





ORIGINAL ARTICLE

Major bleeding in users of direct oral anticoagulants in atrial fibrillation: A pooled analysis of results from multiple population-based cohort studies

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Abstract

Objective: To establish the risk of major bleeding in direct oral anticoagulant (DOAC) users (overall and by class) versus vitamin K antagonist (VKA) users, using health care databases from four European countries and six provinces in Canada.

Methods: A retrospective cohort study was performed according to a similar protocol. First-users of VKAs or DOACs with a diagnosis of non-valvular atrial fibrillation (NVAF) were included. The main outcome of interest was major bleeding and secondary outcomes included gastrointestinal (GI) bleeding and intracranial haemorrhage (ICH). Incidence rates of events per 1000 person years were calculated. Hazard ratios (HRs) and 95% confidence intervals (95% CI) were estimated using a Cox proportional hazard regression model. Exposure and confounders were measured and analysed in a time-dependant way. Risk estimates were pooled using a random effect model.

Results: 421 523 patients were included. The risk of major bleeding for the group of DOACs compared to VKAs showed a pooled HR of 0.94 (95% CI: 0.87–1.02). Rivaroxaban showed a modestly increased risk (HR 1.11, 95% CI: 1.06–1.16). Apixaban and dabigatran showed a decreased risk of respectively HR 0.76 (95% CI: 0.69–0.84) and HR 0.85 (95% CI: 0.75–0.96).

Conclusions: This study confirms that the risk of major bleeding of DOACs compared to VKAs is not increased when combining all DOACs. However, we observed a modest higher risk of major bleeding for rivaroxaban, whereas for

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apixaban and dabigatran lower risks of major bleeding were observed compared to VKAs.

KEYWORDS

atrial fibrillation, cohort studies, directoral anticoagulants, major bleeding, oral anticoagulants, vitamin K antagonists

KEY POINTS

- Until now, this is the largest population-based cohort study that confirms that there is no clinically relevant difference in overall major bleeding risk between VKAs and DOACs as a class.
- Younger patients (<75) tend to have a lower risk for major bleeding while treated with DOACs versus VKAs.
- Rivaroxaban showed a modestly increased risk for major bleeding. Both rivaroxaban and dabigatran increased risk for GI bleeding by approximately 20%.
- All individual DOACs reduced the risk for ICH, which is in line with the clinical trials results.

1 | INTRODUCTION

Since the introduction of the first direct oral anticoagulant (DOAC), dabigatran, the treatment options for the prevention of ischaemic stroke in patients with non-valvular atrial fibrillation (NVAF) have broadened. Other DOACs including rivaroxaban and apixaban followed quickly, and finally edoxaban was also approved for this specific indication. The randomised clinical trials (RCTs) and meta-analysis of these trials showed that the DOACs are at least non-inferior to warfarin, a vitamin K antagonist (VKA), in reducing the risk of stroke and systemic embolism.^{1–5} The risk of haemorrhagic stroke was significantly lower compared to warfarin; it was reduced by 51%.⁵ However, the risk of gastrointestinal bleeding with DOACs was higher compared to warfarin with a relative risk of 1.25%95% confidence interval (95% CI) of 1.01–1.55.⁵ As the outcome of haemorrhagic stroke is more life threatening than gastro-intestinal bleeding the benefit–risk balance can be considered to be more positive than that of warfarin.⁶ Also, the fact that the pharmacokinetic profile of DOACs was more predictable and not so much influenced by external factors such as interacting co-medication or inter-current illnesses, as is the case for warfarin, contributed to the popularity of DOACs as they did not require frequent monitoring of anticoagulant activity at the anti-thrombotic clinic. Therefore, DOACs are currently the preferred treatment over VKAs for the prevention of ischaemic stroke in NVAF in first initiators of oral anticoagulants according to both the European and Canadian guidelines.^{7–9}

Several observational studies have been carried out to investigate if the positive benefit–risk balance would hold in a real-life population, as the clinical trials were conducted in a highly selected group of patients.^{10–15} These studies showed similar results as the RCTs, although the evidence remains inconclusive on specific points. Studies were not large enough to show differences in specific subpopulations such as the elderly, those with impaired renal function and

comorbidities. Also, there is insufficient information available about the direct comparative effectiveness and safety within the class of DOACs as the bleeding risk seems to vary between the different drugs.^{16–19}

The aim of this study was to pool the results from pharmacoepidemiological studies using longitudinal data collected in electronic health care databases from four different countries in Europe and six different provinces in Canada, to characterise the risk of major bleeding and stroke in DOAC users in a real-world setting. This study also assessed differences in safety and effectiveness for the individual DOACs and for different age groups.

2 | METHODS

This study is a follow-up study using the results from multiple retrospective cohort studies that were performed for the European Medicines Agency to study the safety profile of DOACs. A common protocol was used by all centres involved and is registered and accessible under the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) EU PAS register number 16014. In the current article a summary is given of the methodology used for the retrospective cohort studies. More detailed information (e.g., definition of outcomes, variables and exposure) can be found in Appendix A (Chapter 9.1c–9.3c pp. 16–18).

2.1 | Setting

Data were extracted from four European health care databases and six Canadian provinces within the Canadian Network for Observational Drug Effect Studies (CNODES). The following European

databases were used: the Danish National Registers (DK), “Allgemeine Ortskrankenkasse” (AOK) NORDWEST in Germany, Base de Datos para la Investigación Farmacoepidemiológica en Atención Primaria (BIFAP) in Spain and the Clinical Practice Research Datalink (CPRD) in the United Kingdom. The following Canadian provinces were used: British Columbia (BC), Alberta (AB), Saskatchewan (SK), Manitoba (MB), Ontario (ON) and Nova Scotia (NS). Characteristics of these databases such as the number of patients included, type of database, available variables and coding dictionary used are presented in Table 1.

2.2 | Study population

The study population comprised of all new DOAC (dabigatran, rivaroxaban, apixaban) or VKA (warfarin, acenocoumarol, phenprocoumon) users in the period 2008–2015^a (for Canada 2010–2015), aged ≥ 18 years and with a diagnosis of NVAF.

