

**EU PE&PV Research Network under the Framework Service Contract
(nr. EMA/2015/27/PH)**

Final Study Report

Characterising the risk of major bleeding in patients with Non-Valvular Atrial Fibrillation: non-interventional study of patients taking Direct Oral Anticoagulants in the EU

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PASS information

Title	Characterising the risk of major bleeding in patients with Non-Valvular Atrial Fibrillation: non-interventional study of patients taking Direct Oral Anticoagulants in the EU
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Active substance	Vitamin K antagonists (Warfarin ATC B01AA03, Phenprocoumon ATC B01AA04, Acenocoumarol ATC B01AA07, Fluindione ATC B01AA12), Direct factor Xa-inhibitors (Rivaroxaban ATC B01AF01, Apixaban ATC B01AF02) and Direct thrombininhibitors (Dabigatran ATC B01AE07)
Medicinal product	Vitamin K antagonists (Warfarin ATC B01AA03, Phenprocoumon ATC B01AA04, Acenocoumarol ATC B01AA07, Fluindione ATC B01AA12), Direct factor Xa-inhibitors (Rivaroxaban ATC B01AF01, Apixaban ATC B01AF02) and Direct thrombininhibitors (Dabigatran ATC B01AE07)
Product reference	Not applicable
Procedure number	EMA/2014/50/RE
Joint PASS	Yes
Research question and objectives	<p>This report describes a pharmacoepidemiological study using longitudinal data collected in 8 electronic health care databases from 6 EU countries to characterize the risk of major bleeding in Direct Oral Anticoagulant (DOAC) users in a real-world setting to help establish the effectiveness of existing and future risk minimization measures. The research objectives were:</p> <p>Objective 1. The risk of major bleeding, such as gastrointestinal bleeding, intracranial bleeding and haemorrhagic stroke, associated with use of DOACs when compared to other oral anticoagulants (OACs), i.e. vitamin K antagonists (VKAs), in patients with non-valvular atrial fibrillation (NVAf) overall and in relevant clinical and demographical subgroups in a real-life setting.</p> <p>Objective 2. The utilization of DOACs in the EU for treatment of NVAF, including the characterization of new DOAC users in NVAF patients. Objective 3. Prescribers' compliance with recommendations included in sections 4.1, 4.3, 4.4, and 4.5 of the SmPC of each DOAC.</p>
Country(-ies) of study	Denmark, France, Germany, United Kingdom, The Netherlands and Spain
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Marketing authorisation holder(s)	Not applicable

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1. Abstract

Title

Characterising the risk of major bleeding in patients with Non-Valvular Atrial Fibrillation: non-interventional study of patients taking Direct Oral Anticoagulants in the EU.

Keywords

DOAC, NVAF, bleeding

Rationale and background

To describe a pharmacoepidemiological study using longitudinal data collected in 8 electronic health care databases from 6 EU countries to characterize the use of Direct Oral Anticoagulants (DOAC) as well as the risk of major bleeding in a real-world setting to help establish the effectiveness of existing and future risk minimization measures.

Research question and objectives

Objective 1. The risk of major bleeding associated with use of DOACs when compared to other oral anticoagulants (OACs) in patients with non-valvular atrial fibrillation (NVAF) overall and in relevant clinical and demographical subgroups in a real-life setting.

Objective 2. The utilization of DOACs in the EU for treatment of NVAF, including the characterization of new DOAC users in NVAF patients.

Objective 3. Prescribers' compliance with recommendations included in sections 4.1, 4.3, 4.4, and 4.5 of the SmPC of each DOAC.

Abstract objective 1

Aim: To characterize the risk of major bleeding in DOAC users in a real-world setting using longitudinal data collected in four electronic health care databases from different EU countries.

Methods: A study cohort among consisted of 251,719 new users (≥ 18 years) of DOACs or VKAs with non-valvular atrial fibrillation from the UK, Spain, Germany and Denmark. We compared current use of DOACs with current use of VKAs with respect to the occurrence of major bleeding events.

Results: Overall hazard ratios of major bleeding risk for DOACs versus VKAs ranged between 0.84 (Denmark) and 1.13 (UK CPRD). When stratifying according to the type of bleeding event, the risk of gastrointestinal bleeding was statistically significantly increased by 48-67% in users of dabigatran users and 30-50% for rivaroxaban users compared to VKA users in all data sources except for Denmark.

Conclusion: Compared to VKAs, apixaban was not associated with an increased risk of GI bleeding in all data sources and seemed to be associated with the lowest risk of major bleeding events compared to dabigatran and rivaroxaban. Future exploration of reasons for non-adherence to DOAC treatment and its impact on bleeding risk are interesting to explore in more detail.

Abstract objective 2

Aim: To estimate the incidence of Direct Oral Anticoagulant Drug (DOACs) use in non-valvular atrial fibrillation (NVAf) and to describe user and treatment characteristics in 8 European health databases (Mondriaan, Bavarian CD, AOK Northwest, BIFAP, SIDIAP, CPRD, EGB and NRD) representing 6 European countries (Denmark, France, Germany, United Kingdom, The Netherlands and Spain) .

Methods: Descriptive cohort study of new DOAC users with NVAf from January 2008 to December 2015. A common protocol approach was applied to each database. Annual period incidences and direct standardisation by age and sex were performed. A incidence percentage change in DOAC use was assessed from 2012-2013 (apixaban 2013-2014) to 2014-2015. Dose adjustment related to change in age and by renal function as well as concomitant use of potential interacting drugs were assessed.

Results: A total of 186,405 new DOAC users (≥ 18 years) were identified. The standardized incidence increased for all DOACs over the study period, with the highest increase for apixaban (554.5%) followed by rivaroxaban (80.7%). The highest incidence for all DOACs was found in Denmark and Germany, with lower values and slight differences among the remaining databases. The incidence of DOAC use increased for both genders in most databases and especially in those older than 75 years. Concomitant use of contraindicated drugs varied between 16.4% (SIDIAP), and 70.5% (EGB) and dose adjustment ranged from 4.6% in the Spanish (BIFAP) to 15.6% in the French (EGB) study population.

Conclusion: The overall incidence of new DOAC users increased, with the highest increase for apixaban. Cross national drug utilization studies with a standard protocol may help to compare drug use and identify sources of variation enabling health care decisions.

Abstract objective 3

Aim: To analyse prescribers' adherence to registered indications (IC), contraindications (CI), special warnings/precautions (SW/P), and potential drug-drug interactions (pDDIs).

Methods: This retrospective cohort study was conducted in six databases covering regionally / nationally representative populations in 5 European countries. The study cohort consisted of patients (≥ 18 years) initiating dabigatran, rivaroxaban or apixaban between 2008 and 2015. ICs, CIs, SW/Ps, and pDDIs as registered in the Summary of Product Characteristics (SmPC) were mapped to respective coding systems.

Results: Within the study period and the six included database, a DOAC was initiated in 407,576 patients (rivaroxaban: 240,985 (59.1%), dabigatran: 95,303 (23.4%), apixaban: 71,288 (17.5%)). In 2015, non-valvular atrial fibrillation was the most common IC registered, representing more than 60% of incident DOAC users in most databases. Between the databases, a substantial variety was found regarding the proportion of patients with at least one CI (inter-database range: 8.2% to 55.7%) with highest values for dabigatran in most databases. SW/Pc were present in a higher proportion of incident DOAC users (inter-database range: 35.8% – 75.2%) reaching highest values in incident apixaban users. Inter-database range for potential DDIs was 22.4% to 54.1% reaching highest values in dabigatran initiators.

Conclusion: CIs, SW/Ps, and potential DDIs were present in a substantial number of new DOAC users. Differences found between the databases might be related to 'true' differences in prescription behaviour but also due to discrepancies in database characteristics. (EMA/2015/27/PH; EU PAS Register No: 16014).

Marketing Authorisation Holder(s) Not applicable

2. Abbreviations

Abbreviations have been explained in the text.

3. Investigators

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5. Milestones

Milestone	Planned date	Actual date	Comments
Start of data collection	NA	Will be included in the final report	The date from which data extraction starts, will be included in the final report
End of data collection	NA	Will be included in the final report	End of data collection will be the last first prescription/dispensing date of the last patient, will be included in the final report
Registration in the EU PAS Register	NA	7 December 2016	
Interim study report	9 February 2018	9 February 2018	The interim report does not include the results from Denmark. They will be added to the final report. Furthermore, small adjustments to the analyses are currently being made due to quality check of the data and results.
Study report	1 September 2017		Deadlines of milestones were corrected due to the additional time spent on EMA review process. A further extension of the deadlines was requested due to delay in data analysis and change of research group composition.
Manuscripts	1 October 2017	11 June 2018	<p>Working titles of the manuscripts</p> <p>Objective 1: Souverein PC et al. Risk of Major Bleeding associated with the use of non-vitamin K antagonist oral anticoagulants compared to vitamin K antagonists in patients with atrial fibrillation: a European wide population-based cohort study</p> <p>Objective 2: Sabate M et al. Incidence of Direct Oral Anticoagulant use and characteristics of users in 6 European countries (2009-2015)</p> <p>Objective 3: Rottenkolber M, Schmiedl S et al. Prescribers' compliance with SmPC recommendations for dabigatran, rivaroxaban, and apixaban – a European comparative drug utilization study</p> <p>Meta-analysis Objective 1 (joint project with CNODES): Van den Ham et al. Risk of Major Bleeding associated with the use of direct oral anticoagulants compared to vitamin K antagonists in patients with atrial fibrillation: a meta-analysis of results from multiple population-based cohort studies in Canada and Europe</p>
Final study report	1 October 2017	11 June 2018	Final study report revised after receiving comments from EMA (version 2.0, October 2018)

6. Rationale and background

The protocol has been developed under the Framework service contract (nr. EMA/2015/27/PH) with regard to the re-opening of competition no.3. The objective of this study was to describe a pharmacoepidemiological study using longitudinal data collected in 8 electronic health care databases from 6 EU countries to characterize the risk of major bleeding in Direct Oral Anticoagulant (DOAC) users in a real-world setting to help establish the effectiveness of existing and future risk minimization measures. The research undertaken focused on targeted clinical and demographic subgroups for which variations in plasma concentrations might affect the safety of the products.

7. Research question and objectives

The objectives of study were to measure:

Objective 1. The risk of major bleeding, such as gastrointestinal bleeding, intracranial bleeding and haemorrhagic stroke, associated with use of DOACs when compared to other oral anticoagulants (OACs), i.e. vitamin K antagonists (VKAs), in patients with non-valvular atrial fibrillation (NVAF) overall and in relevant clinical and demographical subgroups in a real-life setting. These include patients with chronic kidney disease, with hepatic impairment, the elderly (≥ 75 years), patients with low or high body weight ($< 50\text{kg}$ or $> 100\text{kg}$) and patients treated with contraindicated or potentially hazardous co-medications as listed in sections 4.3, 4.4, and 4.5 of the SmPC of each product. Risk estimates will be provided for all DOACs as a group, as well as for each DOAC separately and in comparison to VKA.

Objective 2. The utilization of DOACs in the EU for treatment of NVAF, including the characterization of new DOAC users in NVAF patients. This includes incidence of use, assessing the degree of switching between different DOACs, other OACs, time on therapy, the degree of dose adjustment, prevalence of concomitant exposure to potentially interacting drugs and the rate of permanent discontinuation.

Objective 3. Prescribers' compliance with recommendations included in sections 4.1, 4.3, 4.4, and 4.5 of the SmPC of each DOAC.

8. Amendments and updates

The amendments are described in the attached study protocol (Annex 2) under "5. Amendments and updates".

9. Research methods

The research methods are described in the attached study protocol (Annex 2). The page numbers referring to the protocol pages are given below.

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9.10. Quality control

This study bears an ENCePP Seal and is registered in the EU PAS register (EUPAS 16014).

The members of the consortium have similar local quality assurance systems in place. In addition, several quality assurance measures are taken that will be maintained in the proposed consortium across the centres, such as adherence to the ENCePP code of conduct and apply for ENCePP Seal, development of protocols according the ENCePP guidance, registration of protocols at the ENCePP registry of studies, sharing and comparison of program codes across centres, documentation of harmonization of coding systems across multiple datasets (exposure, outcome, confounder definitions), blinded conduct of studies. Study protocols are peer-reviewed by an advisor (at least one member of the consortium that is not leading nor actively participating in the study). Regarding conflict of interest, a declaration of conflict of interest by the candidate partners that will be in a position to be principal investigator or co-investigator should be presented to the Steering Committee.

The Division of Pharmacoepidemiology & Clinical Pharmacology is working according to a quality management system based on ISO 9001 principles, at the moment in development towards certification. The quality management system is system and process oriented and based on continuous improvement. All primary and secondary processes within the division are included in the quality system, from creating research proposals, through managing PhD projects to data management, reporting and archival. The system is based upon standard operating procedures implemented throughout the division with regular internal audits as well as external audits that lead to certification. The quality management system is based on national and international external quality requirements where available and pertinent, including the guidelines for Good

Pharmacoepidemiological Practices, ENCePP Guide on Methodological Standards in Pharmacoepidemiology, Good Clinical Practice, and Good Clinical Data management Practice as well national and international guidelines and legislation concerning data-handling and privacy issues.

10. Results

This section includes the main results for each objective. All results (including subgroup and sensitivity analysis) for each objective and database are available in Annex 3.

10.1. Participants

Prescribing of DOACs was assessed in six databases (objective 3) and included in total 407,586 new users (≥ 18 years). The Bavarian database had the highest number of new users (237,864) followed by NR Denmark (97,325), BIFAP (24,977), SIDIAP (23,161), CPRD (23,492) and Mondriaan (767).

DOAC use in patients with non-valvular atrial fibrillation (NVAf) was assessed in eight databases and included a total of 186,405 new users (≥ 18 years) (i.e. including those with prior OAC use). Bavarian Claims database had the highest number of new users (84,276) and the Mondriaan database the one that contributed with the lower new users number (460). See the flow charts in Annex 4 for the number of patients potentially eligible and the number of patients finally included from each database. Patients from CPRD, AOK NORDWEST and BIFAP were assessed for objective 1. Overall, 251,719 patients started oral anticoagulants in CPRD, BIFAP and AOK NORDWEST and NRD,

10.2. Descriptive data

10.2.1. Descriptives study population objective 1

The characteristics of the study population are shown in Table 1. The number of new users of (D)OACs identified totalled 39,129, 51,030, 88,742 and 72,818 in CPRD, BIFAP, AOK NORDWEST and Denmark, respectively. The proportion of female users was similar in CPRD, BIFAP and Denmark, but slightly higher in AOK. The mean age of the users was comparable across data sources (around 75 years), slightly younger in the Danish registers. There were some differences with respect to comorbidities, especially the proportion of patients with a history of cardiovascular diseases was substantially higher in the German database with almost two-third of the patients having such a history, compared to 19-27% in both other data sources. The same was true for e.g. heart failure, diabetes and hypertension, although the prevalence of antihypertensive drug use was comparable between data sources. In contrast, the prevalence of antiplatelet drug use was substantially lower in the German data source, when compared to CPRD and BIFAP (caused by often over-the-counter use of aspirin in Germany). Information on weight, BMI and renal function was only available for CPRD and BIFAP. The proportion of patients with either low or high BMI or having severely reduced renal function was quite low in both sources.

