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ORIGINAL ARTICLE

Impact of anticoagulant exposure misclassification on the bleeding risk of direct oral anticoagulants

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Aims: Drug exposure status based on routinely collected data might be misclassified when the database contains only prescriptions from 1 type of prescriber (e.g. general practitioner and not specialist). This study aims to quantify the impact of such exposure misclassification on the risk of major bleeding and stroke/transient ischaemic attack (TIA) associated with direct oral anticoagulants (DOACs) vs. vitamin K antagonists (VKAs).

Methods: Incident anticoagulant users (>12 mo free of anticoagulation use) in the Dutch PHARMO Database Network between 2008 and 2017 were included. Drug exposure was assessed using pharmacy dispensing information. The risks of hospital admission of major bleeding for DOAC vs. VKA users was assessed with Cox regression analysis, where exposure was based on all dispensings, on general practitioner (GP)-prescribed dispensings only or on specialist-prescribed dispensings only. Hazard ratios (HRs) were estimated also for hospitalization for gastrointestinal bleeding, intracranial bleeding and stroke/TIA.

Results: We included 99 182 VKA-initiators and 21 795 DOAC-initiators. Use of DOAC was associated with a lower risk of major bleeding compared to VKA use; HR 0.79 (95% confidence interval 0.70–0.90), 0.78 (0.68–0.91) and 0.62 (0.50–0.76), for exposure based on complete dispensing information, only GP- and only specialist-prescribed dispensings, respectively. Similar results were found for the other bleeding outcomes. For stroke/TIA the HRs were 0.96 (0.84–1.09), 1.00 (0.84–1.18) and 0.72 (0.58–0.90), respectively.

Conclusion: Including only GP-prescribed anticoagulant dispensings in this case did not materially impact the effect estimates compared to including all anticoagulant dispensings. Including only specialist-prescribed dispensings, however, strengthened the effect estimates.

KEYWORDS

clinical pharmacology, epidemiology, prescribing, haematology, pharmacoepidemiology, methodology, statistics and study design, anticoagulants

1 | INTRODUCTION

Observational studies on safety and effectiveness of pharmacological agents are often performed using routinely collected data from administrative or health-care databases. Different types of databases are available, such as insurance databases, outpatient pharmacy databases, general practitioner (GP) databases or hospital databases. These data sources differ in the information they contain.¹ For example, pharmacy or insurance databases hold information of all prescriptions collected at the pharmacy, whereas GP-databases contain only information about GP prescriptions and hospital databases usually contain only information about specialist prescriptions. The use of a single prescriber prescription database may lead to a misclassification of drug exposure status when a subject is treated for the same condition by 2 different types of prescribers, or is being treated by a prescriber whose prescribing information is not included in the database that is being used.² Moreover, this misclassification can be differential, for example when different prescribers (e.g. specialists and GPs) are treating different types of patients, who have different distributions of (unmeasured) risk factors for developing the outcome, such as frailty,^{3,4} which may lead to selection and information bias. Although these databases are being used widely in pharmacoepidemiology, the extent and impact of such misclassification in research practice is largely unknown.

To provide insight in the impact of exposure misclassification due to differences in data sources used for pharmacoepidemiological studies, we used direct oral anticoagulants (DOACs) and the risk of a major bleeding and stroke/transient ischaemic attack (TIA) as an example. In the first years after licensing, DOACs were prescribed predominantly by specialists, such as cardiologists, internists or orthopaedics.^{5,6} Furthermore, patient characteristics, including risk of stroke and major bleeding, differ between patients who receive their DOAC prescriptions from a GP and those who receive their prescription from a specialist.⁷ Currently, a lot of attention is paid to real-world evidence about the effectiveness and safety of DOACs, as reflected in the number of recent publications and planned studies.^{8,9} Different types of databases are used in these studies, including GP databases, hospital databases, health-care insurance databases and pharmacy databases, with different data capture on drug use.¹⁰⁻³⁹

The primary aim of this study was to quantify the extent to which the estimated effects of DOACs vs. vitamin K antagonists (VKAs) on the risk of major bleeding and stroke are affected by misclassification caused by the use of a database that contains only prescriptions of 1 type of prescriber. Secondary aims were to describe the characteristics of DOAC users treated by the GP only, by the specialist only or by both, and to describe the prescribing patterns over time.

2 | METHODS

To investigate the impact of the absence of prescriptions, we used the PHARMO Database Network, containing - among other things -

What is already known about this subject

- Drug exposure status based on routinely collected data might be misclassified when the database contains only information about prescriptions from 1 type of prescriber.
- This misclassification can be differential, for example when different prescribers are treating different types of patients, with different distributions of risk factors of the outcome.