The date of the first prescription of a VKA or DOAC defined the start of cohort entry (index date). New users were defined as patients initiating a DOAC or a VKA during the study period without any use of these medicines for at least 12 months prior to cohort entry. Each patient was followed until the outcome, the end of valid data collection, discontinuation or switching of treatment, loss to follow-up or death, whichever came first.

2.3 | Outcome definition

The primary outcome of interest was the occurrence of a first recorded major bleeding event during follow-up, including haemorrhagic stroke and/or intracranial bleeding, gastrointestinal bleeding, other extracranial or unclassified bleeding, and traumatic intracranial bleeding. Outcomes were identified using relevant Read codes, ICD-9, ICD-10, or ICPC-2 codes, depending on data source (relevant codes available in Appendix A, Table A3.1, pp. 49–52). Two independent analysis were also performed for gastrointestinal and intracranial bleeding events. Occurrence of any stroke (both ischaemic, haemorrhagic or unspecified stroke and transient ischaemic attacks, TIAs) was evaluated as a secondary outcome.

2.4 | Exposure definition

For each patient a period of current use was defined by constructing treatment episodes of drug usage that allowed for a 30-day permissible gap between the theoretical end date of the prescription and the subsequent prescription. A treatment episode was defined as a series of subsequent prescriptions for VKAs or DOACs, independent of dose changes and constructed according to the method of Gardarsdottir et al.²⁰ The preferred method for calculating the individual prescription duration was by using information on the prescribed number of tablets

and the dosage. If this information was not available in the database, the duration was estimated by using the median time between prescription for the individual patients or using the most frequently occurring estimated prescription duration for the specific drug in the study population. A new row was created in case a patient switched from one type of treatment to another within a treatment episode.

2.5 | Potential confounders

Potential confounders considered in this study were based on the literature review (i.e., risk factors for major bleeding and stroke). Important risk factors considered for major bleeding were thrombocytopenia, hypertension, history of stroke/TIA, history of major bleeding event, presence of malignancy, hepatic impairment, concomitant use of medicines that modify haemostasis or increase the gastrointestinal bleeding risk such as nonsteroidal anti-inflammatory drugs, corticosteroids, selective serotonin reuptake inhibitors, antiplatelet drugs; history of pulmonary embolism (PE) or deep venous thrombosis (DVT) and peptic ulcer diseases. Risk factors for any stroke were prior stroke/TIA, PE/DVT, hypertension, diabetes mellitus, congestive heart failure and other (cardio)vascular disease (angina, myocardial infarction, coronary heart disease, aortic plaque and peripheral arterial disease). Additionally, lab-values on estimated glomerular filtration rate (eGFR) as measure for renal function were used where possible. Sex, weight (<50, 50–100, >100 kg), body mass index (BMI), smoking status and alcohol status were assessed at baseline (i.e., VKA or DOAC initiation) and considered constant throughout follow-up. Age, comorbidities (various time intervals prior to the start of the time period), and co-medication (6 months before each interval) use were considered as time-dependent confounders and their status was updated whenever the exposure status changed, or when exposure state exceeded 6 months at the start of each 6-month interval. It should be noted that not all variables were available in each database (Table 2). Relevant codes can be found in Appendix A, Tables A4.1–A4.3, pp. 65–67.

2.6 | Data analysis

Baseline characteristics were summarised as means and SDs or proportions where appropriate. Crude incidence rates of outcome events per 1000 person years were calculated. Cox proportional hazard regression analysis was used to estimate the risk of study outcomes comparing current use of DOACs and current use of VKAs, expressed as hazard ratios (HRs) with 95% confidence intervals (95% CI). The analysis was adjusted by entering the aforementioned risk factors separately in the model without any selection based on statistical significance. Data were analysed using STATA 13 or SAS 9.3/4 software and data analysts developed their own programs for data preparation and analysis.

TABLE 1 Characteristics of used electronic health care databases

	Germany AOK NORDWEST	Spain BIFAP	UK CPRD	Danish National Registers	Canada CNODES
Source population	2.7 m	7.5 m	12.5 m	5.5 m	Approx. 11 m
Year(s) covered for this study	2008–2015	2008–2015	2008–2015	2008–2015	2010–2015
Type of database	Claims database including data for dispensed and reimbursed drugs	General practice	General practice prescribing data	Dispensing data	Administrative data from publicly funded health insurance programs
Data available since	2007	2002	1987	1994	Before 1990
Demographic variables available					
Date of registration	Yes	Yes	Yes	Yes	Yes
Date of transferring out	Yes	Yes	Yes	Yes	Yes
Date of birth	MM-YY	MM-YY	MM-YY	MM-YY	MM-YY
Gender	Yes	Yes	Yes	Yes	Yes
Drug information available					
Active international coding	ATC	ATC	BNF	ATC	ATC/AHFS
Product coding	PZN	CNF	Product code	Nordic article	DIN
Date of prescribing/dispensing	Primary care sector: Yes Secondary care sector: Yes (only for a few selected [expensive] compounds, but no VKA or DOAC prescriptions)	Yes From 2011 dispensing is also available	Yes	Yes	Yes
Quantity prescribed/dispensed	Yes (package size)	Yes	Yes	Yes	Yes
Dosing regimen	No	Yes	Yes	No	No
Outcome information					
Outpatient primary care diagnosis	ICD-10-GM (quarterly base)	ICPC-2, ICD-9	ICD-9, ICD-10	Yes	ICD-9-CM
Hospital discharge diagnosis	ICD-10-GM	Not systematically recorded	ICD-9, ICD-10	ICD-8, ICD-10	ICD-10-CA
Laboratory tests	No	Yes (as requested by GP)	Yes	No	No
Mortality	No (incompletely recorded, e.g. no follow-up for patients leaving the AOK)	Yes (no cause of death)	Yes	Yes	Yes

Abbreviations: AHFS, American Hospital Formulary Service; AOK NORDWEST, Allgemeine Ortskrankenkasse NORDWEST; ATC, Anatomical Therapeutic Chemical; BIFAP, Base de Datos para la Investigación Farmacoepidemiológica en Atención Primaria; BNF, British National Formulary; CA, Canada; CNF, Código nacional de fármaco; CM, Clinical Modification; CNODES, Canadian Network for Observational Drug Effect Studies; CPRD, Clinical Practice Research Datalink; DIN, Drug Identification Number; DOAC, direct oral anticoagulant; GM, Germany; GP, general practitioners; ICD, International Statistical Classification of Diseases and Related Health Problems; ICPC, International Classification of Primary Care; PZN, Pharmazentralnummer; UK, United Kingdom; VKA, vitamin K antagonist.