Table 1. Baseline characteristics for users of DOACs and VKAs within the different databases in the United Kingdom, Spain, Germany and Denmark (objective 1)

	United Kingdom (CPRD)		Spain (BIFAP)		Germany (AOK Nordwest)		Denmark (National)	
	DOAC (n=5,852)	VKA (n=33,277)	DOAC (n=8,775)	VKA (n=42,255)	DOAC (n=18,566)	VKA (n=70,176)	DOAC (n=28,113)	VKA (n=44,705)
Follow-up, years (mean, SD)	0.8 (0.7)	2.7 (2.0)	1.5 (1.1)	2.6 (1.9)	#	#	1.7 (1.2)	3.7 (2.2)
Females	44.0	43.3	46.4	47.8	54.3	51.9	46.4	41.3
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)	71.4 (11.2)
18-55 years	5.6	5.5	5.0	4.1	7.1	4.9	5.9	8.3
56-65 years	12.9	13.8	12.5	11.0	12.2	11.8	16.3	18.6
66 - 75 years	26.0	27.9	26.9	27.1	25.8	34.7	34.4	33.3
75+ years	55.5	52.8	55.6	57.7	54.8	48.6	43.3	39.7
Weight								
<50 kg	1.1	0.7	2.0	2.0	NA	NA		
50-100 kg	28.1	28.7	39.1	45.2	NA	NA		
>100 kg	6.2	7.0	3.1	4.1	NA	NA		
Missing	64.6	63.6	56.9	49.7	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		
< 20 kg/m2	1.6	1.2	0.5	0.5	NA	NA		
20-24.9 kg/m2	7.5	7.1	6.3	6.4	NA	NA		
25-29.9 kg/m2	12.7	12.9	16.6	19.1	NA	NA		
30-34.9 kg/m2	8.0	8.7	12.6	15.1	NA	NA		
≥35 kg/m2	5.3	6.1	5.3	7.8	NA	NA		
Missing	64.8	63.9	58.7	51.1	NA	NA		
Smoking status								
Never	38.2	37.6	9.5	11.2	NA	NA		
Current	11.2	11.1	35.9	41.6	NA	NA		
Ex	50.4	51.0	4.3	8.1	NA	NA		
Missing	0	0	50.4	39.0	NA	NA		
Alcohol								
Yes	9.6	6.7	18.3	22.6	0.0	0.0	4.8	4.3
Renal function								
Normal (>80 ml/min)	16.6	12.8			NA	NA		
Normal – mildly reduced (CrCl 50-80 ml/min)	45.4	44.9	12.3*	18.0*	NA	NA		
Moderately reduced (CrCl 30-49 ml/min)	20.0	22.1	4.5	6.4	NA	NA		
Severely reduced (CrCl 15-29 ml/min)	0.6	1.4	0.2	0.5	NA	NA		
Very severely reduced (CrCl <15 ml/min)	0.0	0.2	0.0	0.1	NA	NA		
Missing	17.3	18.6	83.0	75.0	NA	NA		
History of disease								
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
Chronic kidney disease**	n/a	n/a	4.9	7.1	5.8	6.6	3.6	5.7
Congestive heart failure	9.6	11.8	10.2	11.9	42.8	42.3	13.7	17.2

Deep vein thrombosis/Pulmonary embolism	2.2	3.2	1.5	2.4	8.1	7.2	2.9	5.1
	United Kingdom (CPRD)		Spain (BIFAP)		Germany (AOK Nordwest)		Denmark (NRD)	
Diabetes mellitus	18.4	17.7	21.8	25.3	43.1	42.8	11.9	13.1
Hypertension	4.6	5.1	4.6	5.4	86.0	85.5	21.2	22.0
Hepatic impairment (moderate/severe)	0,0	0.1	0.2	0.3	14.7	12.1	1.0	1.1
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
Major bleeding event	32.2	29.5	15.7	15.4	33.7	24.5	19.3	17.5
Peptic ulcer disease	6.4	6.0	3.1	4.9	10.8	8.0	6.8	6.9
Stroke/TIA	21.1	17.4	11.8	11.0	25.2	20.6	19.4	17.5
Thrombocytopenia	0.0	0.1	0.2	8.0	1.4	1.5	0.1	0.1
Drug use within six months prior to index date								
antihypertensive drugs***	79.6	83.2	77.4	81.9	93.9	91.0	88.2	89.9
antidiabetic drugs (including insulin)	12.7	13.0	18.3	20.6	20.5	20.9	12.4	12.9
antiplatelet drugs	49.3	58.2	44.1	40.9	22.6	18.1	45.2	52.3
Systemic glucocorticoids	10.7	10.6	7.7	7.8	10.6	8.8	8.8	9.4
NSAIDs	10.8	12.4	28.7	26.2	26.3	23.9	16.0	16.5
SSRIs	8.3	6.4	9.2	8.7	4.7	3.1	8.1	8.0

Abbreviations: VKA, vitamine K antagonist; DOAC, direct oral anticoagulant; BMI, Body mass index; PAD, peripheral artery disease; TIA, transient ischemic attack, CrCl, Creatinine Clearance

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

** For those databases that do not have lab-values available for renal function

*** Antihypertensive drugs include ACE inhibitors, ATII-blockers, beta blockers, calcium channel blockers, diuretics, doxazosine and moxonidin

not possible due to quarterly updates

10.2.2. Descriptives study population objective 2

Baseline characteristics of the study population for objective 2 is presented in Table 2. Note that the number of DOAC users included in objective 2 do not match the numbers for the cohort study described above, as the data selection is different (in objective 1 users can start with an OAC). A total of 186,405 new DOAC users (≥ 18 years) with non-valvular atrial fibrillation (NVAf) were identified. In most databases the proportion of male users were higher than female (ranging from 52.3% in BIFAP to 58.9% in Mondriaan), except for the German AOK NORDWEST and Bavarian databases (46.4% and 47.7% male patients respectively). The mean age ranged from 69.3 (SD 11.3) years in Mondriaan to 75.7 (SD 10.5) years in BIFAP. The largest part of the users were younger than 75 years (ranging from 39.2% in BIFAP to 67.4% in Mondriaan respectively).

A mean of 61.1% (SD= 19.28) (median 58.2; IQR: 32.8) of the users in all databases had comorbidities (hepatic impairment, previous major hemorrhagic episodes, previous cardiovascular events). Most users with a comorbidity were found in the German AOK NORDWEST and Bavarian databases (87.3% and 87.8%, respectively) and the fewest in the Mondriaan database (31.1%). Previous cardiovascular events was the most frequent comorbidity. The proportion of patients having previous cardiovascular events ranged from 25.4% in Mondriaan to 82.9% in AOK. Again

the German AOK NORDWEST and Bavarian databases showed the highest proportion (82.9% and 76.7%). Overall, the proportion of users having previous major hemorrhagic episodes was quite similar in most of the databases ranging from 2.6 % in CPRD to 6.1% in Mondriaan. The highest proportion was observed in the German AOK NORDWEST and Bavarian databases (12.1% and 16.3%).

Data on laboratory values of renal function was scarce and when available the proportion of missing/not registered information was high. Users with moderate reduced kidney function ranged based on lab data from 3.0% in Mondriaan to 22.6% in CPRD. The proportion of users with hepatic impairment was low in most of the databases (ranging from 0% in Mondriaan to 2.6% in EGB). AOK NORDWEST and Bavarian databases showed the highest proportion 14.4% and 17.6%, respectively.

The proportion of patients who received a concomitant interacting drug at baseline and during the follow up ranged from 16.4% in SIDIAP to 70.5% in EGB.

Rivaroxaban was the most used DOAC in all databases (ranging from 46.6% to 62.8% in BIFAP and Mondriaan respectively) except in NRD and SIDIAP where dabigatran had the highest proportion 51.9% and 40% of users respectively. The proportion of comorbidities by individual DOAC was very similar to that of all DOACs, with the exception of apixaban in the Mondriaan database that had a higher proportion of previous major hemorrhagic episodes when compared to all DOAC.

Table 2. Baseline patient characteristics: all DOAC, and individual DOAC (objective 2)

	Netherlands (Mondriaan)		Denmark (NRD)		Germany (AOK NORDWEST)		Germany (Bavarian claims)		Spain (BIFAP)		Spain (SIDIAP)		United Kingdom (CPRD)		France (EGB)	
All DOACs	460		44876		21718		84276		14161		11962		6931		2021	
	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)
Female	189	41.1	20331	45.3	11650	53.6	44070	52.3	6755	47.7	5598	46.8	3049	44.0	867	42.9
Male	271	58.9	24545	54.7	10068	46.4	40206	47.7	7406	52.3	6364	53.2	3882	56.0	1154	57.1
AGE in years (y), mean (S.D.)	69.3	11.3	73.9	10.9	74.8	11.4	74.5	11.0	75.7	10.4	74.6	10.9	74.7	11.0	72.8	12.0
<75	310	67.4	22977	51.2	8795	40.5	36658	43.5	5558	39.2	5165	43.2	3110	44.9	995	49.2
75-79	61	13.3	7258	16.2	4785	22.0	17979	21.3	2647	18.7	2249	18.8	1300	18.8	353	17.5
≥80	89	19.3	14641	32.6	8138	37.5	29639	35.2	5956	42.1	4548	38.0	2521	36.4	673	33.3
CO-MORBIDITIES	143	31.1	29959	66.7	18952	87.3	73488	87.2	6865	48.5	6437	53.8	4337	62.6	1042	51.6
Hepatic impairment	0	0	969	2.1	3119	14.4	14845	17.6	33	0.2	27	0.2	3	0.0	52	2.6
Previous major hemorrhagic episodes	28	6.1	1642	3.6	2634	12.1	13745	16.3	532	3.8	500	4.2	177	2.6	60	3.0
Previous cardiovascular events	117	25.4	29161	65.0	17998	82.9	64618	76.7	5330	37.6	5653	47.3	3107	44.8	996	49.3
Dabigatran	99 (21.5%)		23308 (51.9%)		3968 (18.3%)		14729 (17.5%)		3863 (27.3%)		4784 (40%)		1265 (18.3%)		479 (23.7%)	
Female	38	38.4	10033	43.0	2073	52.2	7601	51.6	1826	47.3	2183	45.6	497	39.3	213	44.5
Male	61	61.6	13275	56.9	1895	47.8	7128	48.4	2037	52.7	2601	54.4	768	60.7	266	55.5
AGE in years (y), mean (S.D.)	72.6	12.0	72.5	10.8	74.4	11.0	74.0	10.7	77.0	10.2	73.7	10.8	73.5	11.1	73.9	11.5
<75	65	65.7	13096	56.2	1708	43.0	6799	46.2	1616	41.8	2239	46.8	632	50.0	207	43.2
75-79	13	13.1	3768	16.2	868	21.9	3107	21.1	800	20.7	932	19.5	221	17.5	90	18.8
≥80	21	21.2	6444	27.6	1392	35.1	4823	32.7	1447	37.5	1613	33.7	412	32.6	182	38.0
CO-MORBIDITIES	25	25.2	14894	63.9	3497	88.1	12795	86.9	1783	46.2	2382	49.8	779	61.6	252	52.6
Hepatic impairment	0	0.0	492	2.1	545	13.7	2422	16.4	8	0.2	6	0.1	0	0.0	10	2.1
Previous major hemorrhagic episodes	3	3.0	762	3.3	517	13.0	2439	16.5	138	3.6	197	4.1	27	2.1	18	3.8
Previous cardiovascular events	25	25.2	14473	62.0	3344	84.3	11064	75.1	1383	35.8	2100	43.9	557	44.0	246	51.4
Apixaban	72 (15.7%)		10358 (23.1%)		5460 (25.1%)		17339 (20.6%)		3693 (26.1%)		2728 (22.8%)		2060 (29.7%)		396 (19.6%)	
Female	36	50	4960	47.9	3078	56.4	9391	54.2	1812	49.1	1296	47.5	935	45.4	175	44.2
Male	36	50	5398	52.1	2382	43.6	7948	45.8	1881	50.9	1432	52.5	1125	54.6	221	55.8
AGE in years (y), mean (S.D.)	7.8	9	75.8	11.0	76.14	11.1	76.0	10.9	74.7	10.5	76.5	10.3	74.9	11.1	73.1	11.8
<75	43	59.7	4551	43.9	1935	35.4	6380	36.8	1289	34.9	1000	36.7	906	44.0	200	50.5

	Netherlands (Mondriaan)		Denmark (NRD)		Germany (AOK NORDWEST)		Germany (Bavarian claims)		Spain (BIFAP)		Spain (SIDIAP)		United Kingdom (CPRD)		France (EGB)	
75-79	11	15.3	1661	10.0	1195	21.9	3749	21.6	660	17.9	487	17.9	401	19.5	59	14.9
≥80	18	25.0	4146	40.0	2330	42.7	7210	41.6	1744	47.2	1241	45.5	753	36.6	137	34.6
CO-MORBIDITIES	21	29.2	7279	70.3	4797	87.8	15440	89.0	1939	52.5	1758	64.4	1236	60.0	191	48.2
Hepatic impairment	0	0.0	230	2.2	796	14.6	3180	18.3	8	0.2	16	0.6	0	0.0	8	2.0
Previous major hemorrhagic episodes	7	33.3	460	4.4	644	11.8	2849	16.4	138	3.6	135	4.9	55	2.7	10	2.5
Previous cardiovascular events	21	29.2	7105	68.6	4592	84.1	13532	78.0	1383	35.8	1548	56.7	968	47.0	183	46.2
Rivaroxaban	289 (62.8%)		11210 (25.0%)		12290 (56.6%)		52208 (61.9%)		6605 (46.6%)		4450 (37.2%)		3606 (52.0%)		1146 (56.7%)	
Female	115	39.8	5338	47.6	6499	52.9	27078	61.9	3117	47.2	2119	47.6	1617	44.8	479	41.8
Male	174	60.2	5872	52.4	5791	47.1	25130	48.1	3488	52.8	2331	52.4	1989	55.2	667	58.2
AGE in years (y), mean (S.D.)	68.3	9.0	75.0	10.8	74,51	11.1	74.2	11.1	75.5	10.5	74.5	11.2	75.1	10.9	72.3	12.2
<75	202	69.9	5330	47.5	5152	41.9	23479	45.0	2653	40.2	1926	43.3	1572	43.6	588	51.3
75-79	37	12.8	1829	16.3	2722	22.1	11123	21.3	1187	18.0	830	18.7	678	18.8	204	17.8
≥80	50	17.3	4051	36.1	4416	35.9	17606	33.7	2765	41.9	1694	38.1	1356	37.6	354	30.9
CO-MORBIDITIES	89	30.8	7786	69.4	10631	86.5	45253	86.7	3143	47.6	2297	51.6	2232	61.9	599	52.3
Hepatic impairment	0	0.0	247	2.2	1778	14.5	9243	17.7	14	1.7	5	0.1	<5	0.1	34	3.0
Previous major hemorrhagic episodes	18	6.4	420	3.7	1473	11.9	8457	16.2	246	3.7	168	3.8	95	2.6	32	2.8
Previous cardiovascular events	77	27.6	7583	67.6	10062	81.8	40022	76.6	2441	36.9	2005	45.1	1582	43.9	567	49.5

10.2.3. Descriptives study population objective 3

Age- and sex-related characteristics of the study population included in objective 3 are presented in Table 3. The majority of users were of male sex in Mondriaan, CPRD, and NR Denmark whereas the proportion of females was higher in Bavarian and SIDIAP. In BIFAP, the proportion of male and female new DOAC users was close to 50%. Comparing the three types of DOACs, similar results were found regarding the proportion of males and females.

Regarding age, the highest proportion of new DOAC users younger than 75 years was found in Mondriaan (68.6%) whereas the lowest proportions were found in BIFAP (43.4%) and CPRD (47.9%). The highest proportion of new DOAC aged 80 years or older were found in BIFAP (38.1%) whereas the lowest proportion was found in Mondriaan (17.2%).

10.3. Outcome data

See Annex 3 with detailed results for all all objectives and databases.