What this study adds

- Direct oral anticoagulants and vitamin K antagonist initiators had different characteristics that also differed between different types of prescribers.
- Including only general practitioner-prescribed anticoagulant dispensings did in this case not materially impact the effect estimates compared to including all anticoagulant dispensings. Including only specialist-prescribed dispensings, however, strengthened the effect estimates.

drug dispensing information from community pharmacies in the Netherlands, including information on the type of prescribing physician for most dispensed prescriptions. This enabled us to carry out separate analyses in which we included all anticoagulant dispensings or only a subset of anticoagulant dispensings that were prescribed by either a GP or a specialist.

The study protocol is based on the protocol of an European Medicines Agency-sponsored study, which aimed at characterising the risk of major bleeding in patients with nonvalvular atrial fibrillation (NVAf).³²

2.1 | PHARMO database network

The PHARMO Database Network contains drug dispensing information from a representative sample of Dutch community pharmacies (Outpatient Pharmacy Database) that is linked with the national registry of hospital discharge diagnoses (Hospital Database) and electronic patient records registered by GPs (GP Database). More than 4 million inhabitants of the Netherlands (approximately 25% of the Dutch population) with an average follow-up of 10 years are included in the PHARMO Database Network.

The Outpatient Pharmacy Database comprises information about basic demographic information and about dispensed drugs, including the type of prescriber (i.e. GP, specialist, or other types of prescribers, such as dentists), type of drug, dispensing date, dose, quantity and the

dosage regimen. Drug type is coded according to the Anatomical Therapeutic Chemical (ATC) Classification System.⁴⁰ The Outpatient Pharmacy Database was used to determine exposure to the anticoagulant drugs and comedication (see section on potential confounders).

The Hospital Database contains information about hospital admissions from the Dutch Hospital Data Foundation. The records include information about discharge diagnoses and hospital admission and discharge dates. Diagnoses are coded according to the International Classification of Diseases (ICD) version 9 (January 2008–September 2015) or version 10 (October 2015–December 2017).^{41,42} Procedures are coded according to the Dutch CBV (operations file), the CVV (Classification of Operations) system, or the Dutch ZA (care activities) procedural codes. The Hospital Database was used to determine the outcomes, the potential indication of the anticoagulant drug use, and other comorbidities (see section on potential confounders).

The GP Database comprises information from electronic patient records registered by GPs. The records include, among other things, information on diagnoses and symptoms, coded according to the International Classification of Primary Care.⁴³ Information from the GP Database was available for approximately 25% of the study population and this information was used to complement the potential indication of the anticoagulant drug use.

2.2 | Exposure–outcome example

2.2.1 | Study population

A cohort was constructed consisting of all incident anticoagulant users between January 2008 and December 2017. Incident users were defined as patients initiating a DOAC ([dabigatran etelixate](#), [rivaroxaban](#), [apixaban](#) and [edoxaban](#)) or VKA ([acenocoumarol](#) and [phenprocoumon](#)) during the study period without any use of either of the 2 drugs for at least 365 days prior to the index date. The index date was defined as the first dispensing date of an anticoagulant drug. Inclusion criteria were an age at index date of 18 years or older and at least 12 months of enrolment in the database prior to the index date. All subjects with a registered knee or hip replacement, a diagnosis of valvular atrial fibrillation, deep venous thrombosis or pulmonary embolism in the 90 days before or after the index date, and without a diagnosis of NVAf in the 90 days before or after the index date, were excluded from the study population. Each subject was followed until the outcome of interest was diagnosed, death, deregistration from the concerning pharmacy or the end of the study period, whichever came first. Subjects were allowed to switch from DOACs to VKAs or vice versa, or to stop using anticoagulant medication.

2.2.2 | Outcome definition

The primary outcome of interest was hospitalization for major bleeding (haemorrhagic stroke/intracranial bleeding, gastrointestinal

bleeding or other extracranial or unclassified bleeding and traumatic intracranial bleeding). Secondary outcomes included hospitalization for gastrointestinal bleeding, intracranial bleeding and stroke (haemorrhagic as well as infarction) and TIA. Only the primary hospitalization diagnoses were used for the outcome assessment. ICD codes for the outcomes are given in Table S2.