TABLE 2 Baseline characteristics for users of DOACs and VKAs within the different databases in the United Kingdom, Spain, Germany, Denmark and Canada

	United Kingdom (CPRD)		Spain (BIFAP)		Germany (AOK NORDWEST)		Denmark		Canada (CNODES)	
	DOAC (n = 5852)	VKA (n = 33 277)	DOAC (n = 8775)	VKA (n = 42 255)	DOAC (n = 18 566)	VKA (n = 70 176)	DOAC (n = 28 113)	VKA (n = 44 705)	DOAC (n = 95 330)	VKA (n = 74 474)
Follow-up, years (mean, SD)	0.8 (0.7)	2.7 (2.0)	1.5 (1.1)	2.6 (1.9)	NA	NA	0.91 (0.89)	1.00 (1.30)	1.8 (1.3)	2.3 (1.4)
Females	44.0	43.3	46.4	47.8	54.6	51.9	46.4	41.3	47.4	46.5
Age										
Mean age at index date (years, SD)	74.8 (11.0)	73.8 (10.4)	75.6 (10.0)	75.4 (10.8)	74.8 (11.4)	73.9 (9.6)	73.4 (11.2)	71.6 (11.2)	77.1 (8.9)	76.1 (10.6)
18–55 years	5.6	5.5	5.0	4.1	7.1	4.9	5.9	8.3	2.1	4.9
56–65 years	12.9	13.8	12.5	11.0	12.2	11.8	16.3	18.6	4.9	8.2
66–75 years	26.0	27.9	26.9	27.1	25.8	34.7	34.4	33.3	33.4	28.6
75+ years	55.5	52.8	55.6	57.7	54.8	48.6	43.3	39.7	59.6	58.3
Weight										
<50 kg	1.1	0.7	2.0	2.0	NA	NA	NA	NA	NA	NA
50–100 kg	28.1	28.7	39.1	45.2	NA	NA	NA	NA	NA	NA
>100 kg	6.2	7.0	3.1	4.1	NA	NA	NA	NA	NA	NA
Missing	64.6	63.6	56.9	49.7	NA	NA	NA	NA	NA	NA
BMI										
Mean BMI at index date (SD)	29.0 (6.3)	29.5 (6.3)	29.7 (5.1)	30.2 (5.3)	NA	NA	NA	NA	NA	NA
<20 kg/m ²	1.6	1.2	0.5	0.5	NA	NA	NA	NA	NA	NA
20–24.9 kg/m ²	7.5	7.1	6.3	6.4	NA	NA	NA	NA	NA	NA
25–29.9 kg/m ²	12.7	12.9	16.6	19.1	NA	NA	NA	NA	NA	NA
30–34.9 kg/m ²	8.0	8.7	12.6	15.1	NA	NA	NA	NA	NA	NA
≥35 kg/m ²	5.3	6.1	5.3	7.8	NA	NA	NA	NA	NA	NA
Missing	64.8	63.9	58.7	51.1	NA	NA	NA	NA	NA	NA
Smoking status										
Never	38.2	37.6	9.5	11.2	NA	NA	NA	NA	NA	NA
Current	11.2	11.1	35.9	41.6	NA	NA	NA	NA	NA	NA
Ex	50.4	51.0	4.3	8.1	NA	NA	NA	NA	NA	NA
Missing	0	0	50.4	39.0	NA	NA	NA	NA	NA	NA
Alcohol										
Yes	9.6	6.7	18.3	22.6	NA	NA	4.8	4.3	5.9	6.8
Renal function										
Normal (>80 ml/min)	16.6	12.8	NA	NA	NA	NA	NA	NA	NA	NA
Normal - mildly reduced (CrCl 50–80 ml/min)	45.4	44.9	12.3 ^a	18.0 ^a	NA	NA	NA	NA	NA	NA
Moderately reduced (CrCl 30–49 ml/min)	20.0	22.1	4.5	6.4	NA	NA	NA	NA	NA	NA

(Continues)

TABLE 2 (Continued)

	United Kingdom (CPRD)		Spain (BIFAP)		Germany (AOK NORDWEST)		Denmark		Canada (CNODES)	
	DOAC (n = 5852)	VKA (n = 33 277)	DOAC (n = 8775)	VKA (n = 42 255)	DOAC (n = 18 566)	VKA (n = 70 176)	DOAC (n = 28 113)	VKA (n = 44 705)	DOAC (n = 95 330)	VKA (n = 74 474)
Severely reduced (CrCl 15–29 ml/min)	0.6	1.4	0.2	0.5	NA	NA	NA	NA	NA	NA
Very severely reduced (CrCl <15 ml/min)	0.0	0.2	0.0	0.1	NA	NA	NA	NA	NA	NA
Missing	17.3	18.6	83.0	75.0	NA	NA	NA	NA	NA	NA
History of disease ever before										
Other cardiovascular disease (angina, myocardial infarction, coronary heart disease, aortic plaque, PAD)	24.8	27.0	19.3	19.6	67.2	65.8	28.1	31.8	55.5	63.5
Chronic kidney disease ^b	n/a	n/a	5.0	7.1	5.8	6.6	3.6	5.7	12.3	22.9
Congestive heart failure	9.6	11.8	10.2	11.9	42.8	42.3	13.7	17.2	33.3	43.1
Deep vein thrombosis/Pulmonary embolism	2.2	3.2	1.5	2.4	8.1	7.2	2.9	5.1	4.8	14.2
Diabetes mellitus	18.4	17.7	21.8	25.3	43.1	42.8	11.9	13.1	41.6	44.7
Hypertension	4.6	5.1	4.6	5.4	86.0	85.5	21.1	22.0	46.4	52.9
Hepatic impairment (moderate/severe)	0.0	0.1	0.2	0.3	14.7	12.1	1.0	1.1	2.3	3.2
Malignancy, including lymphoma and leukaemia and metastatic solid tumour, except malignant neoplasm of the skin	2.0	2.2	0.9	1.2	18.5	17.7	3.2	3.7	23.7	25.2
Major bleeding event	32.2	29.5	15.7	15.4	33.7	24.5	19.3	17.5	25.6	32.1
Peptic ulcer disease	6.4	6.0	3.1	4.9	10.8	8.0	6.8	6.9	15.9	21.1
Stroke/TIA	21.1	17.4	11.8	11.0	25.2	20.6	19.4	17.5	16.3	20.8
Thrombocytopenia	0.0	0.1	0.2	8.0	1.4	1.5	0.1	0.1	0.3	0.8
Drug use within 6 months prior to index date										
Antihypertensive drugs ^c	79.6	83.2	77.4	81.9	93.9	91.0	88.2	89.9	90.3	90.5
Antidiabetic drugs (including insulin)	12.7	13.0	18.3	20.6	20.5	20.9	12.4	12.9	22.7	29.1
Antiplatelet drugs	49.3	58.2	44.1	40.9	22.6	18.1	45.2	52.3	14.3	21.5
Systemic glucocorticoids	10.7	10.6	7.7	7.8	10.6	8.8	8.8	9.4	9.5	11.3
NSAIDs	10.8	12.4	28.7	26.2	26.3	23.9	16.0	16.5	12.9	12.0
SSRIs	8.3	6.4	9.2	8.7	4.7	3.1	8.1	8.0	9.8	10.5