Table 3. Baseline patient characteristics: all DOAC, and individual DOAC (objective 3)

	Sex	Age (years)	Mondriaan		NR Denmark		Bavarian		BIFAP		SIDIAP		CPRD	
			n	%	n	%	n	%	n	%	n	%	n	%
All DOACs	Total	All	767		97325		237864		24977		23161		23492	
	Female	All	331	43.2	47431	48.7	132836	55.8	12491	50.0	11943	51.6	11249	47.9
	Male	All	436	56.8	49894	51.3	105028	44.2	12486	50.0	11218	48.4	12243	52.1
	Total	<75	526	68.6	56591	58.1	121250	51.0	10845	43.4	12600	54.4	11249	47.9
		75-79	109	14.2	14676	15.1	44461	18.7	4617	18.5	4008	17.3	3790	16.1
		>=80	132	17.2	26058	26.8	72153	30.3	9515	38.1	6553	28.3	8453	36.0
	Female	<75	209	27.2	23896	24.6	59584	25.0	4491	18.0	5700	24.6	4459	19.0
		75-79	57	7.4	7478	7.7	25310	10.6	2490	10.0	2254	9.7	1810	7.7
		>=80	65	8.5	15757	16.2	47942	20.2	5510	22.1	3989	17.2	4980	21.2
	Male	<75	317	41.3	32395	33.3	61666	25.9	6354	25.4	6900	29.8	6790	28.9
		75-79	52	6.8	7198	7.4	19151	8.1	2127	8.5	1754	7.6	1980	8.4
		>=80	67	8.7	10301	10.6	24211	10.2	4005	16.0	2564	11.1	3473	14.8
Dabigatran	Total	All	194		44219		30047		7127		10048		3676	
	Female	All	78	40.2	20909	47.3	16255	54.1	3567	50.0	5125	51.0	1622	44.1
	Male	All	116	59.8	23310	52.7	13792	45.9	3560	50.0	4923	49.0	2054	55.9
	Total	<75	134	69.1	26330	59.5	14008	46.6	3336	46.8	5848	58.2	1717	46.7
		75-79	25	12.9	7078	16.0	6176	20.6	1420	19.9	1739	17.3	640	17.4
		>=80	35	18.0	10811	24.4	9863	32.8	2371	33.3	2461	24.5	1319	35.9
	Female	<75	49	25.3	10933	24.7	6363	21.2	1387	19.5	2665	26.5	570	15.5
		75-79	14	7.2	3540	8.0	3459	11.5	806	11.3	973	9.7	307	8.4
		>=80	15	7.7	6436	14.6	6433	21.4	1374	19.3	1487	14.8	745	20.3
	Male	<75	85	43.8	15397	34.8	7645	25.4	1949	27.3	3183	31.7	1147	31.2
		75-79	11	5.7	3538	8.0	2717	9.0	614	8.6	766	7.6	333	9.1
		>=80	20	10.3	4375	9.9	3430	11.4	997	14.0	974	9.7	574	15.6
Rivaroxaban	Total	All	470		37061		167835		12048		8695		14878	
	Female	All	202	43.0	18801	50.7	94348	56.2	6029	50.0	4531	52.1	7268	48.9
	Male	All	268	57.0	18260	49.3	73487	43.8	6019	50.0	4164	47.9	7610	51.1
	Total	<75	330	70.2	23261	62.8	91361	54.4	5449	45.2	4779	55.0	7500	50.4
		75-79	67	14.3	4991	13.5	30104	17.9	2171	18.0	1483	17.1	2269	15.3
		>=80	73	15.5	8809	23.8	46370	27.6	4428	36.8	2433	28.0	5109	34.3
	Female	<75	132	28.1	10370	28.0	45966	27.4	2268	18.8	2161	24.9	3124	21.0
		75-79	32	6.8	2676	7.2	17365	10.3	1157	9.6	868	10.0	1074	7.2
		>=80	38	8.1	5455	14.7	31017	18.5	2604	21.6	1502	17.3	3070	20.6
	Male	<75	198	42.1	12591	34.0	45395	27.0	3181	26.4	2618	30.1	4376	29.4
		75-79	35	7.4	2315	6.2	12739	7.6	1014	8.4	615	7.1	1195	8.0
		>=80	35	7.4	3354	9.0	15353	9.1	1824	15.1	931	10.7	2039	13.7
Apixaban	Total	All	103		16045		39982		5802		4418		4938	
	Female	All	51	49.5	7721	48.1	22233	55.6	2895	49.9	2287	51.8	2359	47.8
	Male	All	52	50.5	8324	51.9	17749	44.4	2907	50.1	2131	48.2	2579	52.2
	Total	<75	62	60.2	7000	43.6	15881	39.7	2060	35.5	1973	44.7	2032	41.2
		75-79	17	16.5	2607	16.2	8181	20.5	1026	17.7	786	17.8	881	17.8
		>=80	24	23.3	6438	40.1	15920	39.8	2716	46.8	1659	37.6	2025	41.0
	Female	<75	28	27.2	2593	16.2	7255	18.1	836	14.4	874	19.8	765	15.5
		75-79	11	10.7	1262	7.9	4486	11.2	527	9.1	413	9.3	429	8.7
		>=80	12	11.7	3866	24.1	10492	26.2	1532	26.4	1000	22.6	1165	23.6
	Male	<75	34	33.0	4407	27.5	8626	21.6	1224	21.1	1099	24.9	1267	25.7
		75-79	6	5.8	1345	8.4	3695	9.2	499	8.6	373	8.4	452	9.2
		>=80	12	11.7	2572	16.0	5428	13.6	1184	20.4	659	14.9	860	17.4

10.4. Main results

10.4.1. Objective 1

Table 4 shows the incidence rates and hazard ratios for the occurrence of a first major bleeding event during follow-up for current users of vitamin K antagonists (VKA) and current users of DOACs. Although there was some variation in incidence rates between data sources, fully adjusted hazard ratios for current use of DOACs vs. VKA were comparable between sources with estimates around unity in three of the four data sources, except for Denmark, where there was a statistically significant 16% lower risk of bleeding events. Generally, there was minimal impact of adjusting for confounding in all data sources. For individual DOACs, only rivaroxaban was associated with an increased risk of bleeding events (in both CPRD and AOK, adjusted HR around 1.27 and 1.20, respectively). Dabigatran and apixaban were not associated with an increased risk of any bleeding in all data sources. When stratifying according to different strengths of individual DOACs no major differences were found in CPRD and BIFAP. In BIFAP dabigatran 75mg had a nonsignificant higher risk estimates of major bleeding, but the number of events was low (n=9, adjusted HR 1.50, 95% CI: 0.82-3.05). In AOK no clear pattern with strength was found with the highest point estimate for dabigatran also found for the 75 mg strength (adjusted HR 1.29, 95% CI 0.77-2.19), whereas the adjusted HR was lower for the 150 mg strength: adjusted HR 0.81 (95% CI: 0.67-0.99). Also among apixaban, the higher strength was associated with a lower risk estimate compared to the lower dose (adjusted HRs 0.66 and 0.87, respectively). For rivaroxaban no major differences were found.

When assessing the type of bleeding event (see Table 5), current DOAC use was associated with an increased risk of gastrointestinal bleeding events compared current VKA use, which was found in three data sources with statistically significant increased risks of 26 to 40%. In the Danish National Registers, the HR was around unity. These effects were mainly driven by dabigatran and rivaroxaban, as the hazard ratio for apixaban was around 1.10 in both BIFAP and CPRD, and protective in both AOK (adjusted HR 0.80, 95% CI: 0.66-0.96) and Denmark (adjusted HR 0.74, 95% CI: 0.60-0.92). The incidences for intracranial bleeding were low in all data sources and point estimates were below 1.0 in all data sources, except for a statistically significant increased risk for rivaroxaban in CPRD (adjusted HR 2.37, 95% CI 1.19-4.71). When expanding the outcome to any stroke or transient ischemic attack the incidence of such events were higher in CPRD compared to the other three data sources, yielding statistically significant increased risk of for all DOACs versus VKA with adjusted HRs ranging between 1.53 for dabigatran and 2.16 for apixaban. In BIFAP (adjusted HRs 1.14-1.20), AOK NORDWEST (adjusted HRs 0.64-0.99) and Denmark (adjusted HRs 0.96-1.10), this effect was not found.

Table 4. Risk of major bleeding in DOAC users compared with VKA users within the different databases in the United Kingdom, Spain, Germany and Denmark

	Number of events	Incidence rate per 1000 person years	Age/sex adjusted Hazard Ratio (95% CI)			Adjusted Hazard Ratio (95% CI)*		
United Kingdom (CPRD)								
Current VKA use	4391	66,8	Reference			Reference		
Current DOAC use	509	78,7	1.22	1.10	1.35	1.13	1.02	1.25
Current dabigatran use	115	71,6	1.11	0.92	1.92	1.04	0.86	1.25
Current rivaroxaban use	289	87,5	1.35	1.19	1.53	1.27	1.12	1.44
Current apixaban use	105	67,5	1.05	0.86	1.28	0.94	0.77	1.15
Spain (Bifap)								
Current VKA use	3826	66,6	Reference			Reference		
Current DOAC use	721	58,7	0.96	0.88	1.04	0.95	0.88	1.04
Current dabigatran use	211	52,6	0.84	0.73	0.94	0.85	0.74	0.98
Current rivaroxaban use	376	62,2	1.02	0.91	1.14	1.02	0.91	1.13
Current apixaban use	134	60,0	1.02	0.86	1.21	0.98	0.82	1.17
Germany (AOK Nordwest)								
Current VKA use	10967	48,7	Reference			Reference		
Current DOAC use	2186	61,3	1.13	1.08	1.19	1.07	1.02	1.12
Current dabigatran use	444	57,7	1.12	1.02	1.23	1.06	0.97	1.17
Current rivaroxaban use	1424	67,6	1.27	1.20	1.34	1.20	1.13	1.27
Current apixaban use	318	46,1	0.78	0.69	0.87	0.73	0.65	0.81
Denmark (NDR)								
Current VKA use	3127	29,5	Reference			Reference		
Current DOAC use	1241	26,6	0.80	0.75	0.86	0.84	0.79	0.90
Current dabigatran use	685	23,1	0.77	0.71	0.84	0.83	0.76	0.90
Current rivaroxaban use	340	35,7	1.09	0.97	1.21	1.11	0.99	1.24
Current apixaban use	215	28,9	0.76	0.66	0.87	0.76	0.66	0.87

Abbreviations: VKA, vitamin K antagonist; DOAC, direct oral anticoagulant

* adjusted for age, sex, BMI, smoking, alcohol, hypertension, renal failure, history of stroke/TIA, deep venous thromboembolism/pulmonary embolism, malignancy, peptic ulcer disease, thrombocytopenia, moderate/severe hepatic impairment, history of major bleeding, use of antiplatelet drugs, NSAIDs, SSRIs, systemic glucocorticoids.

Table 5. Risk of gastrointestinal bleeding, intracranial haemorrhage and stroke in DOAC users compared with VKA users within the different databases in the United Kingdom, Spain, Germany and Denmark.

	Gastrointestinal bleeding					Intracranial Haemorrhage					Stroke				
	# events	Incidence rate per 1000 person	Adjusted Hazard Ratio (95% CI)*			# events	Incidence rate per 1000 person	Adjusted Hazard Ratio (95% CI)*			# events	Incidence rate per 1000 person	Adjusted Hazard Ratio (95% CI)#		
United Kingdom (CPRD)															
Current VKA use	1184	16.5	Reference			94	1.3	Reference			1352	19.1	Reference		
Current DOAC use	168	24.2	1.40	1.17	1.67	15	2.1	1.65	0.90	3.03	205	30.6	1.76	1.50	2.08
Current dabigatran use	44	25.3	1.48	1.09	2.00	<5	1.1	0.87	0.21	3.57	46	27.8	1.53	1.13	2.06
Current rivaroxaban use	92	25.8	1.50	1.19	1.88	11	3.0	2.38	1.20	4.72	102	29.4	1.74	1.40	2.16
Current apixaban use	32	19.4	1.08	0.75	1.56	<5	1.2	0.95	0.22	4.05	57	36.0	2.16	1.63	2.87
Spain (Bifap)															
Current VKA use	864	15.0	Reference			105	1.8	Reference			822	12.9	Reference		
Current DOAC use	232	18.9	1.36	1.17	1.58	11	0.9	0.57	0.30	1.08	190	14.6	1.18	1.00	1.39
Current dabigatran use	90	22.5	1.60	1.28	1.99	5	1.2	0.78	0.32	1.92	61	14.6	1.20	0.93	1.56
Current rivaroxaban use	109	18.0	1.30	1.06	1.59	3	0.5	0.32	0.10	1.02	94	14.9	1.17	0.94	1.46
Current apixaban use	33	14.8	1.05	0.74	1.50	3	1.3	0.87	0.27	2.78	35	18.0	1.14	0.81	1.61
Germany (AOK)															
Current VKA use	3649	16.2	Reference			97	0.4	Reference			4279	19.0	Reference		
Current DOAC use	890	24.9	1.26	1.15	1.39	17	0.5	0.63	0.32	1.23	714	20.0	0.88	0.81	0.95
Current dabigatran use	210	27.3	1.49	1.29	1.71	5	0.6	0.89	0.28	2.83	146	19.0	0.81	0.68	0.95
Current rivaroxaban use	559	26.5	1.36	1.25	1.49	10	0.5	0.64	0.28	1.48	457	21.7	0.99	0.90	1.10
Current apixaban use	121	17.5	0.80	0.66	0.96	2	0.3	0.32	0.04	2.29	111	16.1	0.64	0.53	0.77
Denmark (NDR)															

Current VKA use	1327	12,5	Reference			390	3,7	Reference			1270	12,0	Reference		
Current DOAC use	656	14,1	1.04	0.95	1.15	92	2,0	0.49	0.39	0.62	686	14,7	1.06	0.96	1.16
Current dabigatran use	399	13,4	1.14	1.02	1.27	41	1,4	0.53	0.40	0.29	405	13,7	1.11	0.99	1.24
Current rivaroxaban use	160	16,8	1.11	0.95	1.31	31	3,3	1.30	0.91	0.63	142	14,9	0.95	0.80	1.13
Current apixaban use	96	12,9	0.70	0.57	0.87	20	2,7	1.05	0.66	0.42	138	18,6	0.98	0.82	1.17

Abbreviations: VKA, vitamin K antagonist; DOAC, direct oral anticoagulant

* adjusted for age, sex, BMI, smoking, alcohol, hypertension, renal failure, history of stroke/TIA, deep venous thromboembolism/pulmonary embolism, malignancy, peptic ulcer disease, thrombocytopenia, moderate/severe hepatic impairment, history of major bleeding, use of antiplatelet drugs, NSAIDs, SSRIs, systemic glucocorticoids. # adjusted for age, sex, BMI, smoking, alcohol, hypertension, renal failure, history of stroke/TIA, deep venous thromboembolism/pulmonary embolism, congestive heart failure, diabetes, other cardiovascular disease, renal failure

Subsequently, we assessed the impact of stratifying by sex (Table 6), age above or under 75 years of age (Table 7), weight <50 or >100 kg (Table 8) and renal function (Table 9). There were no major differences observed in risk estimates between males and females in all data sources. Adjusted HRs in patients aged 75 years and older were slightly higher in both CPRD and BIFAP, but not in AOK NORDWEST. In Denmark, adjusted HR in the 75 years and older group were closer to unity than in the under 75 age group, particularly for dabigatran. The number of outcome events in patients in extreme weight categories or having severe renal failure were generally very low in both CPRD and BIFAP (the only two sources having laboratory information available), hampering the possibility to obtain meaningful incidence rates and risk estimates. In Denmark, risk estimates were compared between patients and without a diagnosis of renal impairment, but risk estimates for the comparison of DOACs vs. VKA were similar in both strata.