2.2.3 | Exposure definition

The theoretical duration of each DOAC dispensing (ATC codes B01AE and B01AF; Table S1) and VKA dispensing (ATC code B01AA; Table S1) was based on the dispensing date, quantity, strength and the dosage regimen. In case of missing information about dose regimen, which is often the case with VKAs, the theoretical duration of each dispensing was for each individual defined by the median time between the dispensings. When only 1–3 dispensings were available for an individual patient or when the estimated duration exceeded 100 days, the duration was based on the most frequently occurring estimated dispensing duration for the specific drug in the study. For the construction of the treatment episodes, a maximum gap of 30 days was allowed between the theoretical end of a dispensing and the start of a next dispensing. Overlapping episodes were added to the end of the treatment episode with a maximum of 90 days. If the subsequent dispensing was another type of anticoagulant drug, the patient was considered to have switched therapy and the remaining tablet days from the prior dispensing were disregarded.

2.2.4 | Potential confounders

The assessment of and adjustment for potential confounders were conducted in line with the European Medicines Agency-sponsored study.³² As potential confounders of the relation between DOAC/VKA and the different outcomes, we considered the risk factors for the various outcomes. Important risk factors considered for major bleeding are: thrombocytopenia; hypertension or use of antihypertensive drugs (Table S4); history of stroke/TIA; history of major bleeding event; presence of malignancy; concomitant use of medicines that increase bleeding risk (nonsteroidal anti-inflammatory drugs, corticosteroids, selective serotonin inhibitors and antiplatelet drugs; Table S5); concomitant use of medications that have pharmacokinetic interactions with DOACs (assessed per DOAC separately; see supplementary materials Table S6); history of pulmonary embolism or deep venous thrombosis; peptic ulcer diseases; kidney disease; and hepatic impairment (for ICD codes; see Table S3). Important risk factors considered for stroke/TIA were concomitant use of medications that have pharmacokinetic interactions with DOACs (assessed per DOAC separately), prior stroke/TIA, pulmonary embolism/deep venous thrombosis, hypertension, diabetes mellitus, congestive heart failure, other (cardio)vascular disease (angina, myocardial infarction, coronary heart disease, aortic plaque and peripheral arterial disease), kidney disease and hepatic impairment. The use of comedication was assessed using

the outpatient pharmacy database. The presence or history of comorbidities was assessed using the hospitalization database, or the outpatient pharmacy database in case of medication use as proxy.

Age, comorbidities (various time intervals prior to index date, Table S3), and comedication use (6 months before the index date) were considered as time dependent confounders and their status was updated whenever the exposure status changes, or every 6 months, whichever comes first.

2.3 | Data analysis

Cox proportional hazards regression analysis was applied to estimate the effect of current DOAC treatment compared to current VKA use on the risk of major bleeding and stroke/TIA, with and without adjusting for the abovementioned confounders. We assumed no misclassification of the information available in the data systems and we used all dispensed drugs to determine concomitant medication use or the presence of comorbidities, regardless of the prescribing physician.

The abovementioned analysis was repeated 3 times: (i) using all anticoagulant dispensing information; (ii) using only the information about the anticoagulant dispensings prescribed by GPs; and (iii) using only the information about the anticoagulant dispensings prescribed by specialists. The different effect estimates were compared. In these 3 analyses, the size of the study population, the index date per subject and the time on treatment per subject differed, depending on the anticoagulant dispensings that were included in the exposure assessment. These analyses were repeated for the different outcomes.

Differences in patient characteristics (age, sex and the presence of risk factors for bleeding or stroke) and drug dispensing patterns were also assessed. Patient characteristics were summarized as means and standard deviations or proportions where appropriate and presented stratified by prescriber. Patient characteristics were compared between VKA and DOAC users on index date and differences between these groups were quantified by means of standardized differences.⁴⁴ For all treatment episodes, the initiating prescriber was determined and whether subjects received their prescriptions from multiple types of prescribers. In addition, exposure time caused by specialist-prescribed dispensings and GP-prescribed dispensings was determined for VKA and DOAC use.

Several sensitivity analyses were performed. First, we restricted our analysis to subjects with a registered NVAf diagnosis in the 90 days before or after the index date. Second, we stratified on several characteristics: age (<65, 65–85, >85 y), sex, index date (before or after 1 January 2013, which is halfway the study period) and all DOACs individually.

3 | RESULTS

Based on cohort entry medication, the study included 99 182 VKA initiators and 21 795 DOAC initiators, when all anticoagulant

dispensings were used. When only GP-prescribed dispensings were included, the study included 87 106 VKA initiators and 14 542 DOAC initiators. Including only specialist-prescribed dispensings resulted in 62 566 VKA initiators and 18 809 DOAC initiators. The characteristics of the study populations are presented in Table 1. The mean age for all VKA initiators was 70.1 (\pm 13.7) years and for all DOAC initiators 69.8 (\pm 11.8) years. Of both the VKA and DOAC initiators, 52.6% were men. The characteristics of the DOAC and VKA initiators treated only by a GP, only by a specialist, or treated by both a GP and a specialist are also presented in Table 1. Mean standardized differences of these subpopulation are visually depicted in Figure 1. In general, VKA users who receive their VKA prescriptions only by the specialist have more comorbidities and use more comedication than patients who only receive their VKA prescriptions from the GP. For prescribing of DOACs, the opposite was seen: patients who only receive DOACs from the specialist generally had fewer comorbidities and received fewer comedications.