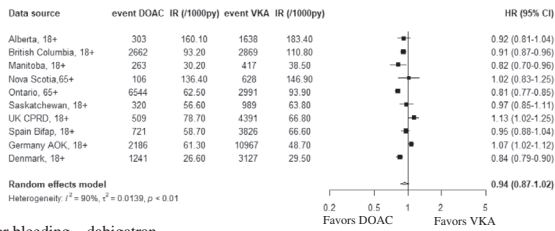
Abbreviations: AOK NORDWEST, Allgemeine Ortskrankenkasse NordWEST; VKA, vitamin K antagonist; BIFAP, Base de Datos para la Investigación Farmacoepidemiológica en Atención Primaria; BMI, Body mass index; CNODES, Canadian Network for Observational Drug Effect Studies; CPRD, Clinical Practice Research Datalink; CrCl, Creatinine Clearance; DOAC, direct oral anticoagulant; NSAIDs, Nonsteroidal anti-inflammatory drugs; PAD, peripheral artery disease; SD, standard deviation; SSRIs, selective serotonin reuptake inhibitors; TIA, transient ischemic attack.

^aCoding of renal function differs in the BIFAP database, where ≥ 60 ml/min is considered normal kidney function, and therefore there is no coding for 80 ml/min.

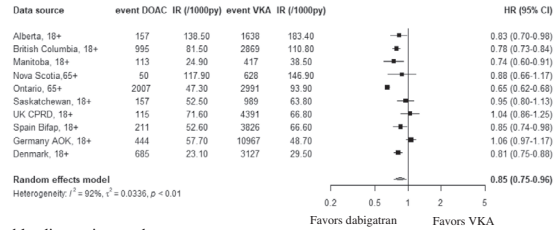
^bFor those databases that do not have lab-values available for renal function.

^cAntihypertensive drugs include angiotensin converting enzyme (ACE) inhibitors, angiotensin II (ATII) -blockers, beta blockers, calcium channel blockers, diuretics, doxazosine and moxonidin.

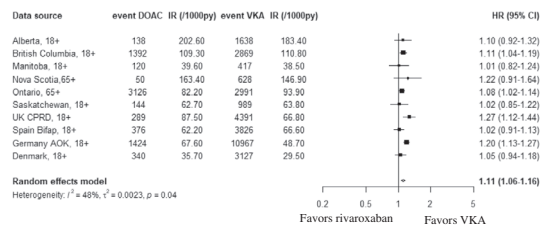
1.1 Major bleeding – overall



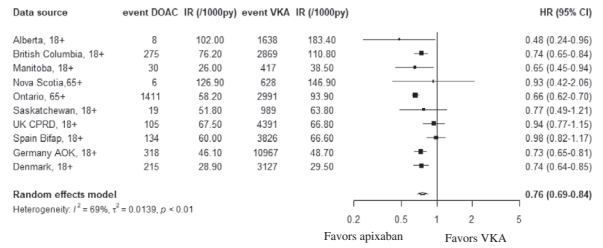
1.2 Major bleeding – dabigatran



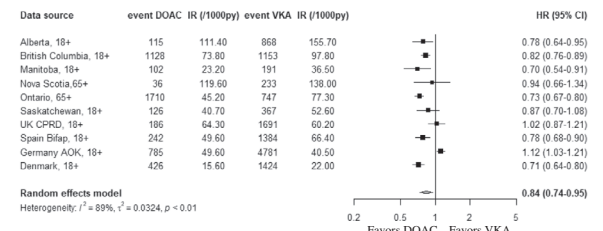
1.3 Major bleeding – rivaroxaban



1.4 Major bleeding – apixaban



1.5 Major bleeding – overall DOAC stratified by age: under 75



1.6 Major bleeding – overall DOAC stratified by age: over 75

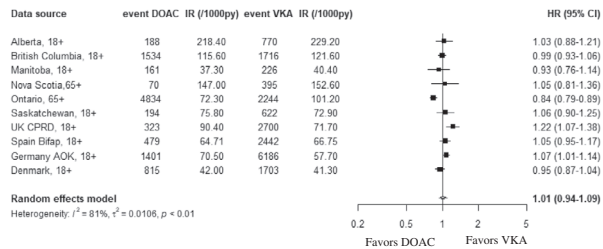


FIGURE 1 Forest plots of major bleeding. (1.1) Major bleeding – overall DOAC. (1.2) Major bleeding – dabigatran. (1.3) Major bleeding – rivaroxaban. (1.4) Major bleeding – apixaban. (1.5) Major bleeding – overall DOAC stratified by age: under 75. (1.6) Major bleeding – overall DOAC stratified by age: over 75. AOK NORDWEST, Allgemeine Ortskrankenkasse NORDWEST; BIFAP, Base de Datos para la Investigación Farmacoepidemiológica en Atención Primaria; CI, confidence interval; CPRD, Clinical Practice Research Datalink; DOAC, direct oral anticoagulants; HR, Hazard Ratio; IR, incidence rate; py, person years; VKA, vitamin K antagonist; W, weight. 18+: patient population of 18 years or older. 65+: patient population of 65 years or older. S: cells with less than five events were suppressed by participating site due to privacy restrictions

2.7 | Pooled analysis

All participating centres performed the analyses independently at their local site according to a common protocol (ENCePP EU PAS register number 16014). Investigators from individual sites were blinded to results from other sites until all analyses were finalised. The HR results were then pooled using a random effects model, assuming that the true effect size may vary between studies. The I^2 was calculated to measure statistical heterogeneity. The analysis was performed using R statistical software version 3.2.3. The results for patients younger and older than 75 were also pooled.