Table 6. Risk of major bleeding in DOAC users compared with VKA users within the different databases in the United Kingdom, Spain, Germany and Denmark, stratified by sex

Exposure	United Kingdom (CPRD)					Spain (Bifap)					Germany (AOK NORDWEST)					Denmark (NDR)				
	# events	Incidence rate per 1000 person years	Adjusted HR (95% CI)*			# events	Incidence rate per 1000 person years	Adjusted HR (95% CI)*			# events	Incidence rate per 1000 person years	Adjusted HR (95% CI)*			# events	Incidence rate per 1000 person years	Adjusted HR (95% CI)*		
Women																				
Current VKA use	1809	62.9	Reference			1605	57.3	Reference			5672	48.9	Reference			1257	28,7	Reference		
Current DOAC use	220	75.9	1.22	1.04	1.42	299	49.1	0.93	0.82	1.06	1234	60.7	1.07	1.00	1.14	572	26,3	0.84	0.76	0.93
Current dabigatran use	44	68.4	1.11	0.82	1.50	84	42.8	0.78	0.63	0.98	265	61.1	1.15	1.01	1.30	328	24,9	0.88	0.78	0.99
Current rivaroxaban use	1330	86.4	1.40	1.16	1.70	154	51.6	0.98	0.83	1.17	796	66.4	1.18	1.09	1.27	149	31,0	0.93	0.78	1.11
Current apixaban use	46	61.3	0.95	0.70	1.28	61	53.8	1.07	0.83	1.39	173	43.1	0.69	0.60	0.81	95	25,5	0.67	0.54	0.83
Males																				
Current VKA use	2582	69.9	Reference			2221	75.5	Reference			5295	48.5	Reference			1870	30,0	Reference		
Current DOAC use	289	81.0	1.09	0.95	1.24	422	68.1	0.98	0.88	1.09	952	62.1	1.09	1.01	1.17	669	26,9	0.85	0.78	0.93
Current dabigatran use	71	73.7	1.02	0.80	1.29	127	62.1	0.90	0.75	1.08	179	53.3	0.96	0.83	1.12	357	21,7	0.76	0.68	0.86
Current rivaroxaban use	159	88.5	1.19	1.00	1.41	222	72.7	1.05	0.91	1.21	628	69.1	1.24	1.14	1.35	191	40,6	1.17	1.01	1.36
Current apixaban use	59	73.3	0.95	0.73	1.24	73	66.4	0.92	0.73	1.17	145	50.2	0.79	0.66	0.93	120	32,4	0.81	0.67	0.98

Abbreviations: VKA, vitamin K antagonist; DOAC, direct oral anticoagulant

*adjusted for age, sex, BMI, smoking, alcohol, hypertension, renal failure, history of stroke/TIA, deep venous thromboembolism/pulmonary embolism, malignancy, peptic ulcer disease, thrombocytopenia, moderate/severe hepatic impairment, history of major bleeding, use of antiplatelet drugs, NSAIDs, SSRIs, systemic glucocorticoids

Table 7. Risk of major bleeding in DOAC users compared with VKA users within the different databases in the United Kingdom, Spain, Germany and Denmark, stratified by age category

Exposure	United Kingdom (CPRD)					Spain (Bifap)					Germany (AOK NORDWEST)					Denmark (NDR)				
	#events	Incidence rate per 1000 person years	Adjusted HR (95% CI)*			#events	Incidence rate per 1000 person years	Adjusted HR (95% CI)*			#events	Incidence rate per 1000 person years	Adjusted HR (95% CI)*			#events	Incidence rate per 1000 person years	Adjusted HR (95% CI)*		
Age < 75																				
Current VKA use	1691	60,2	Reference			1384	66.4	Reference			4781	40.5	Reference			1424	22,0	Reference		
Current DOAC use	186	64,3	1.02	0.87	1.21	242	49.6	0.78	0.68	0.90	785	49.6	1.03	1.03	1.04	426	15,6	0.71	0.64	0.80
Current dabigatran use	48	62,9	1.03	0.77	1.37	74	43.7	0.69	0.55	0.88	154	42.7	0.99	0.84	1.16	239	13,0	0.63	0.55	0.72
Current rivaroxaban use	93	64,5	1.03	0.82	1.28	131	55.6	0.87	0.73	1.05	527	55.8	1.26	1.15	1.38	122	23,9	1.03	0.86	1.24
Current apixaban use	45	65,5	1.01	0.74	1.38	37	44.5	0.69	0.50	0.97	104	37.6	0.80	0.66	0.97	64	17,3	0.67	0.52	0.86
Age ≥ 75																				
Current VKA use	2700	71,7	Reference			2442	66.8	Reference			6186	57.7	Reference			1703	41,3	Reference		
Current DOAC use	323	90,4	1.22	1.07	1.38	479	64.7	1.05	0.95	1.17	1401	70.5	1.07	1.01	1.14	815	42,0	0.95	0.87	1.04
Current dabigatran use	67	79,3	1.06	0.83	1.36	137	59.2	0.94	0.79	1.12	290	70.9	1.13	1.00	1.27	446	39,6	0.97	0.88	1.08
Current rivaroxaban use	196	105,3	1.44	1.23	1.68	245	66.5	1.10	0.96	1.25	897	77.1	1.19	1.11	1.28	218	49,5	1.07	0.93	1.24
Current apixaban use	60	69,1	0.91	0.70	1.18	97	69.2	1.15	0.93	1.41	214	51.8	0.72	0.63	0.82	151	40,6	0.78	0.66	0.93

Abbreviations: VKA, vitamin K antagonist; DOAC, direct oral anticoagulant

* adjusted for age, sex, BMI, smoking, alcohol, hypertension, renal failure, history of stroke/TIA, deep venous thromboembolism/pulmonary embolism, malignancy, peptic ulcer disease, thrombocytopenia, moderate/severe hepatic impairment, history of major bleeding, use of antiplatelet drugs, NSAIDs, SSRIs, systemic glucocorticoids

Table 8. Risk of major bleeding in DOAC users compared with VKA users within the different databases in the United Kingdom and Spain, stratified by weight category

Exposure	United Kingdom (CPRD)					Spain (Bifap)				
	#events	Incidence rate per 1000 person years	Adjusted HR (95% CI)*			#events	Incidence rate per 1000 person years	Adjusted HR (95% CI)*		
< 50 kg										
Current VKA use	21	59.2	Reference			40	61.6	Reference		
Current DOAC use	5	98.2	1.22	0.32	4.61	11	90.3	1.56	0.77	3.17
Current dabigatran use	<5		3.19	0.54	18.85	5	153.9	2.75	1.06	7.13
Current rivaroxaban use	<5		0.70	0.12	4.13	2	30.2	0.52	0.12	2.20
Current apixaban use	<5		0.89	0.09	9.09	4	172.4	2.82	0.93	8.49
> 100 kg										
Current VKA use	316	64.4	Reference			189	68.7	Reference		
Current DOAC use	29	60.5	0.90	0.59	1.35	26	59.4	0.95	0.62	1.46
Current dabigatran use	8	63.3	0.89	0.44	1.83	8	54.3	0.91	0.44	1.86
Current rivaroxaban use	14	58.7	0.90	0.52	1.57	12	55.2	0.87	0.48	1.57
Current apixaban use	7	61.4	0.89	0.41	1.93	6	81.9	1.26	0.55	2.90

Abbreviations: VKA, vitamin K antagonist; DOAC, direct oral anticoagulant

* adjusted for age, sex, BMI, smoking, alcohol, hypertension, renal failure, history of stroke/TIA, deep venous thromboembolism/pulmonary embolism, malignancy, peptic ulcer disease, thrombocytopenia, moderate/severe hepatic impairment, history of major bleeding, use of antiplatelet drugs, NSAIDs, SSRIs, systemic glucocorticoids

Table 9. Risk of major bleeding in DOAC users compared with VKA users within the different databases in the United Kingdom and Spain, stratified by renal function (defined by creatinine clearance, CrCl)

Exposure	United Kingdom (CPRD)					Spain (Bifap)				
	#events	Incidence rate per 1000 person years	Adjusted HR (95% CI)*			#events	Incidence rate per 1000 person years	Adjusted HR (95% CI)*		
normal-mildly reduced (CrCl 50-80 mL/min)										
Current VKA use	2577	69.5	Reference			890	71.9	Reference		
Current DOAC use	333	81.4	1.11	0.98	1.26	130	67.7	1.03	0.85	1.25
Current dabigatran use	75	69.5	1.02	0.81	1.29	39	53.3	0.80	0.58	1.10
Current rivaroxaban use	191	73.5	1.27	1.08	1.48	66	78.0	1.21	0.94	1.56
Current apixaban use	67	91.8	0.89	0.69	1.14	25	73.1	1.14	0.76	1.71
moderately reduced (CrCl 30-49 mL/min)										
Current VKA use	1048	66.6	Reference			384	73.8	Reference		
Current DOAC use	111	79.1	1.19	0.96	1.48	54	66.7	0.92	0.69	1.24
Current dabigatran use	26	77.0	1.13	0.77	1.68	18	74.6	1.06	0.66	1.70
Current rivaroxaban use	66	90.2	1.36	1.04	1.78	19	47.4	0.64	0.40	1.03
Current apixaban use	19	57.0	0.87	0.54	1.39	17	101.3	1.44	0.87	2.36
severely reduced (CrCl 15-29 mL/min)										
Current VKA use	79	85.7	Reference			38	109.3	Reference		
Current DOAC use	<5		1.11	0.37	3.32	1	22.6	0.25	0.03	1.85
Current dabigatran use		0				1	126.8	1.13	0.14	9.08
Current rivaroxaban use	<5		1.21	0.36	4.09	0	0			
Current apixaban use	<5		1.02	0.13	8.20	0	0			
very severely reduced (CrCl<15 mL/min)										
Current VKA use	11	107.7	Reference			2	36.8	Reference		
Current DOAC use	<5		2.13	0.07	67.64	0	0			
Current dabigatran use	<5					0	0			
Current rivaroxaban use	<5		2.13	0.07	67.64	0	0			
Current apixaban use	<5					0	0			

Abbreviations: VKA, vitamin K antagonist; DOAC, direct oral anticoagulant, CrCl, Creatinine Clearance

* adjusted for age, sex, BMI, smoking, alcohol, hypertension, renal failure, history of stroke/TIA, deep venous thromboembolism/pulmonary embolism, malignancy, peptic ulcer disease, thrombocytopenia, moderate/severe hepatic impairment, history of major bleeding, use of antiplatelet drugs, NSAIDs, SSRIs, systemic glucocorticoids

Several sensitivity analyses were performed to assess the robustness of the results obtained. First, the impact of changing the definition of the VKA or DOAC treatment episodes by changing the permissible gap length (reducing the gap to zero days, or expanding it to 60 or 90 days) between prescriptions was assessed in both CPRD, BIFAP and Denmark. Results showed that using a more strict definition resulted in point estimates going marginally up in CPRD and going down in BIFAP, giving stronger effects in both data sources. Being more lenient with respect to the permissible gap resulted in HRs going toward unity in CPRD and going to 1.10 in BIFAP. Impact on estimates in Denmark were minimal compared to the main definition. Second, restriction of our study populations to those patients not having any other indications for VKA or DOAC use than atrial fibrillation did not yield different results in all four data sources. Third, as our primary outcome of any major bleeding also included haematuria, epistaxis and a number of other bleedings one can argue whether they constitute genuinely major bleeding events, we conducted two additional

analysis. First in CPRD, we excluded haematuria from the any bleeding outcome definition, leading to lower number of events and incidence rates of major bleeding, this had no effect on the adjusted HR (adjusted HR 1.11 vs 1.13 in the main analysis). In all data sources, the post-hoc redefinition of major bleeding lead to essentially retaining the GI and intracranial bleeding events with risk estimates reflective of those results (data not shown).

Fourth, as AOK NORDWEST uses hospital admission data for assessment of outcomes, a sensitivity analysis was performed within CPRD using events from hospital admission data (HES), rather than recorded primary care data. The adjusted HR for HES-events in CPRD was 1.14 (95% CI 0.96-1.35), thus similar to the results obtained using all primary care records. The same was true for GI-bleeding events in HES, with the adjusted HR going to 1.33 from the original 1.40. In contrast, results for stroke/TIA yielded a lower, but still statistically increased adjusted HR for DOACs vs VKA (adjusted HR 1.46, 95% CI: 1.08-1.96) compared to the main analysis, with rivaroxaban (adjusted HR 1.50, 95% CI: 1.02-2.22) and especially apixaban (adjusted HR 2.28, 95% CI: 1.38-3.77) driving this effect. Fifth, in BIFAP, similar sensitivity analyses were conducted involving manual review of clinical records for both GI bleeding and stroke. It was found that when restricting the analysis to hospitalized GI bleedings only (defined as any record of a discharge letter, admission or transfusion at the index date or two months after with subsequent manual review and retaining 39.5% of all major bleeding events) the adjusted HR lowered to 1.13 (95% CI: 0.83-1.56) as compared to the adjusted HR of 1.35 when using all bleeding events. Confirmed stroke cases (52.2% of all events used in the main analysis) were defined as events as being mentioned in a discharge letter or in the GP's free text comments. Restricting outcomes to confirmed cases yielded an adjusted HR for current DOAC use vs. VKA of 1.03 (95%CI: 0.80-1.31), thus lowering the HR from 1.80.

Following earlier suggestions, several post-hoc analyses were conducted prevent inclusion of bleeding events that in daily clinical practice are not likely to be really major, such as hematuria and epitaxis. In CPRD, this approach resulted in an adjusted HR of 1.43 for DOACs vs. VKA, (n=209 events vs. 509 events in the primary analysis), resembling the effect observed for GI bleeding individually as this was now the most frequently occurring type of major bleeding event (80.4% of all bleeding events compared to 33.0% of all events in the main analysis). Furthermore, we adjusted the definition of stroke events by excluding all TIAs from the definition in all data sources. Of the 205 events in the initial analysis for stroke/TIA in CPRD, 91 events remained, but this had no effect on the risk estimates obtained (adjusted HR 1.74, 95% CI: 1.36-2.22), with similar risks for individual DOACs. In the other data sources there was no difference in risk estimates well.

10.4.2. Objective 2

10.4.2.1. Incidence

During this period overall DOAC use increased, and the individual DOAC with the highest increase was apixaban followed by rivaroxaban (figure 1). Apixaban displayed the highest standardized incidence percentage change from the first to the last calendar year of use after NVAf indication approval (554.5%) followed by rivaroxaban (80.7%). For 2013-2012 it was highest in EGB (10,550.0) and lowest in Bavarian (218.61) while the values for 2015-2014 were highest in Mondriaan (868.5) and lowest in SIDIAP (35.1). Dabigatran had a negative percentage change in all databases for 2013-2012 (max in EGB and min SIDIAP) except in CPRD and Bavarian CD. Almost the same pattern was observed for 2015-2014 except in CPRD and Mondriaan that had a percentage increase. Rivaroxaban percentage change increased in all databases except in EGB (2013-2012) but also decreased in the two German databases in 2015-2014, being the highest change in the CPRD (120.9%)(Table 10). Incidence values before these dates are scarce in all databases and percentage changes were not calculated.

The standardized figures (Figure 2) show that the incidence of dabigatran increased in all databases up to 2012 when it showed the maximum value in the NRD (15.5 new users per 10,000) except for CPRD and Mondriaan that increased slightly at the end of the study period. The apixaban standardized incidence also increased across the study period in all databases. The maximum value was observed in the NRD database in 2015 (13.6) new users per 10,000). The Bavarian CD database presented the rivaroxaban highest standardized incidence in 2013 (17.6 new users per 10,000) and Mondriaan database the lowest incidence values in 2012 (0.03 new users per 10,000). In 2015 SIDIAP was the database with the lowest incidence of rivaroxaban (3.61 users per 10,000). Figure 3. shows the incidence data for each database and per year for the whole study period.

In 2015, the incidence of DOAC use ranged from 8.5 per 10,000 in Spain (SIDIAP) to 27.6 per 10,000 in Denmark (DK) (Table 11) with a higher incidence in men than in women.

Figure 1. Distribution of the total DOAC crude incidence 2011-2015

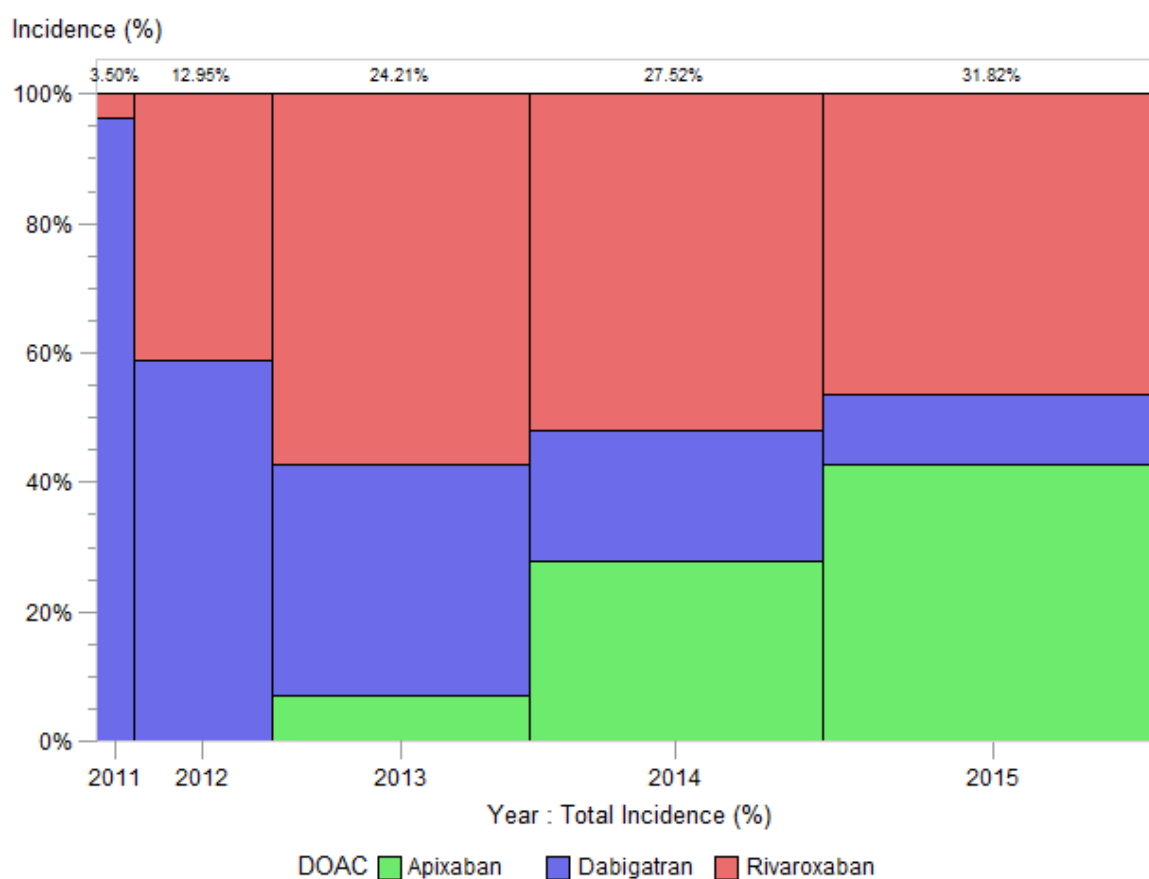


Table 10. Standardized incidence percentage change in DOAC new users with a diagnosis of NVAf in the time periods 2013-2012 and 2015-2014

