabigatran etexilate, rivaroxaban, apixaban, and edoxaban) constitute a newer anticoagulant drug class that is currently recommended as first-line treatment in patients with atrial fibrillation (AF) with an indication for stroke prophylaxis based on the CHA_2DS_2-VASc-score [1]. As with all newly marketed drugs, most knowledge of adverse effects (AEs) associated with NOACs comes from the pivotal clinical trials conducted in the pre-marketing phase of drug development. However, whether knowledge of safety, including AEs, from NOAC trials can be extended to real-life anticoagulant users has been questioned because of the different patient characteristics of real-life users and trial participants [2] and selective prescribing [3]. In addition, clinical trials are designed and powered to explore efficacy rather than safety, so the number of patients exposed during NOAC trials may be too small to enable detection of rare AEs. Thus, data from large cohorts of real-world NOAC users are required to fully characterize AEs associated with NOAC treatment in clinical practice. Such data can be sourced from administrative healthcare registries, including claims databases, clinical databases, or databases based on spontaneous AE reports. To date, most studies based on such observational data provide associations between NOAC use and specific AEs already known from the clinical trials, e.g., bleeding-related AEs [3–5]. However, another and complementary use of observational data when exploring AEs is hypothesis-free computerized screening of large-scale healthcare registries. Unlike spontaneous AE reporting, this approach can identify signals of potential AEs without relying on clinical suspicion [6]. Studies have suggested the symmetry analysis design originally proposed by Hallas [7] in 1996 as a robust and efficient method to screen for signals of AEs [8, 9] because of the high specificity towards known AEs [10] as well as the inherent advantages of a self-controlled design [11].

The overall aim of this study was to provide further knowledge on AEs of NOAC therapy when used in clinical practice. To this end, we used the symmetry analysis design to perform a large-scale hypothesis-free screening of population-based Danish healthcare registry data with the objective to identify signals of known and unknown potential AEs associated with NOAC use in patients with AF.

2 Methods

Using a symmetry analysis design [7], we analyzed the occurrence of events (drug initiation, new diagnosis, and procedures) in a symmetrical time window before and after initiation of a NOAC for AF. Any non-symmetrical distribution of the occurrence of these events before and after NOAC initiation might reflect effects of NOAC treatment.

2.1 Data Sources

Virtually all medical care in Denmark is furnished by the national health authorities, allowing population-based register-linkage studies covering all inhabitants of Denmark [12]. We used data from three nationwide health registries. Data on drug use were retrieved from the National Prescription Registry [13] as filled prescriptions. From the National Patient Register [14], we obtained data on registered in- and outpatient diagnoses (classified according to the *International Statistical Classification of Diseases and Related Health Problems 10th Revision* [*ICD-10*]) and procedures from non-psychiatric hospitals. Finally, we used the Civil Registration System [15] to keep track of the deaths and migrations of study subjects. Data were linked using the set-up provided by Danish Health Data Authorities in Denmark. Definitions of drugs, diseases, and procedures used in this study are detailed in the Electronic Supplementary Material (ESM 1).

2.2 Study Population

We included all Danish individuals who initiated a NOAC for the first time in the period August 2011 (marketing of dabigatran for AF in Denmark) to 31 December 2015. Edoxaban was marketed in Denmark in June 2016 [16] and was therefore not included. To ensure a relatively homogenous population with a high expected treatment persistence, the study population was restricted to individuals who used NOACs for AF [16, 17]. We therefore required individuals to have an AF diagnosis in the Patient Registry, any time either before or up to 90 days after NOAC initiation [18]. Additionally, we excluded individuals with a registered hip or knee replacement surgery within 2 weeks before NOAC initiation or up to 5 weeks after. Lastly, we excluded individuals with a recent (<1 year) registration of a venous thromboembolic event (deep vein thrombosis or lung embolus).

2.3 Symmetry Analysis

The symmetry analysis design was first proposed by Hallas in 1996 [7] and has been described extensively by others [9, 19]. It is a so-called self-controlled design, as patients are compared with themselves, that is, patients' experiences after initiating a NOAC are compared with their experience prior to NOAC initiation [11]. For each individual, we defined the index date as the date of NOAC initiation. Within a time window extending 6 months backward and

6 months forward in time from this fixed date, we identified all incident (i.e., first-ever) drug use as well as incident hospital diagnoses and procedures. The pre-exposure and post-exposure time window was considered as person-time not exposed and exposed to NOAC, respectively. Consider as an example a potential AE that is treated with a drug, e.g., dyspepsia treated with a proton pump inhibitor (PPI). In the absence of an association between the use of NOACs and dyspepsia, we would expect a symmetrical distribution of individuals initiating a PPI prior to NOAC initiation and those initiating a PPI after NOAC initiation [7]. If, on the other hand, use of NOACs was associated with dyspepsia, we would expect an asymmetrical distribution where more people initiated a PPI after NOAC initiation than before NOAC initiation. It can be shown that the ratio of individuals starting, e.g., a drug prior to NOAC initiation versus individuals starting the drug after NOAC initiation (i.e., the sequence ratio [SR]), is an estimate of the incidence rate ratio of the given drug prescribing in follow-up exposed to versus not exposed to NOACs, possibly with a small conservative bias [9].