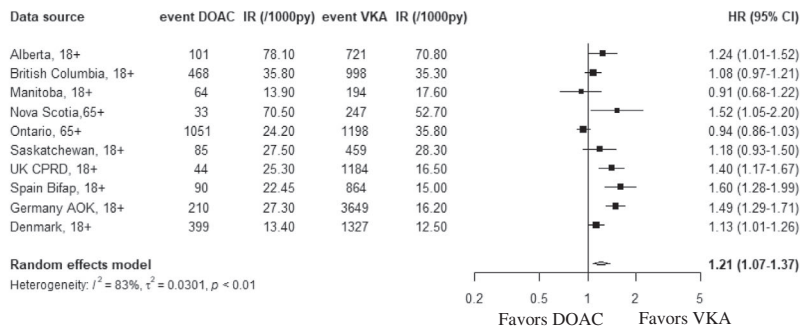
3 | RESULTS

In total 421 523 users of anticoagulants with a diagnosis of NVAF were identified of which 156 636 (37.2%) used a DOAC and 264 887 (62.8%) used a VKA. In the European countries, the use of

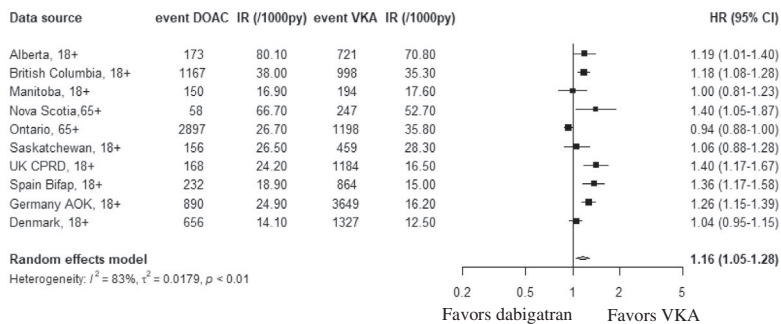
DOACs was lower than of VKAs, ranging from 14.9% in the United Kingdom to 38.6% in Denmark. In Canada the majority of patients were prescribed a DOAC (56.1%). A summary of baseline characteristics of the population is given in Table 2. The mean age of patients was similar across databases and the highest percentage of all VKA and DOAC users were in the 75+ category. It should be noted that two databases in Canada only included patients that were 65 or older of age. The reported history of cardiovascular disease and hypertension was much higher in the AOK NORDWEST and CNODES databases compared to the CPRD and BIFAP databases.

For the primary outcome, major bleeding, the forest plots are shown in Figure 1. The pooled HR for DOACs compared to VKAs was found to be 0.94 with a 95% CI of 0.87–1.02, suggesting some reduction in risk, although the CI including 1 indicates that there is no superiority of DOACs compared to VKAs. Differences were observed between the individual DOACs. Rivaroxaban showed a modest increased risk (HR 1.11, 95% CI 1.06–1.16). On the other hand,

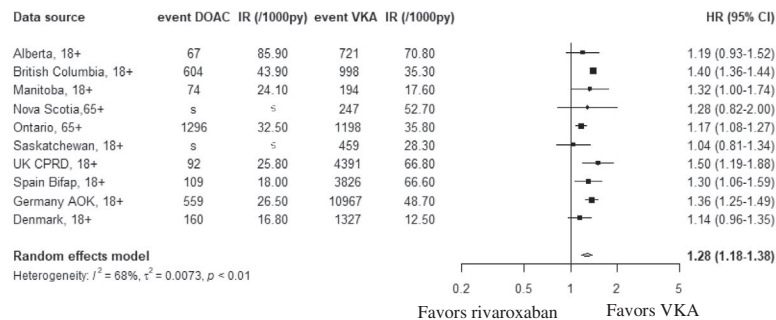
2.1 Gastro-intestinal bleeding – overall



2.2 Gastro-intestinal bleeding – dabigatran



2.3 Gastro-intestinal bleeding – rivaroxaban



2.4 Gastro-intestinal bleeding – apixaban

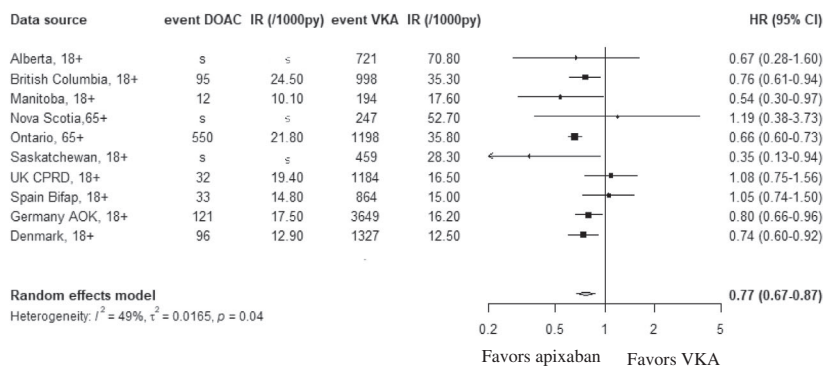
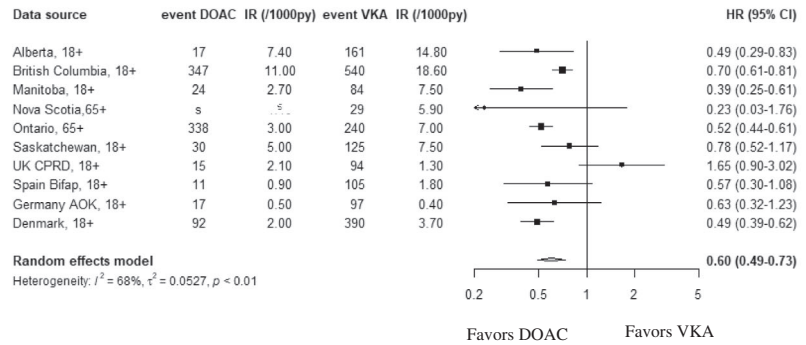