	Incidence percentage change 2013-2012*			Incidence percentage change 2015-2014		
	Dabigatran (%)	Apixaban** (%)	Rivaroxaban (%)	Dabigatran (%)	Apixaban (%)	Rivaroxaban (%)
Netherlands (Mondriaan)	-22.93	833.97	2397.26	32.54	868.50	63.36
Denmark (NPR)	-4.58	268.27	266.94	-63.54	60.94	42.41
Germany (AOK)	-8.04	313.13	98.40	-35.54	80.03	-12.89
Germany (BAVARIAN)	18.43	218.61	67.96	-41.56	47.54	-24.18
Spain (BIFAP)	-15.02	712.82	227.42	-6.08	52.37	12.50
Spain (SIDIAP)	-7.13	462.60	247.88	-5.80	35.13	27.75
United Kingdom (CPRD)	80.98	774.46	732.89	3.55	180.91	120.90
France (EGB)	-69.55	10550.0	-32.33	-56.37	162.44	-16.21

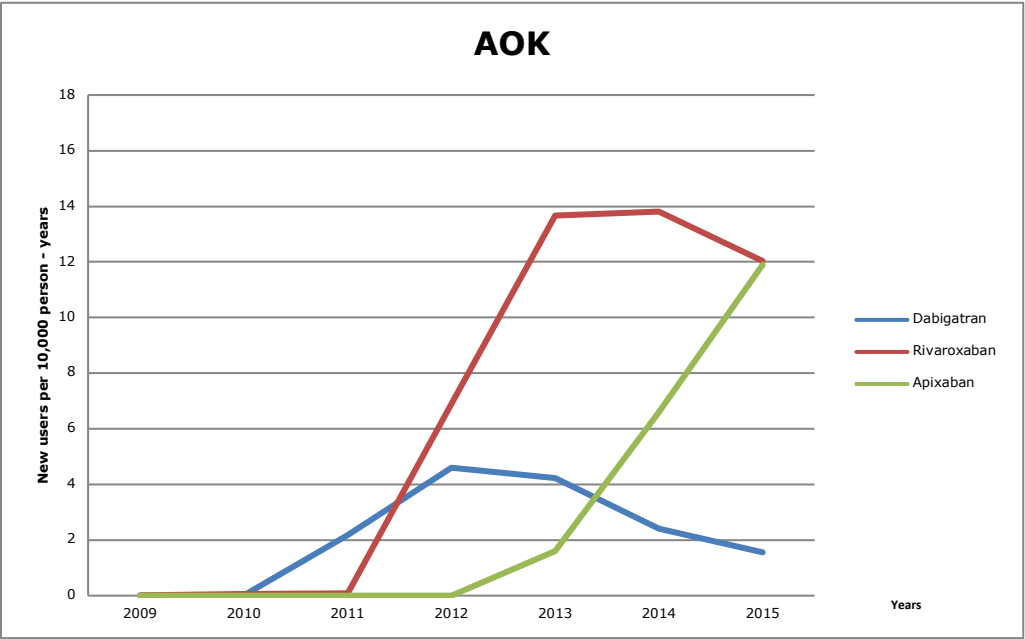
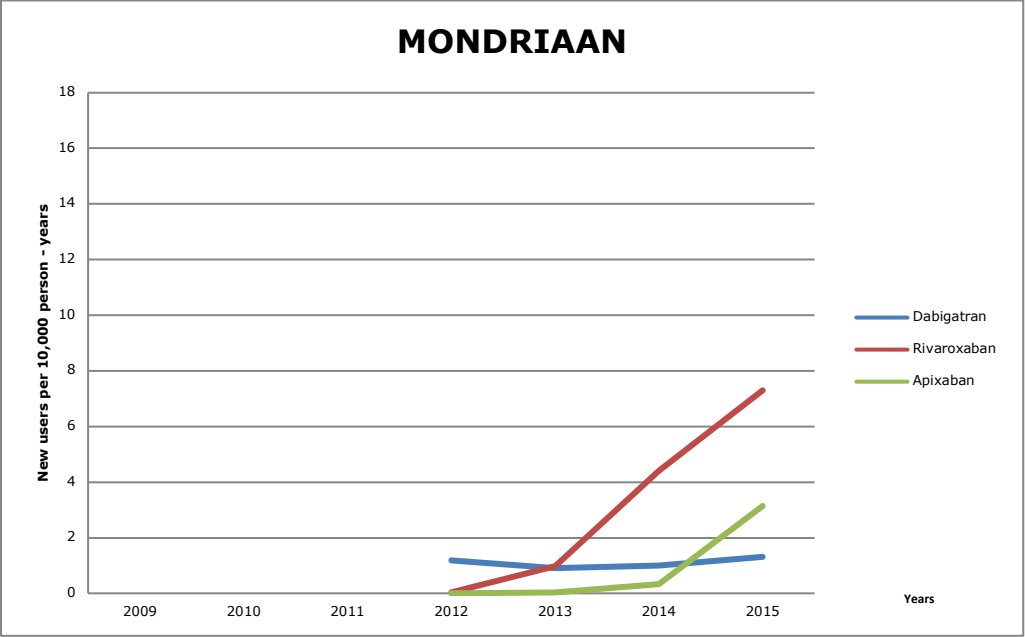
*Data for each DOAC are calculated for 2013-2014 in EGB

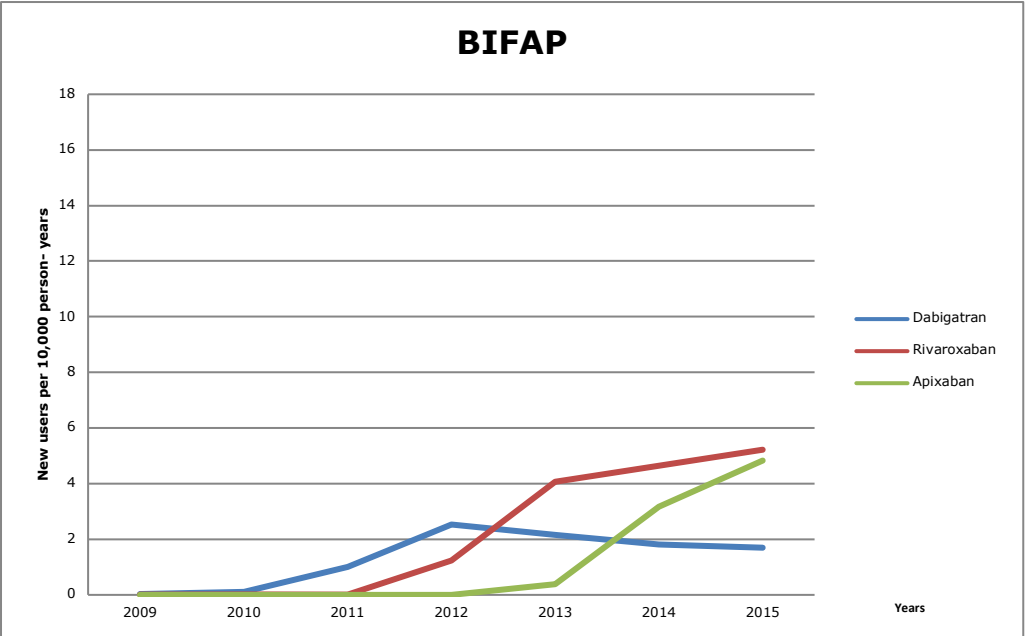
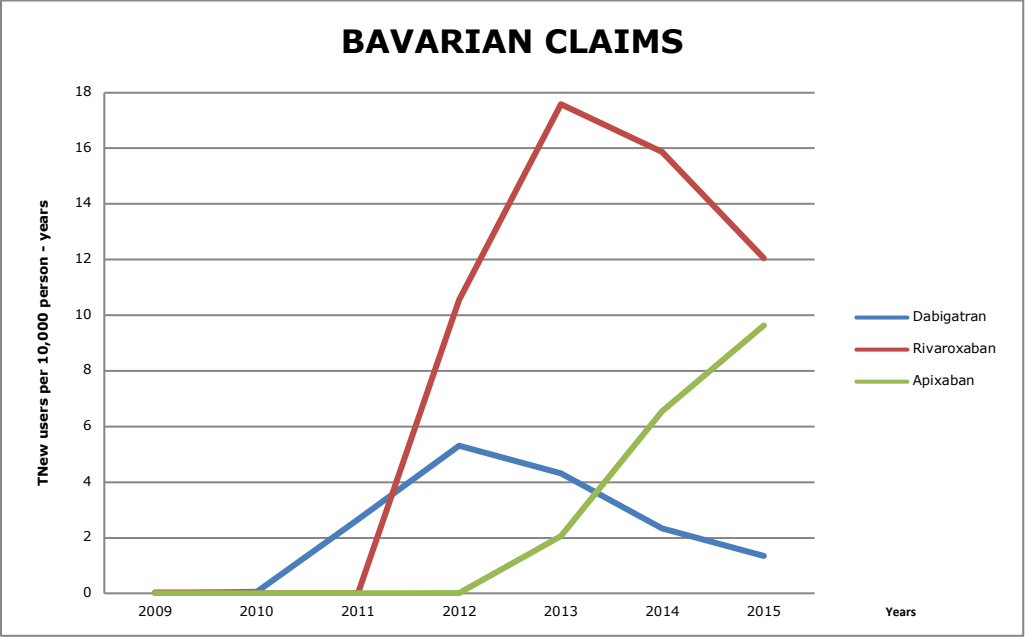
**Data for Apixaban are calculated for 2013-2014 in all databases

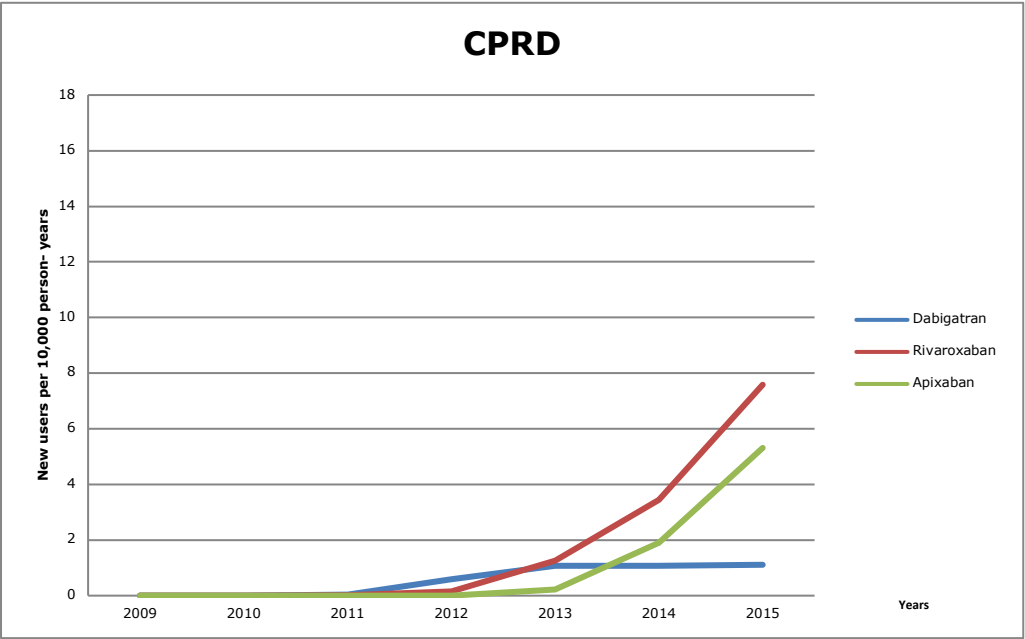
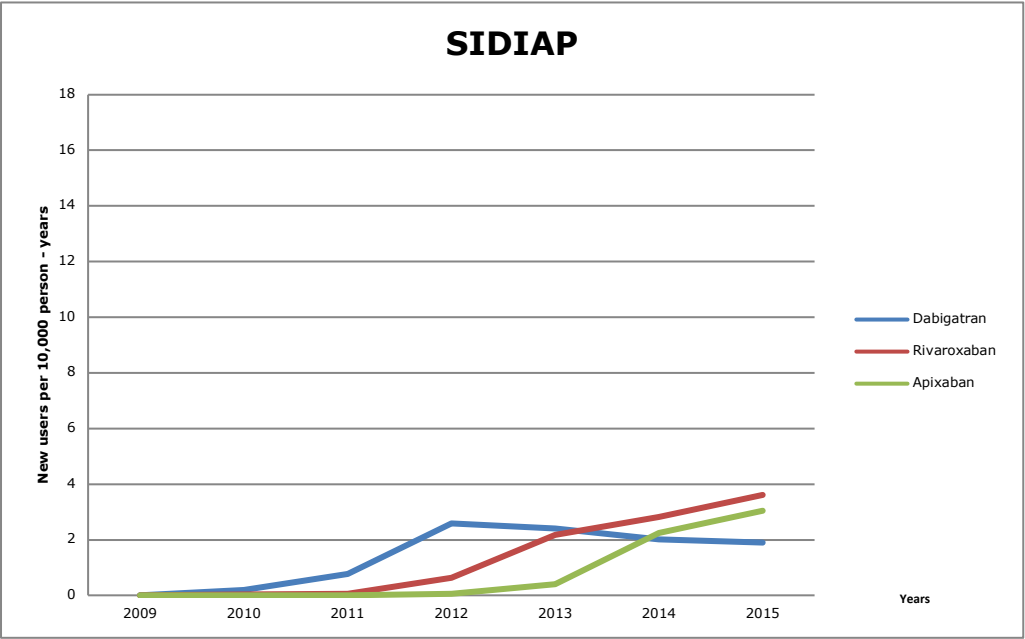
Table 11. Standardised incidences for all DOACs and database (new users per 10000 person-years)

	2008	2009	2010	2011	2012	2013	2014	2015
Netherlands (Mondriaan)					1.21	1.91	5.73	11.75
Germany (AOK NORDWEST)	0.00	0.01	0.08	2.28	11.49	19.56	22.86	25.49
Germany (BAVARIAN CLAIMS)	0.00	0.05	0.10	2.81	15.74	23.88	24.65	22.95
Spain (BIFAP)	0.00	0.04	0.12	1.01	3.77	6.60	9.62	11.75
Spain (SIDIAP)	0.00	0.00	0.22	0.80	3.21	4.96	7.10	8.55
United Kingdom (CPRD)	0.00	0.00	0.04	0.74	2.55	2.55	6.40	14.01
France (EGB)						17.03	11.13	12.32
Denmark (NRD)	0.00	0.14	0.32	7.83	17.41	24.08	26.61	27.56