Importantly, the symmetry analysis design is based on an "intention-to-treat"-like approach, that is, we did not account for persistence with NOAC therapy after the index prescription. However, we have previously shown [17] that only around 20% of NOAC initiators undergo a treatment change (i.e., switching or discontinuation) within 6 months of initiation; we therefore consider "NOAC initiation" as a valid proxy for "exposure to NOAC therapy for 6 months".

2.4 Primary Analysis: Screening for Signals

An overview of the steps of the analyses and data processing is provided in Fig. 1. First, we screened for signals of associations between incident NOAC use and incident drug use (on the drug class level, defined as the fourth level of the anatomical therapeutic chemical classification system), incident hospital diagnoses, and procedures by estimating SRs with 95% confidence intervals (CIs). A basic principle in the symmetry analysis design is that the time window both before and after the exposure event must be truly "at risk" for the given outcome event, otherwise the SR will be biased. Therefore, diagnoses of death, diagnoses serving as study exclusion criteria and contraindications to NOAC use, and initiation of other NOACs were disregarded as outcomes in the analysis, as these events could only occur in the time window after the index prescription according to the study eligibility criteria. The symmetry design can eliminate confounders that are stable over time [7]; therefore, no further confounder adjustment of the SR was performed. Nor did we adjust for potential time trends in the outcome events. This was based on the assumption that no outcomes would show strong enough time trends within the 12-month periods of observation to introduce substantial bias. The exposure event (i.e., NOAC initiation) was fixed in time and therefore not susceptible to bias from time trends. For all pairs of NOAC use and incident drug use, incident hospital diagnoses, or procedures, we calculated the number of patients needed to treat for one additional patient to be harmed (NNTH) [20] and reported the 20 signals with the lowest value, i.e., the largest absolute effect size. Specifically, the NNTH was calculated by dividing the total number of NOAC initiators with the difference between the number of events after and the number of events before NOAC initiation, which is in accordance with the "naturalistic" NNTH measure [21] and the approach described by Altman [22]. An NNTH of 50, for example, means it takes 50 patients initiating NOAC therapy for one additional patient to develop the outcome within 6 months when compared with untreated patients. This translates to an absolute risk increase of about 2.0% compared with non-users. Analyses were performed for all NOACs combined as well as individually to capture signals that were only seen for individual NOACs.

2.5 Categorization of Signals

Each of the identified associations (i.e., the analytical output of the primary analysis) were manually reviewed by two physicians with expertise within the fields of pharmacology and internal medicine (MH, JH) and categorized as "potential AEs" or "other associations". Potential AEs included associations between a NOAC and a specific condition as well as drug or procedure proxies for a condition for which no other plausible explanation seemed reasonable. As several associations were expected to reflect the same underlying condition (e.g., bleeding complications), the signals were grouped into categories based on the study physicians' clinical knowledge and reasoning. Signals that were not regarded as potential AEs were (1) associations between NOACs and other aspects of AF therapy, e.g., initiation of antiarrhythmic drugs; (2) associations likely reflecting the diagnostic work-up (including outcomes hereof) related to either the AF diagnosis (e.g., detection of heart failure in relation to echocardiography and hereafter initiation of anticongestive therapy) or to bleeding complications (e.g., diagnosis of benign colon adenomas secondary to colonoscopy); and (3) non-classifiable associations (e.g., association between NOAC initiation and hospitalization with an unspecified condition).

2.6 Secondary Analysis: Characterization of Identified Associations

To further characterize the associations categorized as potential AEs, we assessed each "AE group" for effect