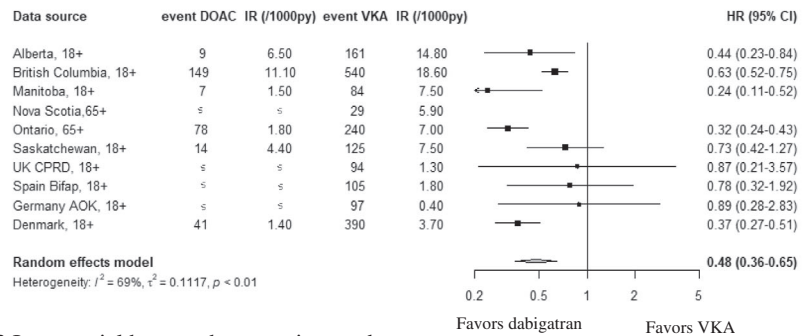
FIGURE 2 Forest plots for gastro-intestinal bleeding. (2.1) Gastro-intestinal bleeding – overall. (2.2) Gastro-intestinal bleeding – dabigatran. (2.3) Gastro-intestinal bleeding – rivaroxaban. (2.4) Gastro-intestinal bleeding – apixaban. AOK NORDWEST, Allgemeine Ortskrankenkasse NORDWEST; BIFAP, Base de Datos para la Investigación Farmacoepidemiológica en Atención Primaria; CI, confidence interval; CPRD, Clinical Practice Research Datalink; DOAC, direct oral anticoagulants; HR, Hazard Ratio; IR, incidence rate; py, person years; VKA, vitamin K antagonist; W, weight. 18+: patient population of 18 years or older. 65+: patient population of 65 years or older. S: cells with less than five events were suppressed by participating site due to privacy restrictions

FIGURE 3 Forest plots for intracranial haemorrhages. (i) Intracranial haemorrhages – overall. (ii) Intracranial haemorrhages – dabigatran. (iii) Intracranial haemorrhages – rivaroxaban. (iv) Intracranial haemorrhages – apixaban. AOK NORDWEST, Allgemeine Ortskrankenkasse NORDWEST; BIFAP, Base de Datos para la Investigación Farmacoepidemiológica en Atención Primaria; CI, confidence interval; CPRD, Clinical Practice Research Datalink; DOAC, direct oral anticoagulants; HR, Hazard Ratio; IR, incidence rate; py, person years; VKA, vitamin K antagonist; W, weight. 18+: patient population of 18 years or older. 65+: patient population of 65 years or older. S: cells with less than five events were suppressed by participating site due to privacy restrictions

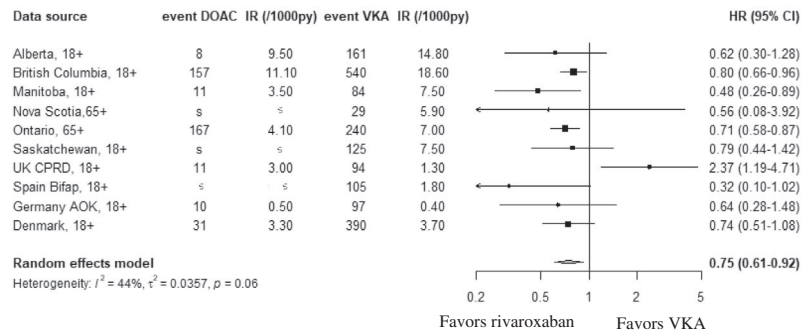
3.1 Intracranial haemorrhages – overall



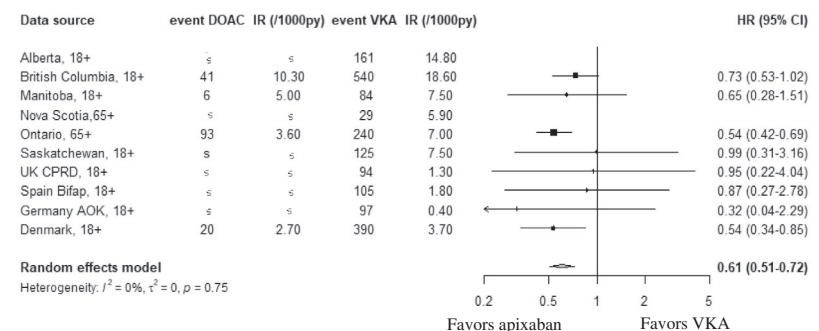
3.2 Intracranial haemorrhages – dabigatran



3.3 Intracranial haemorrhages – rivaroxaban



3.4 Intracranial haemorrhages – apixaban



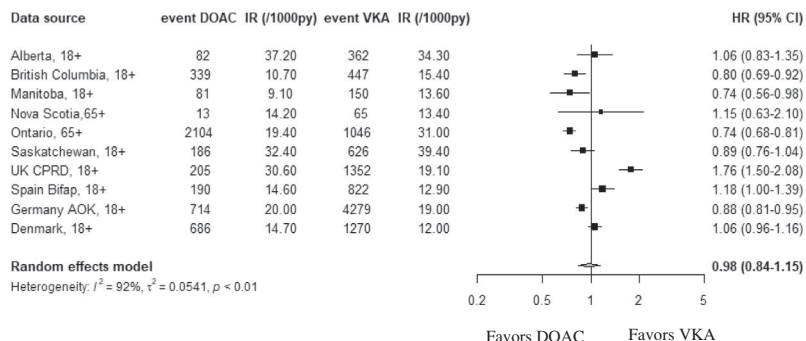
apixaban showed a decreased risk (HR 0.76, 95% CI 0.69–0.84) compared to VKAs, as did dabigatran (HR 0.85, 95% CI 0.75–0.96). Risk differed by age group; for those ≥ 75 years old, HR was 1.01, 95% CI

was 0.94–1.09, while for those < 75 HR was 0.84, 95% CI of 0.74–0.95. However, this was not statistically significant as CIs were still overlapping (Figure 1-1.5,1.6).