Figure 2. Standardized incidences by individual DOAC in each database







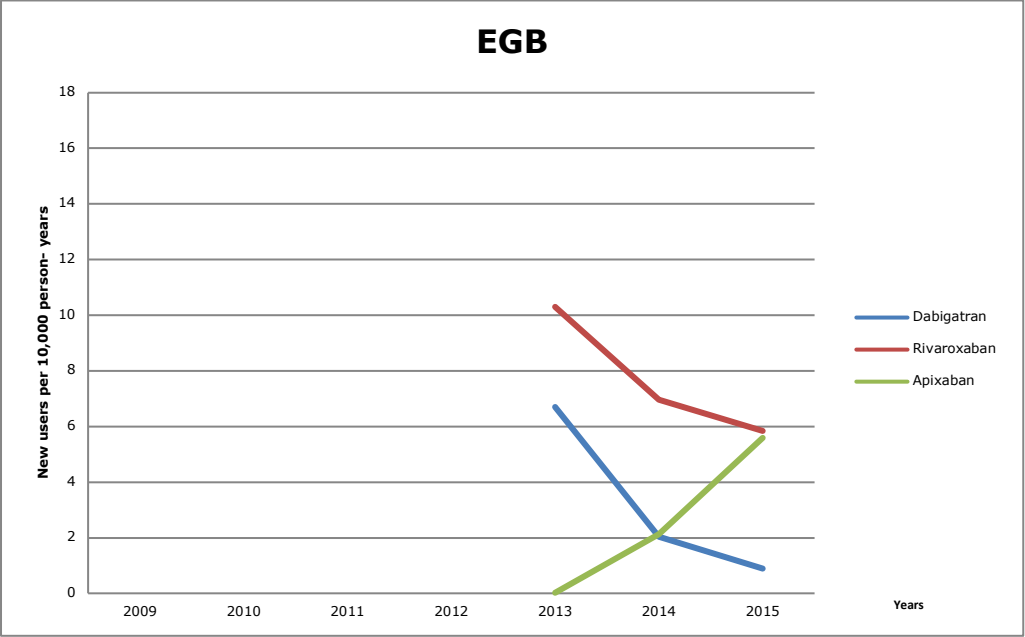
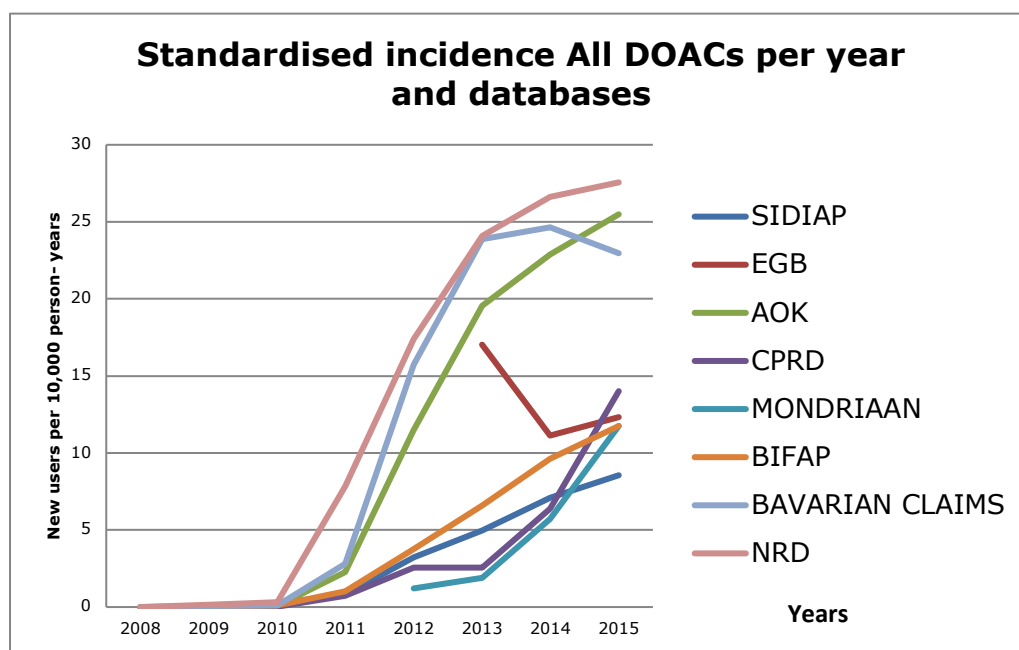


Figure 3. Standardised incidence for all DOACs in each database and all study period



10.4.2.2. Renal function and dose adjustment

Data on laboratory values of renal function was scarce and when available the proportion of missing/not registered information was usually high (range: 3.4% in CPRD to 77.9% in BIFAP, see Table 12). Chronic kidney disease identified through diagnosis codes ranged from 0% of patients in the Mondriaan to 24.1% in the BAVARIAN databases. The registry of laboratory values in Mondriaan, BIFAP, SIDIAP and CPRD identified patients with moderately reduced kidney function from 3.0% of patients in Mondriaan to 22.6% in CPRD. Patients with severely or very severely reduced renal function were very uncommon in these databases. SIDIAP and CPRD that have information on both sources of renal alteration showed discrepant results. The most frequent category in all databases that had this information was "normal-moderate reduced". The proportion of patients with a chronic kidney disease code by individual DOAC is similar to that for all DOAC.

The information on dose adjustment was available in BIFAP, SIDIAP, CPRD and EGB, the proportions varied from 4.6% in BIFAP to 15.6% in EGB. The proportion of dose adjustment related to change in renal function or to change in age was less of 1% in the three databases where this information was available (BIFAP, SIDIAP and CPRD). In the Mondriaan database there were no dose changes recorded. AOK NORDWEST and the Bavarian databases do not have this information registered.

Table 12. Renal function at baseline and dose adjustment: all DOAC and individual DOAC

	Netherlands (Mondriaan)		Denmark (NRD)		Germany (AOK NORTHWEST)		Germany (Bavarian claims)		Spain (BIFAP)		Spain (SIDIAP)		United Kingdom (CPRD)		France (EGB)	
All DOACs	460		44876		21718		84276		14161		11962		6931		2021	
	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)
Chronic kidney disease (by Diagnosis codes)	0	0.0	2055	4.6	4377	20.1	20287	24.1	226	1.6	509	4.3%	309	4.5	58	2.9
Chronic kidney disease (by lab values)			NA	NA	NA	NA	NA	NA							NA	NA
Normal (>80 ml/min)	69	15.0	NA	NA	NA	NA	NA	NA	NA	NA	1881	15.7	1352	19.5	NA	NA
Normal – mildly reduced (CrCl 50-80 ml/min)	110	23.9	NA	NA	NA	NA	NA	NA	NA	NA	2313	19.3	3727	53.8	NA	NA
Moderately reduced (CrCl 30-49 ml/min)	14	3.0	NA	NA	NA	NA	NA	NA	NA	NA	1121	9.4	1565	22.6	NA	NA
Severely reduced (CrCl 15-29 ml/min)	0	0.0	NA	NA	NA	NA	NA	NA	47	0.3	206	1.7	49	0.7	NA	NA
Very severely reduced (CrCl <15 ml/min)	0	0.0	NA	NA	NA	NA	NA	NA	8	0.1	3	0.0	2	0.0	NA	NA
Missing	267	58.0	NA	NA	NA	NA	NA	NA	11033	77.9	6438	53.8	236	3.4	NA	NA
Total dose adjustments*	0	0.0	NA	NA	NA	NA	NA	NA	648	4.6	698	5.8	499	7.2	315	15.6
Related to change in renal function			NA	NA	NA	NA	NA	NA	9	0.1	26	0.2	63	0.9	NA	NA
Related to change in age			NA	NA	NA	NA	NA	NA	109	0.8	31	0.3	4	0.1	NA	NA
Dabigatran	99 (21.5%)		23308 (51.9%)		3968 (18.3%)		14729 (17.5%)		3863 (27.3%)		4784 (40%)		1265 (18.3%)		479 (23.7%)	
Chronic kidney disease (by Diagnosis codes)*	0	0.0	769	3.3	680	17.1	3156	21.4	56	1.4	161	3.4	33	2.0	17	3.5
Chronic kidney disease (by lab values)			NA	NA	NA	NA	NA	NA	NA	NA					NA	NA
Normal (>80 ml/min)	22	22.2	NA	NA	NA	NA	NA	NA	NA	NA	771	16.1	264	20.9	NA	NA
Normal – mildly reduced (CrCl 50-80 ml/min)	24	24.2	NA	NA	NA	NA	NA	NA	NA	NA	909	19.0	691	54.6	NA	NA
Moderately reduced (CrCl 30-49 ml/min)	2	2.0	NA	NA	NA	NA	NA	NA	NA	NA	339	7.1	259	20.5	NA	NA
Severely reduced (CrCl 15-29 ml/min)	0	0.0	NA	NA	NA	NA	NA	NA	7	0.2	44	0.9	1	0.1	NA	NA
Very severely reduced (CrCl <15 ml/min)	0	0.0	NA	NA	NA	NA	NA	NA	3	0.1	1	0.0	0	0.0	NA	NA
Missing	51	51.5	NA	NA	NA	NA	NA	NA	3013	78.0	2720	56.9	50	4.0	NA	NA
Total dose adjustments	0	0.0	NA	NA	NA	NA	NA	NA	218	5.6	322	6.7	89	7.0	68	21.6
Related to change in renal function	0	0.0	NA	NA	NA	NA	NA	NA	4	0.1	6	0.1	5	0.4	NA	NA
Related to change in age	0	0.0	NA	NA	NA	NA	NA	NA	39	1.0	16	0.3	0	0	NA	NA
Apixaban	72 (15.7%)		10358 (23.1%)		5460 (25.1%)		17339 (20.6%)		3693 (26.1%)		2728 (22.8%)		2060 (29.7%)		396 (19.6)	
Chronic kidney disease (by Diagnosis codes)*	0	0.0	666	6.4	1210	22.2	4765	27.5	76	2.1	141	5.2	84	4.1	9	2.3
Chronic kidney disease (by lab values)			NA	NA	NA	NA	NA	NA							NA	NA
	Netherlands (Mondriaan)		Denmark (NRD)		Germany (AOK)		Germany (Bavarian)		Spain (BIFAP)		Spain (SIDIAP)		United Kingdom		France (EGB)	

					NORTHWEST		claims)						(CPRD)			
	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)
Normal (>80 ml/min)	7	9.7	NA	NA	NA	NA	NA	NA	NA	NA	394	14.4	136	6.6	NA	NA
Normal – mildly reduced (CrCl 50-80 ml/min)	24	33.3	NA	NA	NA	NA	NA	NA	NA	NA	559	20.5	510	24.8	NA	NA
Moderately reduced (CrCl 30-49 ml/min)	2	2.8	NA	NA	NA	NA	NA	NA	NA	NA	368	13.5	494	24.0	NA	NA
Severely reduced (CrCl 15-29 ml/min)	0	0.0	NA	NA	NA	NA	NA	NA	20	0.5	75	2.7	44	2.1	NA	NA
Very severely reduced (CrCl <15 ml/min)	0	0.0	NA	NA	NA	NA	NA	NA	1	0.0	2	0.1	0	0.0	NA	NA
Missing	46	63.9	NA	NA	NA	NA	NA	NA	2830	76.6	1330	48.8	24	1.2	NA	NA
Total dose adjustments	0	0.0	NA	NA	NA	NA	NA	NA	125	3.4	104	3.8	100	4.9	38	12.1
Related to change in renal function	0	0.0	NA	NA	NA	NA	NA	NA	1	0.0	7	0.3	14	0.7	NA	NA
Related to change in age	0	0.0	NA	NA	NA	NA	NA	NA	12	0.3	6	0.2	0	0	NA	NA
Rivaroxaban	289	(62.8%)	11210	(25.0%)	12290	(56.6%)	52208	(61.9%)	6605	(46.6%)	4450	(37.2%)	3606	(52.0%)	1146	(56.7%)
Chronic kidney disease (by Diagnosis codes)*	0	0.0	620	5.5	2487	20.2	12366	23.7	94	1.4	207	4.6	192	5.3	32	2.8
Chronic kidney disease (by lab values)			NA	NA	NA	NA	NA	NA							NA	NA
Normal (>80 ml/min)	40	13.8	NA	NA	NA	NA	NA	NA	NA	NA	716	16.1	689	19.1	NA	NA
Normal – mildly reduced (CrCl 50-80 ml/min)	62	21.5	NA	NA	NA	NA	NA	NA	NA	NA	845	19.0	1955	54.2	NA	NA
Moderately reduced (CrCl 30-49 ml/min)	10	3.5	NA	NA	NA	NA	NA	NA	NA	NA	414	9.3	816	22.6	NA	NA
Severely reduced (CrCl 15-29 ml/min)	0	0.0	NA	NA	NA	NA	NA	NA	20	0.3	87	2.0	24	0.7	NA	NA
Very severely reduced (CrCl <15 ml/min)	0	0.0	NA	NA	NA	NA	NA	NA	4	0.1	0	0.0	2	0.1	NA	NA
Missing	177	61.2	NA	NA	NA	NA	NA	NA	5190	78.6	2388	53.7	120	3.3	NA	NA
Total dose adjustments	0	0.0	NA	NA	NA	NA	NA	NA	341	5.2	272	6.1	310	8.6	209	66.3
Related to change in renal function	0	0.0	NA	NA	NA	NA	NA	NA	4	0.1	13	0.3	44	1.2	NA	NA
Related to change in age	0	0.0	NA	NA	NA	NA	NA	NA	58	0.9	9	0.2	0	0.0	NA	NA

10.4.2.3. Concomitant interacting drugs

The proportion of patients who have received a concomitant interacting drug at baseline and during the follow up ranged from 16.4 % in SIDIAP to 70.5 % in EGB database (see Table 13).

Concomitant use of contraindicated anticoagulants varied between 0.4% (CPRD), and 24.3% (EGB). NSAIDs varied from 4.3% (Mondriaan) to 26.0% (Bavarian CD) and antiplatelet drugs from 1% in SIDIAP to 18.1% in EGB respectively. The most frequent concomitant interacting drugs were heparins in AOK, BIFAP, Bavarian CD databases (8.4%, 10.44%, 12.0% respectively), amiodarone in EGB, NRD, and SIDIAP (42.2%, 6.2%, 5.7% respectively) and verapamil in Mondriaan (4.1%). Among selective serotonin reuptake inhibitors, potential interacting drugs only for dabigatran, the highest proportion was observed in the CPRD and NRD (9.1% and 5.3% respectively). There were some differences between databases in the same country, in Spain, between SIDIAP (16%) and BIFAP (48%).

The figures for the proportion of patients using concomitant interacting drugs for each individual DOAC are quite similar to those of all DOACs. Dabigatran was the DOAC with the highest proportion of concomitant interacting drugs ranging from 21.2% in Mondriaan to 76.0% in EGB. Apixaban was the DOAC with the lowest proportion, ranging from 10.7% in SIDIAP to 64.9% in EGB.

Not many differences are seen in the figures either in the most frequent group or the most frequent drug concomitantly used across the individual DOAC compared to all DOACs.

10.4.2.4. Switchers and discontinuers all DOAC

Information about switching and discontinuing can be found in Table 14. The highest percentage of all DOAC switchers was observed in the AOK NORTHWEST database (16%) and the lowest one in the Mondriaan database (2.4%). The cumulative percentage of all DOAC switchers at 12 months ranges from 2.4% in Mondriaan to 13.1% in the EGB databases. The highest percentage of switchers was observed for dabigatran in the AOK NORTHWEST database (28.4%) and the lowest one for rivaroxaban in the Mondriaan database (1.4%). The cumulative percentage of switchers at 12 months ranged for dabigatran from 5.0% in Mondriaan to 20% in EGB.

Dabigatran is the DOAC with the highest percentage of discontinuers in all databases except in the Bavarian where rivaroxaban had the highest proportion of discontinuers. The highest percentage of all DOAC discontinuers was observed in the Bavarian CD (79.4%) and the lowest one in the CPRD database (17.7%). The cumulative percentage of all DOAC discontinuers at 12 months ranged from 16% in the CPRD databases to 63.9% in Bavarian CD. The highest percentage of discontinuers was observed for rivaroxaban in the Bavarian CD (81.8%) and the lowest for apixaban in the Mondriaan database (12.9%). The cumulative percentage of discontinuers ranged from 12.3% for apixaban in CPRD to 68.2% for rivaroxban in Bavarian CD.

The mean treatment duration was quite similar when comparing databases except in the Mondriaan database where the mean treatment duration was lower (118.9 days SD 139.6 for apixaban to 179 SD 224.2 for dabigatran). In the rest of databases dabigatran in SIDIAP had the highest mean treatment time (443.1 days SD 438.4) and apixaban in EGB had the lowest one (199.8 days SD 157.1). In all databases apixaban had the lowest mean duration time.

In the sensitivity analysis taking into account a permissible gap of 60 days the percentage of discontinuers decreased ranging from 11.2% in the CPRD database to 34.1% in the SIDIAP database.

Table 13. Concomitant treatment at baseline and during follow up: all DOAC, and individual DOAC.