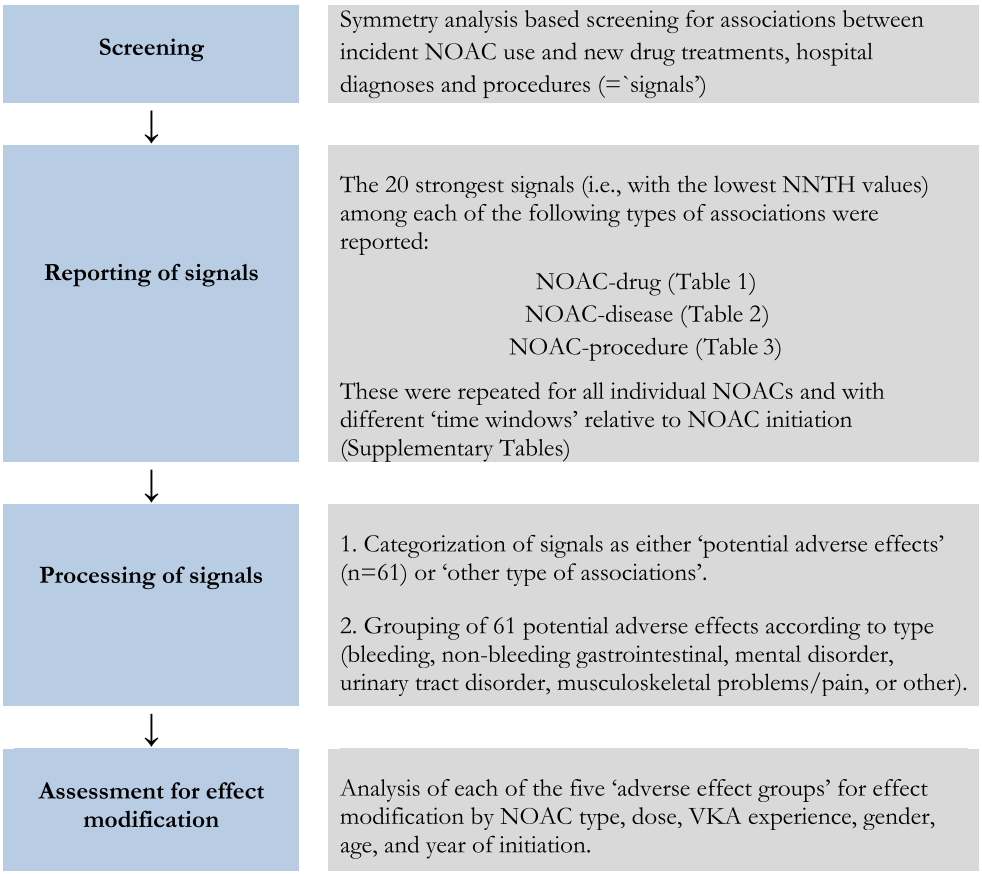

Fig. 1 Flow and overview of the analyses and signal processing. *GI* gastrointestinal, *NOAC* non-vitamin K antagonist oral anticoagulant, *NNTH* number needed to treat for one additional patient to be harmed, *VKA* vitamin K antagonist

modification, i.e., varying strength of the given association between subgroups of the study population. We investigated the following characteristics: (1) choice of NOAC (dabigatran, rivaroxaban, or apixaban); (2) start dose based on the prescribed tablet strength on the index prescription, normal or reduced (reduced dose: ≤ 110 mg for dabigatran, ≤ 15 mg for rivaroxaban, and ≤ 2.5 mg for apixaban); (3) previous vitamin K antagonist (VKA) experience (yes/no; ≥ 1 vs. 0 VKA prescription filled within 2 years before NOAC initiation); (4) sex; (5) age categories (<65, 66–79, and ≥ 80 years); and (6) early (2011–2013) or late (2014–2015) NOAC initiation. The effect modification of a given association was assessed through calculation of strata-specific SR ratios using one of the categories as the reference while accounting for the other potential effect modifiers through multivariable analysis. Each effect modification estimate thus provided a relative effect of a specific characteristic applicable to any subgroup accounted for in the analysis. Effect modification of an association would be reflected as either a stronger (odds ratio [OR] > 1) or weaker (OR < 1) association in a subgroup of patients in the strata.

2.7 Sensitivity Analysis

To assess how the choice of time window in the symmetry analysis affected the results [23], we performed sensitivity analyses after changing the ± 6-month time window to ± 3 and ± 12 months.

2.8 Other

All calculations were performed using STATA release 14.1 (StataCorp, College Station, TX, USA). According to Danish law, ethical approval is not required for purely registry-based studies [24].

3 Results

We identified 50,627 patients with AF starting NOAC use between 2011 and 2015 (ESM 2). Their median age was 74 years, with an interquartile range of 67–82, and 27,903 (55%) were men. The most commonly used NOAC was dabigatran (52%), followed by apixaban (24%) and rivaroxaban (24%). Most patients (69%) were anticoagulant naïve (i.e., had not used a VKA previously).