3.1 | Prescribing physicians

Figure 2 shows the number of initiators per prescriber type for VKAs and DOACs. From 2012, the number of people who started using VKA decreased rapidly and was replaced by DOAC initiators. For about 25% of all VKA initiators, the first anticoagulant dispensed was prescribed by a specialist, compared to 50% for the DOAC initiators. In total, GP-prescribed dispensings accounted for about 80% of all VKA exposure time and about 65% of all DOAC exposure time.

During the whole study period, about half of the VKA and DOAC users had their prescriptions issued by both a GP and a specialist (Figure 3). There were more VKA users who had the prescriptions only issued by a GP compared to the DOAC users (35.7 vs. 18.6%). Consequently, more DOAC users had their prescriptions only issued by the specialist compared to the VKA users (31.1 vs. 11.2%).

3.2 | Primary outcomes

There were 3372 major bleeding events during VKA exposure and 390 during DOAC exposure. For exposure based only on GP-prescribed dispensings, 2706 events occurred during VKA exposure and 248 during DOAC exposure. For exposure based on specialist-prescribed dispensings only, these numbers were 828 and 135 for VKA and DOAC exposure, respectively. Compared to current VKA use, crude hazard ratios of current use of DOACs for major bleeding were 0.77 (95% confidence interval 0.69–0.85), 0.83 (0.73–0.95) and 0.61 (0.51–0.73), for exposure based on complete dispensing information, only GP- and only specialist-prescribed dispensings, respectively. The adjusted hazard ratios of current use of DOACs for major bleeding were 0.79 (0.70–0.90), 0.78 (0.68–0.91) and 0.62 (0.50–0.76), respectively. The effects of DOAC use on gastrointestinal bleeding, intracranial bleeding and stroke/TIA are presented in Table 2, stratified by prescriber.

TABLE 1 Baseline characteristics of subjects with index use of VKA or DOAC, stratified per prescribing physician (general practitioner, specialist or both)

	VKA			DOAC		
	All subjects	Subjects treated by GP only	Subjects treated by specialist only	All subjects	Subjects treated by GP only	Subjects treated by GP & specialist
Number of subjects	99 182	35 500	11 046	21 795	4314	7000
Age (y), mean (standard deviation)	70.1 (13.7)	70.97 (14.1)	69 (14.4)	69.78 (11.8)	71.98 (12.4)	67.18 (12.1)
Sex, n males (%)	52 168 (52.6)	17 702 (49.9)	6185 (56)	11 469 (52.6)	2165 (50.2)	3652 (52.2)
Diagnosis of NVAF \pm 3 months from index date	32 234 (32.5)	9015 (25.4)	3682 (33.3)	8415 (38.6)	1686 (39.1)	2096 (29.9)
Use of comedication, n (%)						
Glucocorticosteroids	11 152 (11.2)	3533 (10)	1533 (13.9)	2280 (10.5)	464 (10.8)	682 (9.7)
NSAIDs	14 750 (14.9)	4788 (13.5)	1557 (14.1)	3549 (16.3)	631 (14.6)	1443 (20.6)
Antiplatelet agents	39 178 (39.5)	10 841 (30.5)	4462 (40.4)	8121 (37.3)	1564 (36.3)	2074 (29.6)
SSRIs	3670 (3.7)	1410 (4)	357 (3.2)	762 (3.5)	183 (4.2)	197 (2.8)
Presence or history of comorbidities, n (%)						
Malignancy	3259 (3.3)	1014 (2.9)	616 (5.6)	600 (2.8)	130 (3)	210 (3)
Thrombocytopenia	174 (0.2)	38 (0.1)	44 (0.4)	36 (0.2)	9 (0.2)	11 (0.2)
Major bleeding	1134 (1.1)	381 (1.1)	167 (1.5)	193 (0.9)	45 (1)	55 (0.8)
Alcohol abuse	355 (0.4)	109 (0.3)	55 (0.5)	116 (0.5)	36 (0.8)	31 (0.4)
Gastrointestinal ulcer	206 (0.2)	59 (0.2)	37 (0.3)	17 (0.1)	4 (0.1)	2 (0)
Hepatic failure	273 (0.3)	76 (0.2)	52 (0.5)	40 (0.2)	2 (0)	14 (0.2)
Stroke/TIA	3159 (3.2)	1056 (3)	239 (2.2)	735 (3.4)	237 (5.5)	124 (1.8)
DVT/PE	466 (0.5)	214 (0.6)	71 (0.6)	89 (0.4)	17 (0.4)	32 (0.5)
Other cardiovascular disease	10 733 (10.8)	2752 (7.8)	1487 (13.5)	1558 (7.1)	331 (7.7)	412 (5.9)
Renal failure	2811 (2.8)	823 (2.3)	572 (5.2)	524 (2.4)	140 (3.2)	126 (1.8)
Hypertension	69 019 (69.6)	23 841 (67.2)	7398 (67)	14 884 (68.3)	2972 (68.9)	4159 (59.4)
Diabetes mellitus	17 670 (17.8)	6217 (17.5)	1751 (15.9)	3563 (16.3)	782 (18.1)	886 (12.7)
Congestive heart failure	27 313 (27.5)	9029 (25.4)	3422 (31)	4114 (18.9)	950 (22)	972 (13.9)