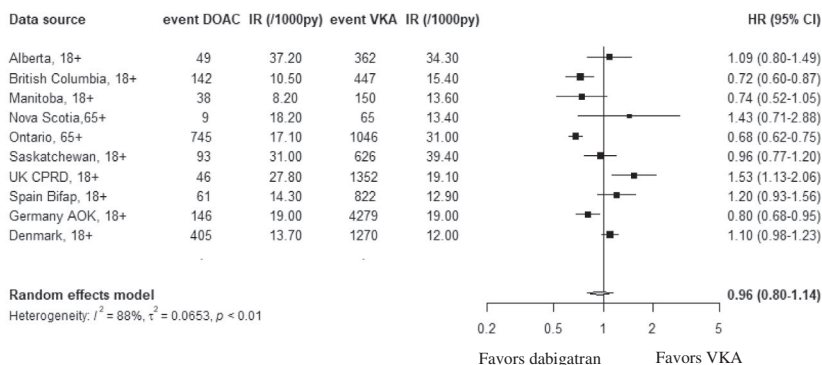
In Figures 2 and 3, the forest plots for specific bleeding events are shown. Figure 2 shows that the overall risk for GI bleeding for DOACs compared to VKAs observed was slightly higher (HR 1.16,

95% CI 1.05–1.28). When assessing the different DOACs separately, a lower risk compared to VKAs was observed for apixaban with a HR of 0.77 and a 95% CI of 0.67–0.87. A higher risk was observed for

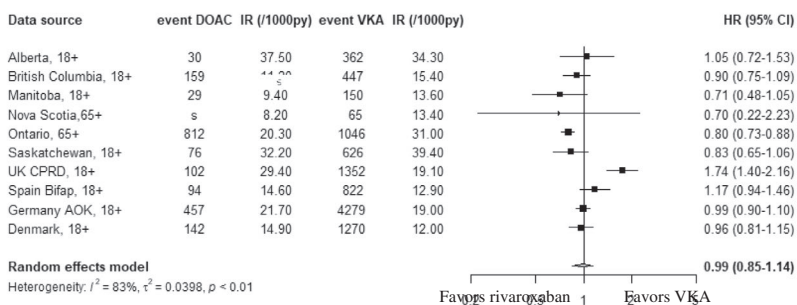
4.1 Stroke – overall



4.2 Stroke – dabigatran



4.3 Stroke – rivaroxaban



apixaban

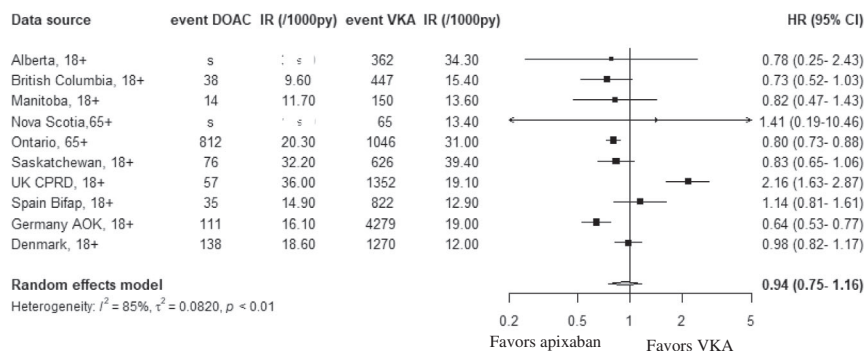


FIGURE 4 Forest plots for stroke. (i) Stroke – overall. (ii) Stroke – dabigatran. (iii) Stroke – rivaroxaban. (iv) Stroke – apixaban. AOK: Nordstern Allgemeine Ortskrankenkasse NORDWEST; BIFAP, Base de Datos para la Investigación Farmacoepidemiológica en Atención Primaria; CI, confidence interval; CPRD, Clinical Practice Research Datalink; DOAC, direct oral anticoagulants; HR, Hazard Ratio; IR, incidence rate; py, person years; VKA, vitamin K antagonist; W, weight. 18+: patient population of 18 years or older. 65+: patient population of 65 years or older. S: cells with less than five events were suppressed by participating site due to privacy restrictions

rivaroxaban (HR 1.28, 95% CI 1.18–1.38) and for dabigatran (HR 1.21, 95% CI 1.07–1.37) compared to VKAs. A 40% (95% CI of 27%–51%) lower risk for ICH was observed for DOACs compared to VKAs (Figure 3). Lower risks were also observed for the separate DOACs ranging from 25% for rivaroxaban to 52% for dabigatran. However, results of the independent DOACs for this outcome should be interpreted with caution as in some databases event numbers in the DOAC arm were very low, which could bias results. Figure 4 illustrates that there were no significant differences found for stroke between DOACs and VKAs (HR 0.98, 95% CI 0.84–1.15).

4 | DISCUSSION

This study observes that there is no clinically relevant difference in overall major bleeding risk between VKAs and DOACs as a class when pooling results from large population-based cohort studies using a common protocol from different healthcare databases in Europe and Canada. However, it seemed that younger patients (<75) tend to have a lower risk for major bleeding while treated with DOACs versus VKAs. When stratifying the results for the different DOACs independently, only rivaroxaban showed a modest increased risk for major bleeding. For the secondary outcome, GI bleeding, we found differences in results for the different DOACs. Apixaban showed a lower risk for GI bleeding, while rivaroxaban and dabigatran showed a 21%–28% increased risk, respectively, when compared to VKAs. It was also confirmed that there was a 40% decrease in risk of ICH for all DOACs when compared to VKAs. No difference was found for overall stroke risk.