Among the 60 strongest signals associating initiation of any NOAC with a new drug prescription, diagnosis, or procedure, 28 were categorized as potential AEs (Tables 1, 2, 3). Of these, the highest-ranking signals were all related to drug initiation: osmotically acting laxatives (NNTH 133; 95% CI 101–186), sedative benzodiazepines (NNTH 174; 95% CI 133–234), and topical anal corticosteroids (NNTH 176; 95% CI 134–238). The highest-ranking NOAC–diagnosis and NOAC–procedure pairs were hemorrhage of anus or rectum (NNTH 269; 95% CI 193–397) and colonoscopy (NNTH 301; 95% CI 193–595), respectively. In the screening of the individual NOACs (Tables 1, 2, 3 in ESM 3), 30 additional potential AEs were identified, and another three came from the sensitivity analyses using different time windows (Tables 4 and 5 in ESM 3). This yielded a total of 61 signals of potential AEs; 22 NOAC–drug pairs, 22 NOAC–diagnosis pairs, and 17 NOAC–procedure pairs. These signals could be grouped into five distinctive types of AEs: bleeding ($n = 17$), non-bleeding gastrointestinal (GI) AEs ($n = 8$), mental disorders ($n = 7$), urinary tract disorder (including infections) ($n = 10$), and musculoskeletal problems, including pain

Table 1 The 20 strongest signals from the symmetry analyses of non-vitamin K antagonist oral anticoagulant (NOAC)–drug pairs

Rank	Drug (ATC code)	Drug before/after NOAC ($n = 50,627$)	NNTH (95% CI)	SR (95% CI)	Categorization of signal[a]
1	Antiarrhythmics, class III (C01BD)	465/1354	57 (49–67)	2.91 (2.63–3.24)	Other
2	Aldosterone antagonists (C03DA)	701/1281	87 (72–108)	1.83 (1.67–2.01)	Other
3	Antiarrhythmics, class Ic (C01BC)	111/530	121 (93–156)	4.77 (3.92–5.91)	Other
4	Osmotically acting laxatives (A06AD)	1098/1480	133 (101–186)	1.35 (1.25–1.46)	Potential AE
5	Benzodiazepines, sedatives (N05BA)	294/585	174 (133–234)	1.99 (1.74–2.30)	Potential AE
6	Topical corticosteroids for treatment of hemorrhoids/anal fissures (C05AA)	279/566	176 (134–238)	2.03 (1.76–2.35)	Potential AE
7	Verapamil (C08DA)	281/554	185 (140–252)	1.97 (1.71–2.28)	Other
8	ACE inhibitors (C09AA)	902/1175	201 (146–300)	1.30 (1.20–1.42)	Other
9	Benzodiazepines, hypnotics (N05CD)	36/298	193 (127–281)	8.28 (6.01–12.05)	Potential AE
10	Angiotensin II antagonists (C09CA)	600/852	201 (146–300)	1.42 (1.28–1.58)	Other
11	Selective serotonin reuptake inhibitors (N06AB)	443/694	202 (149–290)	1.57 (1.39–1.77)	Potential AE
12	Other antidepressants (N06AX)	416/660	207 (153–299)	1.59 (1.41–1.80)	Potential AE
13	Proton pump inhibitors (A02BC)	1273/1515	209 (140–377)	1.19 (1.11–1.28)	Potential AE
14	Phenylpiperidine opioids (N02AB)	210/445	215 (160–299)	2.12 (1.81–2.51)	Potential AE
15	Propulsives (A03FA)	456/690	216 (157–320)	1.51 (1.35–1.71)	Potential AE
16	Potassium (A12BA)	1889/2123	216 (136–471)	1.12 (1.06–1.20)	Other
17	Iron bivalent, oral (B03AA)	341/554	238 (172–350)	1.62 (1.42–1.86)	Potential AE
18	Loop diuretics (C03CA)	1880/2089	242 (147–604)	1.11 (1.04–1.18)	Other
19	Digitalis glycosides (C01AA)	1699/1901	251 (153–613)	1.12 (1.05–1.20)	Other
20	Contact laxatives (A06AB)	693/893	253 (172–433)	1.29 (1.17–1.43)	Potential AE

These were defined as signals with the lowest number needed to treat for one additional patient to be harmed (NNTH) when analyzing subjects following a NOAC → drug order and subjects following the opposite order

ACE angiotensin-converting enzyme, *AE* adverse effect, *AF* atrial fibrillation, *ATC* anatomical therapeutic chemical classification system, *CI* confidence interval, *NNTH* number needed to treat for one additional patient to be harmed, *NOAC* non-vitamin K antagonist oral anticoagulant, *SR* sequence ratio

[a]Signals categorized as 'other' include (1) associations between NOACs and other aspects of AF therapy, (2) associations likely reflecting the diagnostic work-up (including outcomes hereof) related either to the AF diagnosis or to bleeding complications, and (3) non-classifiable associations

Table 2 The 20 strongest signals from the symmetry analyses of non-vitamin K antagonist oral anticoagulant (NOAC)–disease pairs