Abbreviations: DOAC: direct oral anticoagulant; DVT: deep venous thrombosis; GP: general practitioner; NSAIDs: nonsteroidal anti-inflammatory drugs; NVAF: nonvalvular atrial fibrillation; PE: pulmonary embolism; SSRIs: selective serotonin inhibitors; TIA: transient ischaemic attack; VKA: vitamin K antagonist

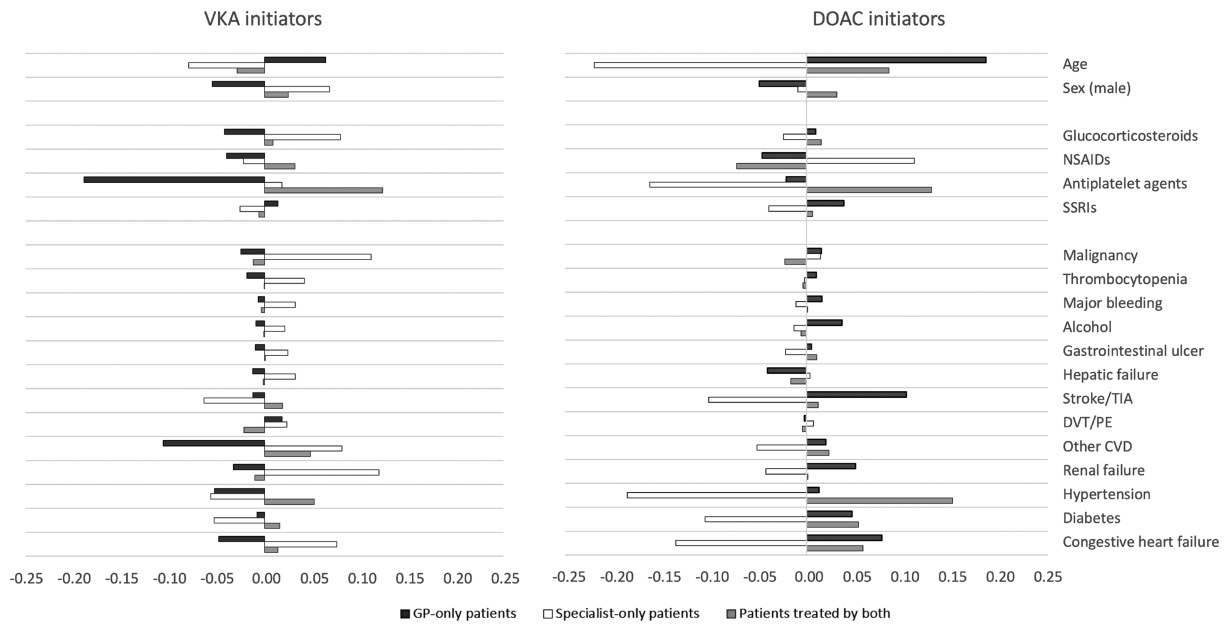
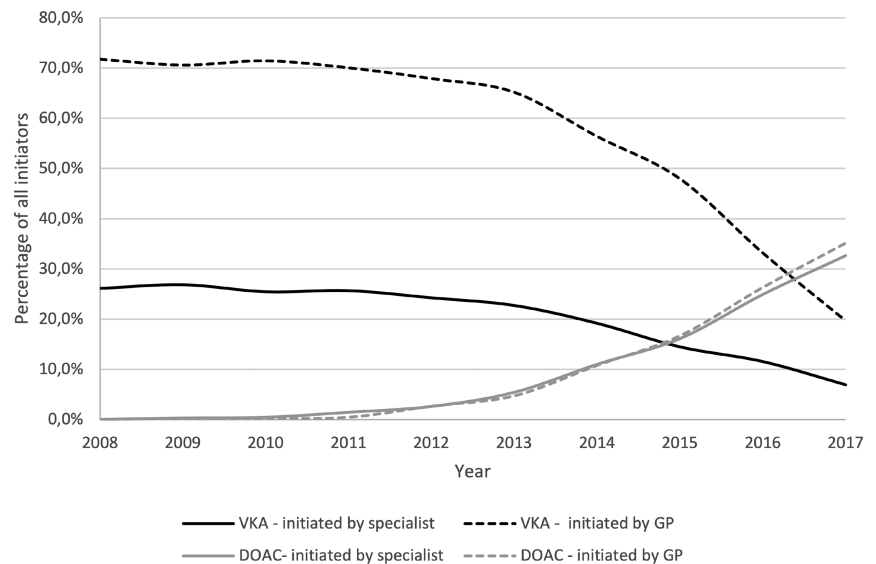