	Netherlands (Mondriaan)		Denmark (NRD)		Germany (AOK NORDWEST)		Germany (Bavarian claims)		Spain (BIFAP)		Spain (SIDIAP)		United Kingdom (CPRD)		France (EGB)	
All DOACs	460		44876		21718		84459		14161		11962		6931		2021	
	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)
CONCOMITANT MEDICATION (potential interacting medicine products)	94	20.4	17456	38.9	10585	48.7	44394	52.7	6781	47.9	1963	16,4	1785	25.8	1425	70.5
Concomitant treatment with any other anticoagulants (contraindicated)	21	4.6	474	1.0	3730	17.2	17153	20.4	1425	10.1	355	3.0	29	0.4	492	24.3
Most frequent drug	Vitamin K antagonists	3.9	Vitamin K antagonists	0.6	Heparin group	8.4	Heparin group	12.0	Heparin group	10.4	Heparin group	2.9	Vitamin K antagonists	0.4	Heparin group	12.2
Platelet aggregation inhibitors excl. heparin	23	5.0	6455	14.4	2140	9.9	9298	11.0	1859	13.1	123	1.0	849	12.2	365	18.1
Strong CYP3A4 and/or P-gp inhibitor co-medication	0	0.0	230	0.5	329	1.5	1746	2.0	282	2.0	107	0.9	29	0.4	3	0.1
Most frequent drug			Dronedarone	0.3	Dronedarone	1.3	Dronedarone	1.9	Dronedarone	1.6	Dronedarone	0.8	Dronedarone	0.4	Cyclosporine	0.1
Not strong CYP3A4 and/or P-gp inhibitors	30	6.5	5473	7.3	2203	10.1	8172	9.7	1592	11.2	712	5.9	623	9.0	900	44.5
Most frequent drug	Verapamil	4.1	Amiodarone	6.2	Amiodarone	6.7	Amiodarone	6.5	Amiodarone	8.8	Amiodarone	5.7	Amiodarone	6.4	Amiodarone	42.2
CYP3A4 and/or P-gp inducers	1	0.2	194	0.4	189	0.9	556	0.7	80	0.5	26	0.2	36	0.5	5	0.2
Most frequent drug	Carbamazepine	0.2	Carbamazepine	0.3	Carbamazepine	0.7	Carbamazepine	0.5	Carbamazepine	0.2	Rifampicin	0.1	Phenytoin	0.3	Rifampicin / Carbamazepine	0.1
Transporter interaction: CYP3A4 and/or P-gp	8	1.7	456	1.0	123	0.6	160	0.2	139	0.1	58	0.5	10	0.1	21	1.0
Most frequent drug	Naproxen	1.3	Fluconazole	0.7	Naproxen	0.3	Naproxen	0.1	Naproxen	0.5	Naproxen	0.3	Naproxen	0.2	Fluconazole	0.6
Non steroidal antiinflammatory drug (NSAID)	20	4.3	5878	13.1	5319	24.5	21935	26.0	3337	23.6	696	5.8	313	4.5	308	15.2
Other drugs (only for dabigatran)	9	2.0	2704	6.0	361	4.5	1417	1.7	507	3.6	257	2.1	700	10.1	47	2.3
	Netherlands (Mondriaan)		Denmark (NRD)		Germany (AOK NORDWEST)		Germany (Bavarian claims)		Spain (BIFAP)		Spain (SIDIAP)		United Kingdom (CPRD)		France (EGB)	
	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)
Selective serotonin reuptake inhibitors (SSRIs)	3	0.7	2380	5.3	304	1.4	1145	1.4	411	2.9	210	1.8	629	9.1	39	1.9
Serotonin-norepinephrine reuptake inhibitors	6	1.3	406	0.9	63	0.3	346	0.4	126	0.9	64	0.5	83	1,2	10	0.5

(SNRIs)																
DABIGATRAN	99		23308		3968		14729		3863		4784		1265		479	
CONCOMITANT MEDICATION (potential interacting medicine products)	21	21.2	10994	47.2	2381	60.0	9446	64.1	2128	55.1	1035	21.6	462	36.5	364	76.0
Concomitant treatment with any other anticoagulants (contraindicated)	4	4.0	271	1.2	997	25.1	3758	25.5	444	11.5	178	3.7	15	1.2	156	32.6
Most frequent drug	Vitamin K antagonists	4.0	Vitamin K antagonists	0.7	Heparin group	11.5	Heparin group	15.0	Heparin group	11.4	Heparin group	3.7	Vitamin K antagonists	0.9	Heparin group	12.3
Platelet aggregation inhibitors excl. heparin	6	6.1	4086	17.5	436	11.0	1874	12.7	506	13.1	52	1.1	194	15.3	101	21.1
Strong CYP3A4 and/or P-gp inhibitor co-medication	0	0.0	154	0.7	65	1.6	386	2.6	87	2.2	52	1.1	6	0.5	1	0.2
Most frequent drug			Dronedarone	0.4	Dronedarone	1.4	Dronedarone	2.5	Dronedarone	1.8	Dronedarone	0.9	Dronedarone	0.5	Cyclosporine	0.2
Not strong CYP3A4 and/or P-gp inhibitors	5	5.0	3406	14.6	528	13.3	1810	12.3	525	13.6	330	6.9	184	14.5	228	47.6
Most frequent drug	Verapamil	3.0	Amiodarone	7.1	Amiodarone	6.6	Amiodarone	7.1	Amiodarone	10.3	Amiodarone	6.4	Amiodarone	7.7	Amiodarone	44.9
CYP3A4 and/or P-gp inducers	0	0.0	99	0.4	52	1.3	96	0.7	28	0.7	15	0.3	3	0.2	2	0.4
Most frequent drug			Carbamazepine	0.3	Carbamazepine	1	Carbamazepine	0.5	Phenytoin	0.3	Rifampicin	0.2	Phenytoin	2 (0.2%)	Rifampicin / Carbamazepine	0.1
Transporter interaction: CYP3A4 and/or P-gp	NA		NA		NA		NA o 0		NA		NA		NA		NA	
Non steroidal antiinflammatory drug (NSAID)	5	5.0	3571	15.3	1166	29.4	4849	33.0	978	25.3	364	7.8	72	5.7	64	13.4
Other drugs (only for dabigatran)	9	9.0	2704	11.6	361	9.1	1417	9.6	507	13.1	257	5.4	117	9.2	47	9.8

	Netherlands (Mondriaan)		Denmark (DNR)		Germany (AOK NORDWEST)		Germany (Bavarian claims)		Spain (BIFAP)		Spain (SIDIAP)		United Kingdom (CPRD)		France (EGB)	
	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)
Selective serotonin reuptake inhibitors (SSRIs)	3	3.0	2380	10.2	304	7.7	1145	7.8	411	10.6	210	4.4	108	8.5	39	8.1
Serotonin-norepinephrine reuptake inhibitors (SNRIs)	6	6.01	406	1.7	63	1.6	346	2.3	126	3.3	64	1.3	10	0.8	10	2.1
APIXABAN	72		10358		5460		17339		3693		2728		2060		396	
CONCOMITANT MEDICATION (potential interacting medicine products)	8	11.1	2824	27.3	2074	38.0	8102	46.8	1582	42.8	293	10.7	462	22.4	257	64.9
Concomitant treatment with any other anticoagulants (contraindicated)	2	2.7	66	0.6	544	10.0	2803	16.2	318	8.6	57	2.1	2	0.1	56	14.4
Most frequent drug	Vitamin K antagonists / Heparin group	1.4	Vitamin K antagonists	0.4	Heparin group	4.9	Heparin group	10.2	Heparin group	8.6	Heparin group	2.0	Vitamin K antagonists	0.1	Heparin group	9.3
Platelet aggregation inhibitors excl. heparin	2	2.8	1011	9.8	433	7.9	2094	12.0	454	12.3	20	0.7	224	10.9	57	14.4
Strong CYP3A4 and/or P-gp inhibitor co-medication	0	0.0	33	0.3	56	1.0	309	1.8	68	1.8	16	0.6	11	0.5	2	0.5
Most frequent drug			Itraconazole	0.2	Dronedarone	0.9	Dronedarone	1.6	Dronedarone	1.5	Dronedarone	0.5	Dronedarone	0.5	Cyclosporin	0.5
Not strong CYP3A4 and/or P-gp inhibitors	4	5.5	1058	10.2	452	8.3	1507	8.7	375	10.1	139	5.1	176	8.5	204	51.5
Most frequent drug	Verapamil / Amiodarone	2.7	Amiodarone	6.0	Amiodarone	6.1	Amiodarone	6.3	Amiodarone	7.8	Amiodarone	5.0	Amiodarone	7.0	Amiodarone	49.5
CYP3A4 and/or P-gp inducers	0	0.0	34	0.3	32	0.6	102	0.6	16	0.4	4	0.1	10	0.5	1	0.2
Most frequent drug			Carbamazepine	0.3	Carbamazepine	0.5	Carbamazepine	0.4	Carbamazepine	0.2	Carbamazepine / phenytoin	0.1	Carbamazepine	0.2	Carbamazepine	0.2
Transporter interaction: CYP3A4 and/or P-gp	0	0.0	61	0.6	56	1.0	118	0.7	65	1.8	32	1.2	42	2.0	5	1.3
Most frequent drug			Naproxen	0.6	Naproxen	1.0	Naproxen	0.7	Naproxen	1.8	32	1.2	Naproxen	2.0	Naproxen	1.3
Non steroidal antiinflammatory drug (NSAID)	2	2.8	987	9.5	1024	18.5	3616	20.9	753	20.4	93	3.4	85	4.1	45	11.4

	Netherlands (Mondriaan)		Denmark (DNR)		Germany (AOK NORDWEST)		Germany (Bavarian claims)		Spain (BIFAP)		Spain (SIDIAP)		United Kingdom (CPRD)		France (EGB)	
	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)
RIVAROXABAN	289		11210		12290		52208		6605		4450		3606		1146	
CONCOMITANT MEDICATION (potential interacting medicine products)	65	22.5	3638	32.4	6130	49.9	26846	51.4	3071	47.5	635	14.3	861	23.9	804	70.2
Concomitant treatment with any other anticoagulants (contraindicated)	15	5.2	137	1.2	2189	17.8	10592	20.3	663	10.4	120	2.7	12	0.3	280	24.4
Most frequent drug	Vitamin K antagonists	4.5	Vitamina K antagonists	0.6	Heparin group	9.0	Vitamin K antagonists	10.6	Heparin group	10.4	Heparin group	2.6	Vitamin K antagonists	0.3	Heparin group	13.1
Platelet aggregation inhibitors excl. heparin	14	4.8	1358	12.1	1271	10.3	5330	10.2	899	13.6	51	1.1	431	12.0	207	18.1
Strong CYP3A4 and/or P-gp inhibitor co- medication	0	0.0	43	0.4	208	1.7	1051	2.0	127	1.9	39	0.9	12	0.3	0	0.0
Most frequent drug			Dronedarone	0.2	Dronedarone	1.5	Dronedarone	1.8	Dronedarone	1.5	Dronedarone	0.7	Dronedarone	0.3		
Not strong CYP3A4 and/or P-gp inhibitors	20	6.9	1009	9.0	1223	9.9	4855	9.3	692	10.5	243	5.5	263	7.3	468	40.8
Most frequent drug	Verapamil	4.5	Amiodarone	4.6	Amiodarone	6.9	Amiodarone	6.4	Amiodarone	8.5	Amiodarone	5.2	Amiodarone	5.7	Amiodarone	38.5
CYP3A4 and/or P- gp inducers	0	0.0	61	0.5	105	0.8	358	0.7	36	0.5	7	0.2	23	0.6	2	0.2
Most frequent drug			Carbamazepine	0.4	Carbamazepine	0.7	Carbamazepine	0.5	Carbamazepine	0.3	Rifampicin	0.1	Phenytoin	0.4	Rifampicin / Phenytoin	0.9
Transporter interaction: CYP3A4 and/or P- gp	3	1.0	395	3.5	199	1.6	42	0.08	74	1.1	26	0.6	80	2.2	16	1.4
Most frequent drug	Fluconazole	0.7	Fluconazole	3.0	Fluconazole	0.4	Erytromycin	0.07	Fluconazole	0.8	Fluconazole	0.5	Erythromycin	1.3	Fluconazole	1.1
Non steroidal antiinflammatory drug (NSAID)	25	8.6	1320	11.8	3129	25.4	13470	25.8	1606	24.3	239	5.4	156	4.3	199	17.4

Table 14. Switchers and discontinuers: all DOAC, by individual DOAC (at 3, 6, 12 months)

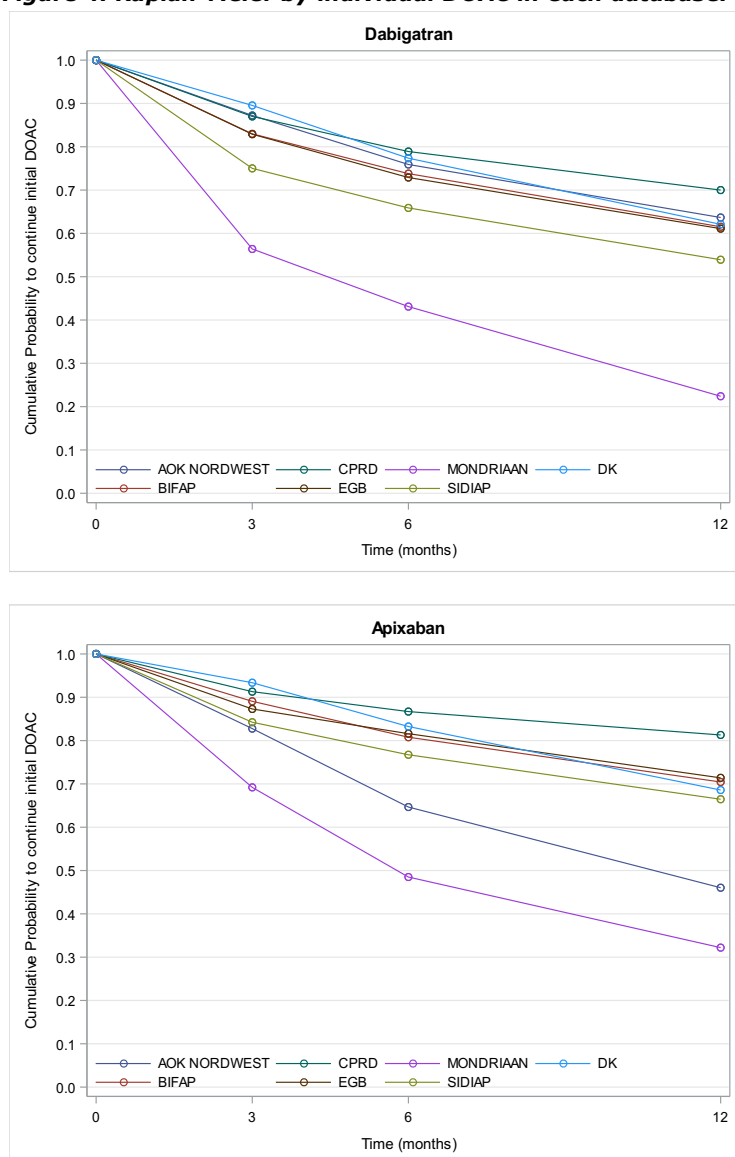
	Netherlands (Mondriaan)	Denmark (NRD)	Germany (AOK NORDWEST)	Germany (Bavarian claims)	Spain (BIFAP)	Spain (SIDIAP)	United Kingdom (CPRD)	France (EGB)
All DOACs	460	44876	21718	84459	14161	11962	6931	2021
Number of switchers related to any DOACs N° (%)	11 (2.4%)	5665 (12.6%)	3491 (16.1%)	11671 (13.8%)	1249 (8.8%)	753 (6.3%)	457 (6.6%)	312 (15.4%)
Switchers at 1-3 months N° (%)	10 (2.2%)	2914 (6.5%)	1217 (5.6%)	84459 (7.2%)	859 (6.1%)	393 (3.3%)	294 (4.2%)	172 (8.5%)
Switchers at 1-6 months N° (%)	10 (2.2%)	3906 (8.7%)	1827 (8.4%)	7442 (8.8%)	1000 (7.1%)	485 (4.0%)	363 (5.2%)	219 (10.8%)
Switchers at 1-12 months N° (%)	11 (2.4%)	4734 (10.5%)	2455 (11.3%)	9289 (11.0%)	1121 (7.9%)	606 (5.1%)	417 (6.0%)	263 (13.1%)
Number of discontinuers related to any DOACs N° (%)	241 (52.4%)	17795 (39.6%)	11170 (51.4%)	66905 (79.4%)	4540 (32.1%)	5451 (45.6%)	1228 (17.7%)	621 (30.7%)
Discontinuers at 1-3 months N° (%)	165 (35.9%)	3678 (8.2%)	3158 (14.5%)	32859 (39.0%)	1809 (12.8%)	2433 (20.3%)	638 (9.2%)	290 (14.3%)
Discontinuers at 1-6 months N° (%)	203 (44.1%)	7731 (12.2%)	5961 (27.4%)	41785 (49.6%)	2680 (18.9%)	3281 (27.4%)	888 (12.8%)	414 (20.5%)
Discontinuers at 1-12 months N° (%)	235 (51.1%)	12316 (27.4%)	8435 (38.8%)	53857 (63.9%)	3612 (25.5%)	4234 (35.4%)	1109 (16.0%)	538 (26.6%)
Dabigatran	99	23308	3968	14769	3863	4784	1265	479
Number of switchers related to Dabigatran N° (%)	5 (5.1%)	3942 (16.9%)	1126 (28.4%)	3907 (26.5%)	488 (12.6%)	457 (9.5%)	183 (14.5%)	120 (25.0%)
Switchers at 1-3 months N° (%)	4 (4.0%)	1854 (7.9%)	351 (8.8%)	1835 (12.4%)	310 (8.0%)	218 (4.5%)	105 (8.3%)	54 (11.3%)
Switchers at 1-6 months N° (%)	4 (4.0%)	2452 (10.9%)	531 (13.4%)	2326 (15.7%)	371 (9.6%)	272 (5.7%)	139 (11.0%)	72 (15.0%)
Switchers at 1-12 months N° (%)	5 (5.0%)	3158 (13.5%)	708 (17.8%)	2906 (19.7%)	422 (10.9%)	352 (7.3%)	161 (12.7%)	96 (20.0%)
Number of discontinuers related to Dabigatran N° (%)	67 (67.7%)	11688 (50.1%)	2387 (60.2%)	10497 (71.3%)	1615 (41.8%)	2798 (58.5%)	353 (27.9%)	184 (38.4%)
Mean treatment duration days (SD)	179.2 (224.2)				397.1 (415.2)	443.1 (438.4)	348.2 (328.5)	360.4 (337.5)
Discontinuers at 1-3 months N° (%)	40 (40.4%)	2335 (10.1%)	485 (12.2%)	3850 (26.1%)	603 (16.0%)	1174 (24.5%)	146 (11.5%)	73 (15.2%)
Discontinuers at 1-6 months N° (%)	50 (50.5%)	4794 (20.6%)	921 (23.2%)	4739 (32.2%)	885 (23.0%)	1574 (32.9%)	225 (17.8%)	111 (23.2%)
Discontinuers at 1-12 months N° (%)	64 (64.6%)	7559 (32.4%)	1368 (34.5%)	6172 (41.9%)	1225 (31.7%)	2053 (42.9%)	294 (23.2%)	151 (31.5%)
Apixaban	72	10358	5460	17405	3693	2728	2060	396
Number of switchers related to Apixaban N° (%)	2 (2.8%)	540 (5.2%)	366 (6.7%)	1015 (5.8%)	197 (5.3%)	75 (2.7%)	58 (2.8%)	27 (6.8%)
Switchers at 1-3 months N° (%)	2 (2.8%)	346 (3.3%)	201 (3.7%)	718 (4.1%)	148 (4.0%)	47 (1.7%)	41 (2.0%)	22 (5.6%)
Switchers at 1-6 months N° (%)	2 (2.8%)	436 (4.2%)	266 (4.9%)	838 (4.8%)	170 (4.6%)	57 (2.1%)	48 (2.3%)	27 (6.8%)
Switchers at 1-12 months N° (%)	2 (2.8%)	514 (5.0%)	337 (6.2%)	971 (5.6%)	191 (5.2%)	67 (2.4%)	54 (2.6%)	27 (6.8%)
Number of discontinuers related to Apixaban N° (%)	31 (12.9%)	2475 (23.9%)	2468 (45.2%)	13691 (79.0%)	846 (23.0%)	848 (31.1%)	269 (13.1%)	76 (19.2%)
Mean treatment duration days (SD)	118.9 (139.6)				236.8 (203.2)	266.3 (214.7)	217.2 (193.9)	199.8 (157.1)
Discontinuers at 1-3 months N° (%)	19 (26.4%)	576 (5.6%)	781 (14.3%)	7410 (42.7%)	357 (10.0%)	409 (15.0%)	152 (7.4%)	44 (11.1%)
Discontinuers at 1-6 months N° (%)	27 (37.5%)	1319 (12.7%)	1525 (27.9%)	9587 (55.3%)	571 (15.5%)	566 (20.7%)	210 (10.2%)	59 (14.9%)
Discontinuers at 1-12 months N° (%)	31 (43.1%)	2079 (20.1%)	2132 (39.0%)	12060 (69.5%)	770 (20.8%)	728 (26.7%)	254 (12.3%)	75 (18.9%)