Rank	Diagnosis (ICD-10 code)	Diagnosis before/after NOAC ($n = 50{,}627$)	NNTH (95% CI)[a]	SR (95% CI)	Categorization of signal[b]
1	Cardiac arrhythmia (I49.9)	563/850	176 (132–250)	1.51 (1.36–1.68)	Other
2	Hemorrhage of anus/rectum (K62.5)	224/412	269 (193–397)	1.84 (1.57–2.17)	Potential AE
3	Other general examinations (Z00.8)	180/366	272 (195–396)	2.03 (1.71–2.44)	Other
4	Palliative care (Z51.5)	95/220	405 (269–635)	2.32 (1.84–2.98)	Other
5	Unspecified hematuria (R31.9)	264/385	418 (269–762)	1.46 (1.25–1.71)	Potential AE
6	Dietary counselling/surveillance (Z71.3)	169/284	440 (287–754)	1.68 (1.40–2.05)	Other
7	Chronic intractable pain (R52.1)	58/139	625 (377–1101)	2.40 (1.79–3.31)	Potential AE
8	Personal history of diseases of the respiratory system (Z87.0)	30/107	657 (372–1162)	3.57 (2.45–5.54)	Other
9	General disability (R67.9)	72/146	684 (407–1280)	2.03 (1.55–2.73)	Other
10	Nausea and vomiting (R11.9)	148/214	767 (430–1897)	1.45 (1.18–1.80)	Potential AE
11	Sleep apnea (G47.3)	97/158	830 (466–1880)	1.63 (1.28–2.12)	Potential AE
12	Other difficulties with micturition (R39.1)	308/369	830 (413–4956)	1.20 (1.03–1.40)	Potential AE
13	Abnormal finding on diagnostic imaging of lung (R91.9)	257/315	873 (437–4529)	1.23 (1.04–1.45)	Other
14	Observation for suspected malignant neoplasm (Z03.1)	1449/1500	993 (308–∞)	1.04 (0.96–1.11)	Other
15	Acute renal failure, unspecified (N17.9)	135/185	1013 (518–3549)	1.37 (1.11–1.72)	Potential AE
16	Benign neoplasm: Colon, unspecified (D12.6)	122/169	1077 (544–3905)	1.39 (1.11–1.76)	Other
17	Other cystitis (N30.8)	89/132	1177 (591–3899)	1.48 (1.15–1.96)	Potential AE
18	Heart disease, unspecified (I51.9)	284/326	1205 (508–∞)	1.15 (0.98–1.35)	Other
19	Loss of appetite (R63.0)	32/74	1205 (604–2764)	2.31 (1.57–3.62)	Potential AE
20	Melaena (K92.1)	122/163	1235 (590–6373)	1.34 (1.07–1.70)	Potential AE

These were defined as signals with the lowest number needed to treat for one additional patient to be harmed (NNTH) when analyzing subjects following a NOAC → disease order and subjects following the opposite order

AE adverse effect, *AF* atrial fibrillation, *CI* confidence interval, *ICD-10* International Statistical Classification of Diseases and Related Health Problems Tenth Revision, *NNTH* number needed to treat for one additional patient to be harmed, *NOAC* non-vitamin K antagonist oral anticoagulant, *SR* sequence ratio

[a]In case of a statistically non-significant SR, the upper limit of the 95% CI of the corresponding NNTH will be infinite

[b]Signals categorized as 'other' include (1) associations between NOACs and other aspects of AF therapy, (2) associations likely reflecting the diagnostic work-up (including outcomes hereof) related either to the AF diagnosis or to bleeding complications, and (3) non-classifiable associations

($n = 9$). Remaining signals ($n = 10$) were grouped as "no category". Table 6 in ESM 3 shows the grouping of all potential AEs, and Table 7 in ESM 3 shows the considerations behind classifying drug and procedure signals as (proxies for) potential AEs.

Table 4 shows the results of the analysis assessing whether the strength of the associations between NOAC and the individual types of AEs were modified by different drug and patient characteristics. The most pronounced effect modifiers were age at NOAC initiation and previous VKA use, showing consistently stronger associations among the oldest patients (≥ 80 years) and among first-time anticoagulant users when compared with younger patients and previous VKA users, respectively. Apart from mental disorder AEs, all associations were less pronounced for apixaban than for dabigatran and rivaroxaban. The associations between NOAC use and bleeding, non-bleeding GI AEs, and urinary tract disorder were all modified by NOAC dose, with attenuated associations among users of low-dose NOACs compared with users of standard-dose NOACs. None of the associations were modified significantly by sex.