FIGURE 1 Standardized mean differences of the baseline characteristics of VKA or DOAC initiators stratified per prescribing physician (GP, specialist, or both), compared to all VKA or DOAC initiators. VKA: vitamin K antagonist; DOAC: direct oral anticoagulant; GP: general practitioner; NVAF: nonvalvular atrial fibrillation; NSAIDs: nonsteroidal anti-inflammatory drugs; SSRIs: selective serotonin inhibitors; TIA: transient ischaemic attack; DVT: deep venous thrombosis; PE: pulmonary embolism

FIGURE 2 Distribution of anticoagulant initiators per study drug and prescriber type, per calendar year. VKA: vitamin K antagonist; DOAC: direct oral anticoagulant; GP: general practitioner



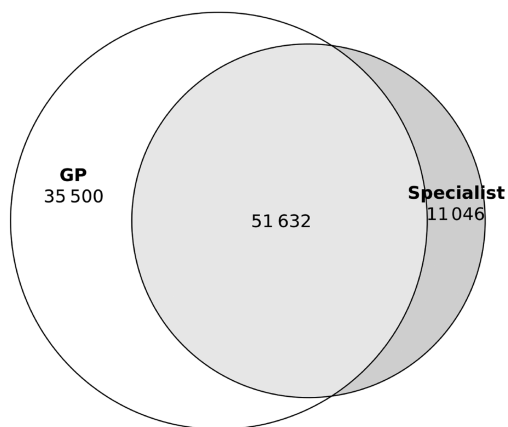
3.3 | Sensitivity analyses

The results of sensitivity analyses are presented in the supplementary materials (Tables S7–S11). Stratification per age category did not result in materially different effect estimates (Table S7). Restriction to only subjects with a registered NVAF indication showed the same patterns as the primary analysis. For the risk of gastrointestinal bleeding, the HRs were 1.07 (0.83–1.37), 1.18 (0.88–1.57) and 0.74 (0.50–1.11) for complete dispensing information, or for only GP- and specialist-prescribed dispensings, respectively. For the risk of intracranial bleeding, the HRs were 0.80 (0.54–1.18), 0.87 (0.55–1.37)

and 0.62 (0.33–1.16) and for the risk of stroke, the HRs were 0.89 (0.73–1.08), 1.02 (0.80–1.30) and 0.67 (0.49–0.91).

Stratification by sex generally showed lower effect estimates for men, except for the effect estimates for stroke/TIA, when only GP-prescribed dispensing information was used, compared to complete dispensing information (Table S9). Analysing the different DOACs separately did show the same patterns as the primary analysis, except for edoxaban (Table S10). There were, however, only a few edoxaban users, resulting in wide confidence intervals. Stratification on index date showed lower effect estimates for the subjects with an index date before 2013 than for subjects with an index date after 2013. The

VKA initiators



DOAC initiators

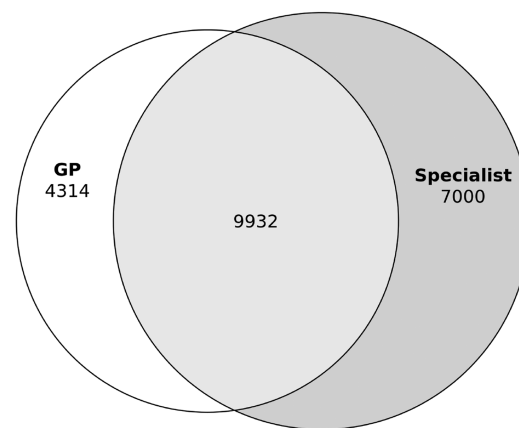


FIGURE 3 Number of VKA and DOAC initiators treated by the general practitioner, by the specialist, or by both. VKA: vitamin K antagonist; DOAC: direct oral anticoagulant; GP: general practitioner