Several observational studies have been carried out to address the safety and effectiveness of DOACs. Although these studies differ in characteristics of the study population, study design, reporting of outcomes of interest and treatment comparisons, the results found are generally in line: DOACs are safe and effective alternatives to warfarin.^{11,15–17,21,22} Similar to our study, it was found in a propensity-weighted nation-wide cohort study in Denmark that rivaroxaban is associated with higher risk of major bleeding versus VKA.¹¹ A study conducted in the United Kingdom in two health care databases, including CPRD (which was also used in this study), also concluded that apixaban showed lower risks on major bleeding as well as on ICH and GI-bleeding compared to warfarin.²³ Although they did not find higher risks for bleeding with rivaroxaban compared to warfarin as we do, they did find an increased risk of all-cause mortality.

The finding that rivaroxaban is associated with a higher risk for bleeding is also seen in the United States. Studies carried out in the United States in claims databases also found that rivaroxaban had a worse safety profile than dabigatran and apixaban.^{16,24} A very recent study among 221 228 AF patients captured in healthcare claims databases in the United States it was found in a secondary analysis that apixaban and dabigatran had a more pronounced decrease risk of major bleeding.²⁵ However, no significant difference in bleeding risk was found between rivaroxaban and warfarin in this study (HR 1.02, 95% CI 0.94–1.12). Another study from the same authors directly compared apixaban users and rivaroxaban users from the Optum

claims database and found that apixaban was associated with a lower rate of stroke or systematic embolism (HR 0.82, 95% CI 0.68–0.98) as well as bleeding (HR 0.58, 95% CI 0.52–0.66), compared with rivaroxaban.²⁶ It is hypothesised that higher bleeding rates in users of rivaroxaban may be explained by the fact that rivaroxaban is the only once daily dosed DOAC which causes a higher peak plasma level in patients than DOACs that are dosed twice a day.²⁷

It is reassuring that similar results are found in studies that assess the performance of individual DOACs by comparing them indirectly against warfarin, as the current study, and studies that make direct comparisons between the individual DOACs.

The occurrence of atrial fibrillation increases with age, and increasing age is also a very important independent risk factor for stroke, which makes optimal treatment with oral anticoagulants in this patient population crucial.²⁸ It has been shown that the net clinical benefit for treatment with oral anticoagulants is the greatest in the elderly.²⁹ When stratifying the results for the different age groups it was found that the risk on major bleeding did not increase in patients with age ≥ 75 for DOACs versus warfarin. However, no difference is observed in the risk of bleeding between warfarin and DOACs, which means that other factors may determine treatment decisions. Other patient-specific characteristics that can be considered are cognitive impairment (most DOACs are suitable to include in blister packs and dosette boxes), concomitant interacting medicines and comorbidities such as the presence of chronic kidney disease.^{30,31}

Although many observational studies have been carried out in the last few years since the introduction of the DOACs, we think this observational study provides additional evidence for the safety of DOACs and the individual DOACs. To our knowledge this is the largest sample size showing the effect of the medicines prescribed in clinical/daily practice using multiple health care databases within Europe and Canada, and by pooling the results we have a precise estimate reflected in the narrow 95% CIs. Especially for the outcome ICH, which is a rare one, this is very valuable. Another advantage of this study is the number of geographical areas covered, which increases the applicability of the results. We have tried to limit differences in results due to methodological choices by using a common protocol harmonising the choices in study design and the definition and the coding of outcomes and exposures. As a result this study is better able to detect an overall effect than when aggregated data from multiple studies with different set-up and quality are pooled. Having a network of databases ready that can look at benefits and risks of drugs, according to a common protocol will increase consistency in the results across these databases in different countries and will increase the value of observational drug research.³²

We have corrected in all the analyses for confounding by including risk factors for major bleeding. However, in some databases we were unable to adjust for renal function, weight/BMI, smoking or alcohol status which may cause residual confounding since they may also determine the treatment decision. Also, unobserved confounding may still be present, mainly those determining the treatment selection by the physician who may choose the safer one (in terms of haemorrhagic effect) among patients at higher risk.

The definition of major bleeding was mainly based on medical codes and not specified based on measures such as haemoglobin levels and the units of blood needed for transfusion, which are the additional criteria from the international society on thrombosis and haemostasis. Therefore it is not certain that all the events identified are indeed major. However, a sensitivity analysis was performed in all databases where only hospitalised cases were taken into account (CNODES Canada, CPRD UK, Denmark, AOK NORDWEST Germany) or cases that were validated by reviewing medical records (Bifap Spain), but results remained consistent to the primary analysis.

In the current study we did not look at the impact of different dosages of DOACs on bleeding events, although we know from clinical practice that doses are adjusted for those patients that have a higher risk for bleeding.³³ It should also be noted that different VKAs, such as warfarin, acenocoumarol and phenprocoumon, were pooled together in the analysis, although they do differ with respect to pharmacokinetic profile.

5 | CONCLUSION

This study shows that the risk of major bleeding of DOACs compared to VKAs is not different for DOACs as a class. When stratifying the result for different DOACs, the risk for major bleeding was elevated for rivaroxaban compared to VKAs. The risk on gastro-intestinal bleeding was elevated for both rivaroxaban and dabigatran 20%. The risk for ICH was reduced for all individual DOACs versus VKA.

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CONFLICT OF INTEREST

Other than the direct funders of the study (European Medicines Agency and Canadian Institutes of Health Research), authors Hendrika A. van den Ham, Patrick C. Souverein, Olaf H. Klungel, Pierre Ernst, Sophie Dell’Aniello, Birgit Grave, Marietta Rottenkolber, Consuelo Huerta, Elisa Martín Merino, Luz M León-Muñoz, Dolores Montero and Helga Gardarsdottir had nothing to disclose. Marie L. De Bruin reports grants from Novo Nordisk, grants from Ferring Pharmaceuticals, grants from LEO Pharma, grants from Lundbeck, outside the submitted work. Sven Schmiel reports a lecture fee from Daiichi Sankyo Deutschland GmbH. Robert W. Platt reports personal fees from

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ETHICS STATEMENT

Each data source has their own ethical guidelines and data protection procedure in place. For more information about the data sharing regarding this study, please contact the principal investigator.

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ENDNOTE

^a Although the first DOAC for the indication NVAf was registered in Europe since 2011 and in Canada in 2010, DOACs were already on the market since 2008 for the prevention/treatment of deep venous thrombosis and pulmonary embolism.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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