As a post hoc analysis, we repeated the primary analysis restricted to anticoagulant-naïve NOAC initiators, i.e., initiators without any VKA fill in the 2 years prior to NOAC initiation ($n = 35{,}148$, similar distribution of NOACs as in the overall study population). The objectives of this analysis were to (1) explore AEs from NOAC therapy in anticoagulant-naïve NOAC initiators only and (2) explore potential biases that may have affected the results of the main analysis (see Sect. 4). The results of the subgroup analysis including initiators of all NOACs are

Table 3 The 20 strongest signals from the symmetry analyses of non-vitamin K antagonist oral anticoagulant (NOAC)–procedure pairs

Rank	Procedure (procedure code)	Procedure before/after NOAC ($n = 50,627$)	NNTH (95% CI)	SR (95% CI)	Categorization of signal[a]
1	Cardioversion (BFFA0)	1583/3623	24 (22–27)	2.29 (2.16–2.43)	Other
2	Electrophysiological computer mapping (UFYA01)	208/625	121 (96–154)	3.00 (2.58–3.53)	Other
3	Catheter ablation, atrial flutter (BFFB03)	109/393	178 (133–239)	3.61 (2.94–4.50)	Other
4	General intravenous anesthesia (NAAC1)	63/345	180 (128–247)	5.48 (4.25–7.28)	Other
5	CT scan of the heart (UXCC00A)	502/754	201 (147–293)	1.50 (1.34–1.68)	Other
6	Catheter ablation, atrial fibrillation (BFFB04)	109/339	220 (160–304)	3.11 (2.53–3.90)	Other
7	Specialized rehabilitation (AWG1)	116/322	246 (177–345)	2.78 (2.26–3.46)	Other
8	Colonoscopy (KUJF32)	739/907	301 (193–595)	1.23 (1.12–1.35)	Potential AE
9	Cystoscopy (KUKC02)	355/484	392 (251–742)	1.36 (1.19–1.57)	Potential AE
10	Pulmonary function testing, diffusion capacity (WL1LBXXXX)	555/684	392 (239–878)	1.23 (1.10–1.38)	Potential AE
11	Pulmonary function testing, whole body plethysmography (WLHLBXXXX)	366/485	425 (265–864)	1.33 (1.16–1.52)	Potential AE
12	Electrophysiological test (UFYA00)	129/241	452 (295–755)	1.87 (1.52–2.33)	Other
13	Uroflowmetry (ZZ1280)	343/443	506 (300–1181)	1.29 (1.12–1.49)	Potential AE
14	Preventive interventions (BQF)	197/286	569 (343–1185)	1.45 (1.22–1.75)	Other
15	Sigmoidoscopy (KUJF42)	250/331	625 (357–1583)	1.32 (1.13–1.57)	Potential AE
16	Endoscopic polypectomy, colon (KJFA15)	248/323	675 (376–1887)	1.30 (1.11–1.54)	Other
17	Thyroid scintigraphy (WEEGS10XX)	215/290	675 (382–1733)	1.35 (1.14–1.62)	Other
18	Digital rectal examination (ZZ1110)	261/336	675 (374–1954)	1.29 (1.10–1.52)	Potential AE
19	CT urography (UXCD62)	376/449	694 (361–3061)	1.19 (1.04–1.37)	Potential AE
20	Symptom screening, EORTC (ZZ1550A)	64/124	844 (476–1741)	1.94 (1.45–2.66)	Other

These were defined as signals with the lowest number needed to treat for one additional patient to be harmed (NNTH) when analyzing subjects following a NOAC → procedure order with subjects following the opposite order

AE adverse effect, *AF* atrial fibrillation, *CI* confidence interval, *CT* computerized tomography, *EORTC* European Organisation for Research and Treatment of Cancer, *NNTH* number needed to treat for one additional patient to be harmed, *NOAC* non-vitamin K antagonist oral anticoagulant, *SR* sequence ratio

[a]Signals categorized as 'other' include (1) associations between NOACs and other aspects of AF therapy, (2) associations likely reflecting the diagnostic work-up (including outcomes hereof) related either to the AF diagnosis or to bleeding complications, and (3) non-classifiable associations

presented in comparison with the main analysis in Table 8A–C in ESM 3. While there was almost complete overlap between the specific NOAC–drug, NOAC–diagnosis, and NOAC–procedure signals reaching the top 20 in the main and the subgroup analysis, the associations were consistently stronger in the subgroup analysis regardless of categorization or type of AE: 59 of 60 signals showed higher SR and lower NNTH in the subgroup analysis. This was especially pronounced for signals potentially reflecting bleeding and non-bleeding GI AEs.

4 Discussion

Using a hypothesis-free screening approach based on the symmetry analysis design, we systematically assessed the occurrence of potential AEs after initiation of NOAC treatment among patients with AF. After manual assessment of all observed associations, we identified 61 potential AE signals, of which 84% could be categorized as related to either bleeding, non-bleeding GI events, mental disorder, urinary tract disorder, or musculoskeletal problems. Analyses of effect modification generally found these associations to be more pronounced among older patients and first-time users of oral anticoagulants and most to be attenuated among users of apixaban and low-dose NOAC therapy.