TABLE 2 Hazard ratios for exposure to DOACs compared to exposure to VKAs for the different outcomes

Included prescriptions	Person-years (×1000)		No of events		Hazard ratios (95% confidence interval)	
	VKA	DOAC	VKA	DOAC	Crude	Adjusted
Any bleeding						
All dispensings	214.71	31.14	3372	390	0.77 (0.69–0.85)	0.79 (0.70–0.90)
GP-prescribed dispensings	177.06	18.76	2706	248	0.83 (0.73–0.95)	0.78 (0.68–0.91)
Specialist-prescribed dispensings	45.85	12.22	828	135	0.61 (0.51–0.73)	0.62 (0.50–0.76)
Gastrointestinal bleeding						
All dispensings	217.43	31.44	1342	200	0.98 (0.85–1.14)	0.95 (0.80–1.13)
GP-prescribed dispensings	179.17	18.95	1056	126	1.07 (0.89–1.29)	0.99 (0.80–1.22)
Specialist-prescribed dispensings	46.23	12.30	350	68	0.72 (0.56–0.94)	0.65 (0.48–0.87)
Intracranial bleeding						
All dispensings	218.88	31.62	771	69	0.59 (0.46–0.75)	0.67 (0.51–0.89)
GP-prescribed dispensings	180.32	19.06	635	44	0.62 (0.45–0.84)	0.65 (0.46–0.92)
Specialist-prescribed dispensings	46.47	12.35	176	24	0.52 (0.34–0.80)	0.58 (0.36–0.93)
Stroke/TIA						
All dispensings	215.46	31.14	2341	329	0.93 (0.83–1.04)	0.96 (0.84–1.09)
GP-prescribed dispensings	177.75	18.77	1860	219	1.07 (0.93–1.23)	1.00 (0.84–1.18)
Specialist-prescribed dispensings	46.04	46.04	570	113	0.75 (0.62–0.92)	0.72 (0.58–0.90)

Abbreviations: DOAC: direct oral anticoagulant; GP: general practitioner; TIA: transient ischaemic attack; VKA: vitamin K antagonist

estimates for the analyses with only GP-prescribed dispensing information were however in line with the estimates obtained with the complete dispensing information (Tables S11).

4 | DISCUSSION

Compared to using all dispensing information, including only anticoagulant dispensings prescribed by GPs did not materially impact the effect estimates of DOAC use compared to VKA use on the risk of major bleeding and stroke/TIA. However, including only dispensings

issued by the specialist, strengthened the effect estimates, compared with the analysis including all dispensing information.

Using only the GP- or specialist-prescribed dispensings lead to misclassification of the exposure status in different ways. Some subjects were later enrolled in the study, some subjects had exposure misclassification during their study follow-up, and other subjects were completely left out of the study population. In total, GP-prescribed dispensings accounted for about 80% of all VKA exposure time and about 65% of all DOAC exposure time.

In addition, subjects treated only by the GP, only by the specialist or treated by both had different characteristics that also differed

between initiators of VKAs and DOACs. Also, the proportion of subjects with a registered NVAF diagnosis differed: subjects with only DOAC dispensings prescribed by the GP had more often a registered NVAF diagnosis compared to subjects with only DOAC dispensings prescribed by the specialist (39.1% vs. 29.9%), whereas the opposite was true for the VKA users (25.4 vs. 33.3%).

Including prescription information from only 1 type of prescriber might have led to different biases in this case study. First, a proportion of subjects was left out of the study sample completely. Because this was unlikely to be a random process, this may have led to a sample that was not representative of the entire treated population (selection bias). The characteristics of DOAC users treated only by the GP, only by the specialist or by both differed, and we also saw these differences in characteristics when comparing initiators of VKAs with initiators of DOACs. Second, because not all information on exposures was recorded correctly, information bias could occur. For some subjects, the extent of misclassified exposure time was larger than for others, and this too was associated with measured patient characteristics that were related to the outcome. Although these measured patient characteristics could be adjusted for in the analysis of the study, misclassification may also depend on unmeasured patient characteristics, suggesting differential misclassification.

We note that the estimates from the analyses with only the GP-prescribed dispensings were in line with the analyses with all dispensings. This can be explained by the fact that the GP-prescribed dispensings accounted for the majority of all dispensings, resulting in only limited exposure misclassification. However, analyses based on only specialist prescriptions dispensed showed more extreme effect estimates of the risk of bleeding and the risk of stroke/TIA, when compared to using all dispensing information. This was confirmed in the various sensitivity analyses conducted. Since the specialist prescriptions accounted for only 20 and 35% of all VKA and DOAC prescriptions dispensed respectively, selection and information bias might have caused these deviating results and the study population in this analysis might not be representative of the overall population treated. In addition, the involvement of a cardiologist is associated with lower risk of bleeding and stroke in patients treated with anticoagulant drugs,^{7,45} therefore these results should be interpreted within the context of secondary care.