The primary strength of the study is the use of data that are routinely collected as part of the clinical care of patients, allowing an open-ended assessment of potential AEs associated with the use of NOACs without having to rely on reporting or clinical suspicion at the level of the single physician. Further, the use of the self-controlled symmetry design eliminates confounding by patient characteristics by comparing exposed and non-exposed person-time within the same individuals [7]. However, the study

Table 4 Multivariable analysis for effect modification of adverse effects associated with non-vitamin K antagonist oral anticoagulant (NOAC) use

Characteristics	Bleeding (n = 12 742)	Non-bleeding GI (n = 9903)	Mental (n = 5195)	Urinary tract (n = 7552)	Musculoskeletal/pain (n = 8577)
Choice of NOAC					
Dabigatran	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
Rivaroxaban	0.83 (0.75–0.91)	0.88 (0.79–0.98)	0.90 (0.77–1.05)	1.00 (0.89–1.13)	1.09 (0.98–1.22)
Apixaban	0.58 (0.52–0.64)	0.86 (0.76–0.96)	1.14 (0.97–1.35)	0.94 (0.83–1.07)	1.02 (0.91–1.14)
Start dose of NOAC					
Normal	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
Reduced	0.73 (0.67–0.80)	0.80 (0.73–0.88)	1.01 (0.88–1.16)	0.86 (0.77–0.96)	0.96 (0.86–1.07)
Previous VKA use					
No	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
Yes	0.50 (0.47–0.54)	0.57 (0.53–0.62)	0.63 (0.56–0.71)	0.79 (0.72–0.87)	0.59 (0.54–0.65)
Sex					
Female	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
Male	0.97 (0.90–1.05)	0.96 (0.89–1.05)	0.91 (0.81–1.03)	1.03 (0.94–1.14)	0.97 (0.89–1.06)
Age category (years)					
<65	0.82 (0.73–0.93)	0.87 (0.75–1.01)	0.80 (0.66–0.97)	0.90 (0.76–1.05)	1.11 (0.97–1.26)
65–69	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
≥ 80	1.21 (1.11–1.32)	1.17 (1.06–1.29)	1.34 (1.16–1.54)	1.21 (1.08–1.35)	1.16 (1.04–1.29)
Year of initiation					
Early NOAC initiator (2011–2013)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
Late NOAC initiator (2014–2015)	1.02 (0.94–1.11)	0.95 (0.86–1.04)	1.22 (1.06–1.39)	1.02 (0.92–1.14)	0.70 (0.63–0.77)

An adjusted odds ratio (aOR) above and below 1.0, respectively, indicates a stronger and an attenuated association between NOAC and the adverse effect type within the subgroup compared with the reference

Adjusted for the other potential effect modifiers, e.g. the aORs for the associations between NOAC use and the specific AE types stratified by sex are adjusted for choice of NOAC, start dose of NOAC, previous VKA use, age category, and year of initiation

AE adverse effect, *aOR* adjusted odds ratio, *CI* confidence interval, *GI* gastrointestinal, *NOAC* non-vitamin K antagonist oral anticoagulant, *ref.* reference, *VKA* vitamin K antagonist

Data are presented as aOR (95% CI)

should be interpreted in the light of some limitations. First, the classification and grouping of the potential AEs was an inherently subjective process based on the experience of two study physicians. To achieve transparency, we report the potential associations in full in Tables 1–5 in ESM 3 as well as the underlying rationale for the classification of associations that were considered to be proxies for potential AEs (Table 7 in ESM 3). As another limitation to the study, many of the associations are judged through proxies, e.g., PPI use as a proxy for dyspepsia, which likely have varying specificities for the AE in question. Further, while an open-ended screening approach can uncover both known and previously unknown associations, asymmetries in a symmetry analysis can reflect a range of different underlying mechanisms [19], AEs being only one of these. As amply illustrated by the present study, identification of associations that should receive further attention therefore requires a substantial amount of post-processing, filtering through the potential signals (Fig. 1). The associations reported in our study must be viewed as the product of a post-processed hypothesis-generating approach, not as evidence of causality, and should be interpreted with caution.

The well-established risk of bleeding complications during NOAC therapy was indeed reflected in the signals produced by the screening. With regard to bleeding type, NOAC therapy seemed to be associated with an increased risk of, in particular, GI bleeding and hematuria, which corresponds well with the findings of other studies [4, 5, 25]. However, the specific results may be biased by treatment choices made for patients with a bleeding event in the period leading up to NOAC initiation (i.e., the pre-exposure period in the symmetry analysis). A recent bleeding event is known to negatively affect the probability of oral anticoagulant therapy initiation [26, 27]. Bleedings are therefore likely to be less frequent in the period leading up to NOAC initiation in patients with AF who are eventually selected for NOAC initiation than among all patients with AF who could be considered eligible for NOAC initiation. This would lead to an upwards bias of the SR,

thereby mimicking or inflating an AE signal for bleeding. The effect of such a bias related to the decision to initiate anticoagulant therapy or not would be expected to be most pronounced in patients not using oral anticoagulant therapy in the pre-exposure period. Thus, the finding of even stronger associations between NOAC initiation and bleeding events in the post hoc analysis based on anticoagulant-naïve NOAC initiators alone supports the presence of such an upward bias in our analysis. Further, although consistent with findings from clinical trials [25, 28, 29], our findings of a lower relative risk of bleeding in users of apixaban and reduced-dose NOACs may be explained by apixaban and reduced-dose NOAC therapy being preferred treatment choices in patients with prior bleeding events [30, 31]. Bleeding events are therefore likely "less underrepresented" in the pre-exposure period in initiators of these types of NOAC treatments, leading to lower SRs relative to other NOACs and standard-dose therapy in our analysis. Also, the risk of bleeding after NOAC initiation appeared to be markedly lower in previous users of VKA (i.e., switchers from VKA to NOAC) than in anticoagulant-naïve initiators in the secondary analysis. There seems to be several possible and potentially complementary explanations for this finding. First, the risk of bleeding may be higher in anticoagulant-naïve NOAC initiators than in initiators with previous anticoagulant experience. This would be in accordance with prior findings of an elevated bleeding risk during the first months of anticoagulant (VKA) therapy [32], which have in part been explained by initiation of anticoagulant therapy triggering latent bleedings [33]. A lower bleeding risk in prevalent anticoagulant users would thus likely reflect the depletion of susceptible individuals from the treated population, as bleeding often leads to discontinuation of anticoagulant therapy [34, 35]. Second, keeping in mind the potential impact of barriers to NOAC initiation described above, the apparent difference in bleeding risk may also reflect that bleeding is a more important barrier to NOAC initiation in anticoagulant-naïve users than in prevalent anticoagulant users. Finally, a bleeding event during VKA therapy is an important reason for switching from VKA to NOAC therapy [36, 37]. Thus, relative to VKA users not switching to NOAC, bleeding events are likely more common in the period prior to NOAC initiation in VKA-experienced initiators, leading to a lower SR for bleeding in this group.

Most of the AEs identified in the screening were also described in the randomized controlled trials exploring NOAC use in AF [28, 38, 39], but this was not the case for mental disorders. Nevertheless, we found a relatively strong association between NOAC use and initiation of antidepressants, sedatives/hypnotics, and antipsychotics. These signals may be due to time-dependent confounding, as several studies have found high rates of depression in patients with newly diagnosed cardiovascular disease, including AF [40, 41]. While this interpretation assumes an overrepresentation of newly diagnosed mental disease after NOAC initiation, the opposite could also be the case; that is, an underrepresentation in the period leading up to NOAC initiation. If so, the observed association rather reflects mental disease being a barrier to initiation of oral anticoagulant therapy in clinical practice [42, 43], similar to what was described above for bleeding. The strengthening of the apparent increased risk for mental disease after NOAC initiation among anticoagulant-naïve NOAC initiators supports both suggested interpretations.

Like bleedings, the non-bleeding GI AEs identified in our analysis (e.g., dyspepsia, constipation, and diarrhea) are well-known AEs of therapy with NOACs, and especially with dabigatran [28, 44]. Thus, the presence of such symptoms prior to NOAC initiation may have affected treatment choices [45], potentially introducing channeling bias in our analyses. Therefore, we chose to not speculate on the observed differences in risk for this AE type between NOACs but rather to acknowledge the identification of these signals in our screening, along with the signals concerning bleeding, as supporting of the high specificity of the symmetry analysis in the detection of known AEs [10].

Although urinary tract disorders and musculoskeletal problems, including pain, were reported as AEs in the clinical trials [28, 38, 39], they are yet to be confirmed in clinical practice. As such, the results concerning these AEs seem less likely to have been affected by channeling bias as described above for the well-established AEs such as bleeding [19]. With regards to urinary tract disorders, our findings of an apparent dose–response pattern, increasing risk with increasing age, and consistent estimates between the main and the subgroup analysis are all supportive of a potentially causal association with NOAC therapy. However, the results concerning the potential association between NOAC therapy and musculoskeletal problems seem less clear. Both potential AEs should be explored further in future studies.

5 Conclusion

Using the symmetry analysis design to screen for potential AEs associated with NOAC use in patients with AF in clinical practice, we were able to confirm the majority of the AEs observed in the randomized controlled trials. Further, we identified potential AEs that deserve further investigation, as well as characteristics potentially associated with the risk of experiencing AEs in general. Although the symmetry analysis-based screening identified known AEs such as bleedings, the strength of the associations

between NOAC initiation and known AEs were difficult to interpret as they seemed prone to channeling bias.

Compliance with Ethical Standards

Conflict of interest Maja Hellfritzsch declares speaker honoraria from Bristol-Myers Squibb and Pfizer. Lotte Rasmussen, Jesper Hallas, and Anton Pottegård declare participation in research projects funded by Boehringer-Ingelheim, with funds paid to the institution at which they were employed (no personal fees).

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