The strength of this study was that the utilization and prescribing patterns found in this study were in line with previously found results, such as the sharp increase in DOAC use from 2012 and the percentage of subjects that has only DOAC prescriptions issued by the GP or specialist over time.^{7,46,47} Also the estimates for the bleeding risk of DOAC use compared to VKA use were comparable with estimates found in other observational studies.^{21,34,48}

One limitation of this study is that the exposure information from pharmacies is still a proxy for actual use of the drug and could also be prone to misclassification. This can happen for example when subjects do pick up the drug, but do not start actually using it.⁴ This is, however, not very likely when subjects repeatedly pick up the prescriptions. Moreover, we do not expect that this possible misclassification would have influenced our conclusions, since this could occur for both the GP

and the specialist-prescribed dispensings. Inpatient dispensing information was also lacking in this study, which could occur either at the start of the anticoagulant treatment, or during the treatment. Most anticoagulant treatments are, however, initiated in outpatient care and the allowance for a 30-day gap between the theoretical end of a dispensing and the start of a new dispensing would have covered the gaps during treatment hospitalizations. We therefore expect no material effect of these missing dispensings either. Allowing this 30-day gap could also have filled the gaps caused by subjects switching prescriber type, which could have hindered our primary question. However, in the Netherlands, drugs for chronic diseases are most often prescribed for 90 days, so these gaps would not have been filled.

We also did not have complete information about the indication for the anticoagulant treatment. The inclusion criterion in this study was incident anticoagulant use, rather than a diagnosis of NVAF, which is more commonly used. This resulted in a heterogeneous study population. Since DOACs were approved for the indication NVAF between April 2011 and September 2012, we performed a sensitivity analysis in which we stratified between subjects included before and after January 2013 (Table S11). This analysis confirmed our findings from the main analysis. We also performed a sensitivity analysis with only subjects with a registered diagnosis of NVAF (Table S8). This analysis, however, excluded the subjects who did have a diagnosis of NVAF that was not recorded in our databases, which could have led to selection bias.⁴⁹ The results of this analysis again did not lead to any other conclusions.

In addition, there was limited information about the dose regimen of the VKA treatment, since these dose regimens are highly flexible. Therefore, a proxy was used to estimate the time on treatment. This exposure misclassification was expected to be nondifferential, and to have no relation with the prescribing physician. Therefore, we expect this not to affect our conclusions. Last, misclassification of the outcome could have occurred. Again, we do not expect that this misclassification would differ between the GP-prescribed and the specialist-prescribed subjects, and thus affecting the conclusions.

To conclude, including only GP-prescribed anticoagulant dispensings did not materially impact the effect estimates of bleeding risk of the use DOACs compared to the use of VKAs in this study. However, including only specialist-prescribed dispensings did have impact on the effect estimates. Specifying the setting in which the study was performed (primary or secondary care) is thus of importance when reporting on the safety and effectiveness of anticoagulant drugs. Whether the same results would be obtained if other databases had been used, or with other drug–outcome relationships, remains unknown, and is highly dependent on the specific characteristics of the database that is being used: which patients, prescriptions or dispensings are included in the database and which are not? Since misclassification in a particular database that contains only prescriptions of 1 type of prescriber is likely to be drug and context-specific, we recommend further research, for example with other drug exposure–outcomes relations or other databases. For now, we recommend using databases that are as complete as possible in terms of prescriptions history for patients without regards to type of prescriber to avoid exposure misclassification and, as a result, biased results.

COMPETING INTERESTS

No authors report any conflict of interest.

CONTRIBUTORS

M.H. was involved in the conception and design of the study, statistical analysis and interpretation of data, drafting and critical revision of the manuscript. R.G. was involved in conception and design of the study and critical revision of the manuscript. P.S. was involved in acquisition of data and critical revision of the manuscript. A.B. was involved in conception and design of the study, interpretation of data and critical revision of the manuscript. O.K. was involved in conception and design of the study, interpretation of data and critical revision of the manuscript. H.G. was involved in conception and design of the study, interpretation of data and critical revision of the manuscript.

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DATA AVAILABILITY STATEMENT

Data subject to third party restrictions. The datasets generated during and/or analysed during the current study are not publicly available due to privacy reasons. Access to data can be requested from the PHARMO Institute for Drug Outcomes Research under strict conditions.

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