	Netherlands (Mondriaan)	Denmark (NRD)	Germany (AOK NORDWEST)	Germany (Bavarian claims)	Spain (BIFAP)	Spain (SIDIAP)	United Kingdom (CPRD)	France (EGB)
Rivaroxaban	289	11210	12290	52285	6605	4450	3606	1146
Number of switchers related to Ribaroxavan N° (%)	4 (1.4%)	1183 (10.5%)	1999 (16.3%)	6749 (12.9%)	564 (8.5%)	221 (5.0%)	216 (6.0%)	165 (14.4%)
Switchers at 1-3 months N° (%)	3 (1.1%)	714 (6.4%)	665 (5.4%)	3518 (6.7%)	401 (6.1%)	128 (2.9%)	148 (4.1%)	96 (8.3%)
Switchers at 1-6 months N° (%)	3 (1.1%)	928 (8.3%)	1030 (8.4%)	4278 (8.2%)	459 (7.0%)	156 (3.5%)	176 (4.9%)	120 (10.5%)
Switchers at 1-12 months N° (%)	4 (1.4%)	1062 (9.5%)	1410 (11.5%)	5412 (10.3%)	508 (7.7%)	187 (4.2%)	202 (5.6%)	140 (12.2%)
Number of discontinuers related to any Rivaroxaban N° (%)	143 (51.3%)	3632 (32.4%)	6315 (51.4%)	42717 (81.8%)	2079 (31.5%)	1805 (40.5%)	606 (16.8%)	361 (31.5%)
Mean treatment duration days (SD)	177.7 (199.2)				342.1 (322.4)	339.2 (313.9)	246.7 (235.8)	362.5 (333.2)
Discontinuers at 1-3 months N° (%)	106 (38.0%)	767 (6.8%)	1892 (15.4%)	21599 (41.4%)	849 (13.0%)	850 (19.1%)	340 (9.4%)	173 (15.1%)
Discontinuers at 1-6 months N° (%)	126 (45.2%)	1618 (14.4%)	3515 (28.6%)	27459 (52.6%)	1224 (19.0%)	1141 (25.6%)	453 (12.6%)	244 (21.3%)
Discontinuers at 1-12 months N° (%)	140 (50.2%)	2678 (23.9%)	4935 (40.2%)	35625 (68.2%)	1617 (24.0%)	1453 (32.6%)	561 (15.5%)	312 (27.2%)

10.4.2.5. Kaplan-Meier curves (Available in: AOK NORTHWEST, BIFAP, SIDIAP, CPRD and EGB)

Regarding the Kaplan-Meier figures (Figure 4) for all individual DOACs the CPRD was the database that showed the highest probability of continuing with therapy and the Mondriaan database was the ones that showed the lowest probability. Apixaban had the highest survival probability (at 12months: 0.81 in CPRD to 0.32 in Mondriaan), dabigatran showed the lowest survival probabilities (at 12 months maximum 0.7 in the CPRD; and minimum 0.022 in the Mondriaan). The differences between each individual DOAC curves were statistically significant (log-rank test p values < 0.05) in all databases (Table 15).

Figure 4. Kaplan-Meier by individual DOAC in each database.



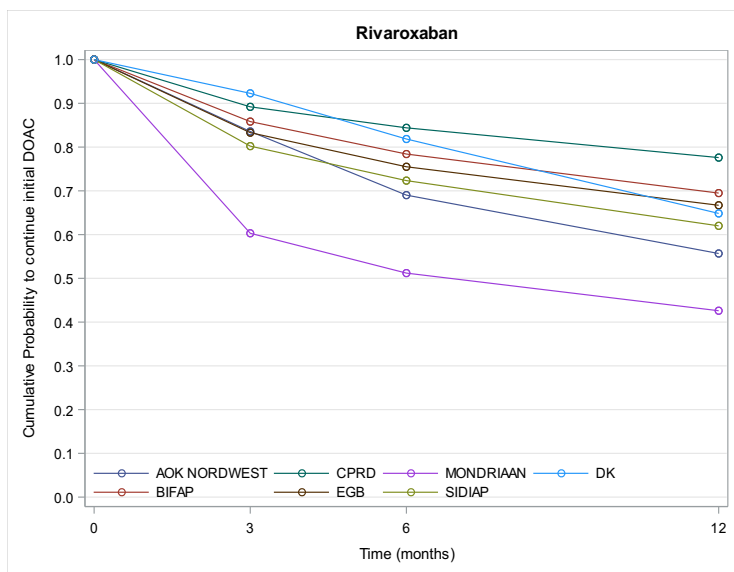
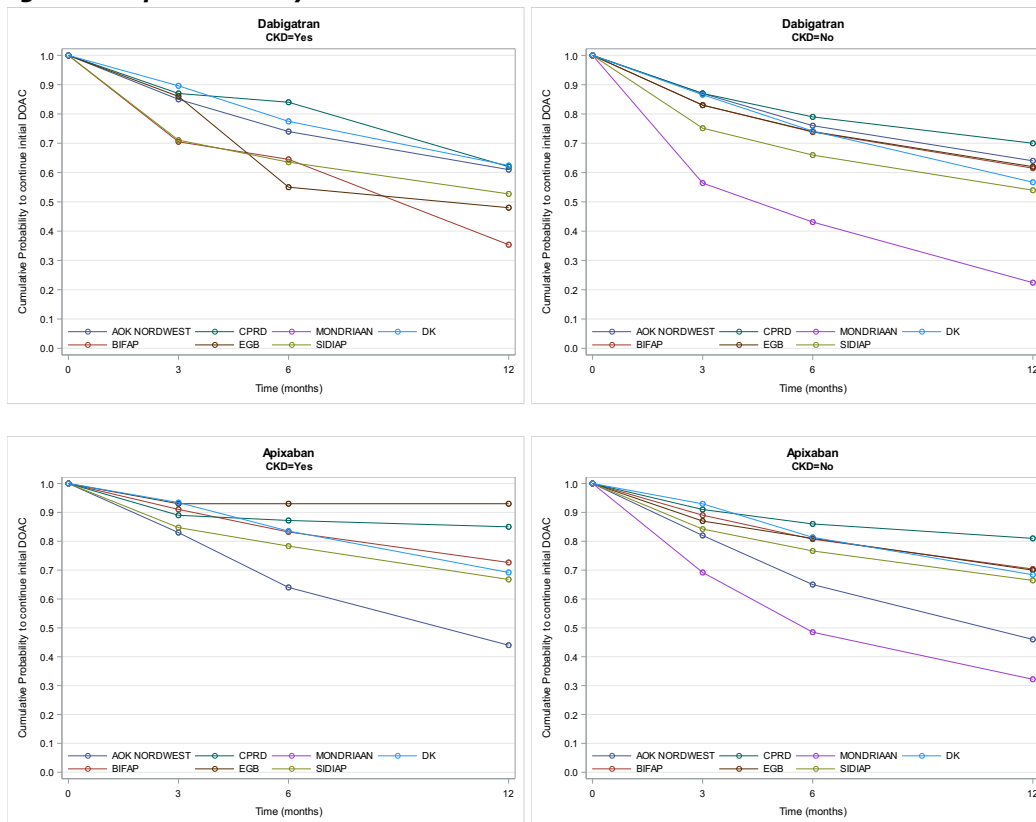


Figure 5. Kaplan-Meier by individual DOAC in each database and CKD



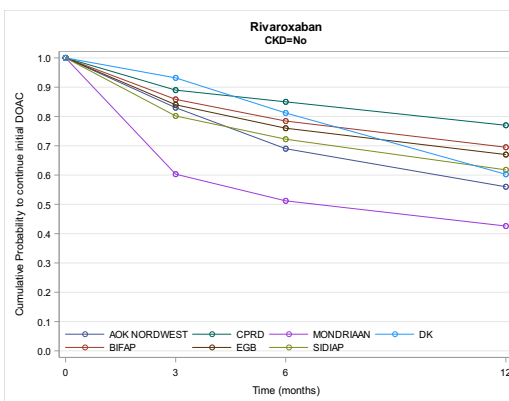
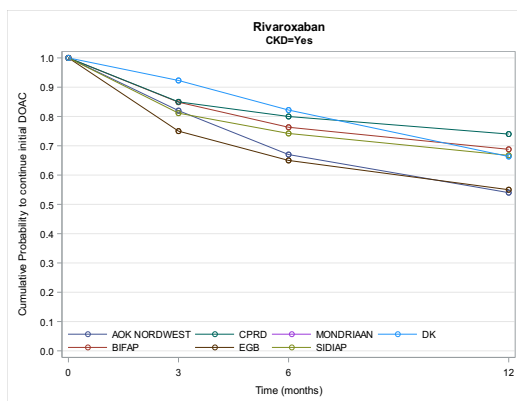


Table 15. Survival probabilities at 3, 6, 12 and 36 months by individual DOAC in each database.

	Netherlands (Mondriaan)			Germany (AOK NORDWEST)			Germany (Bavarian claims)			Spain (BIFAP)		
	Survival probability	CI 95%	Number of discontinuers/ number left	Survival probability	CI 95%	Number of discontinuers/ number left	Survival probability	CI 95%	Number of discontinuers/ number left	Survival probability	CI 95%	Number of discontinuers/ number left
Dabigatran												
3m	0.56	(0.46 - 0.67)	40 / 49	0.87	(0.86 - 0.88)	495 / 3370	pending			0.83	(0.82 -0.84)	603 / 2668
6m	0.43	(0.33 - 0.53)	51 / 32	0.76	(0.75 - 0.77)	929 / 2879	pending			0.74	(0.72 - 0.75)	885 / 2144
12m	0.22	(0.13 - 0.32)	64 / 13	0.64	(0.62 - 0.65)	1383 / 2306	pending			0.62	(0.60 -0.63)	1217 / 1518
Apixaban												
3m	0.69	(0.57 - 0.81)	18 / 32	0.83	(0.82 - 0.84)	797 / 3717	pending			0.89	(0.88 -0.90)	357 / 2500
6m	0.49	(0.34 - 0.63)	27 / 19	0.65	(0.63 -0.66)	1542 / 2429	pending			0.81	(0.79 - 0.82)	571 / 1884
12m	0.32	(0.16 -0.49)	31 / 6	0.46	(0.44 - 0.48)	2138 / 1158	pending			0.70	(0.69 - 0.72)	764 / 939
Rivaroxaban												
3m	0.60	(0.54 - 0.66)	106 / 145	0.84	(0.83 - 0.84)	1920 / 9700	pending			0.86	(0.85 -0.87)	849 / 4576
6m	0.51	(0.45 - 0.57)	126 / 99	0.69	(0.68 - 0.70)	3566 / 7559	pending			0.78	(0.77 -0.79)	1224 / 3727
12m	0.43	(0.36 -0.49)	140 / 49	0.56	(0.55 - 0.57)	4947 / 5266	pending			0.69	(0.68 - 0.71)	1600 / 2506
log-rank test	pending			< 0.001						< 0.001		

Table 15. Survival probabilities at 3, 6, 12 and 36 months by individual DOAC in each database (cont.).

	Spain (SIDIAP)			United Kingdom (CPRD)			France (EGB)			Denmark (NRD)		
	Survival probability	CI 95%	Number of discontinuers/ number left	Survival probability	CI 95%	Number of discontinuers/ number left	Survival probability	CI 95%	Number of discontinuers/ number left	Survival probability	CI 95%	Number of discontinuers/ number left
Dabigatran												
3m	0.75	(0.74 - 0.76)	1174 / 3402	0.87	(0.85 - 0.89)	147 / 910	0.83	(0.79 - 0.86)	73 / 333	0.89	(0.89 - 0.90)	2335 / 18929
6m	0.66	(0.64 - 0.67)	1574 / 2838	0.79	(0.76 - 0.81)	226 / 705	0.73	(0.68 - 0.77)	111 / 265	0.77	(0.77 - 0.78)	4797 / 14909
12m	0.54	(0.52 - 0.55)	2053 / 1982	0.70	(0.67 - 0.73)	295 / 463	0.61	(0.56 - 0.66)	151 / 187	0.62	(0.61 - 0.63)	7559 / 10488
Apixaban												
3m	0.84	(0.83 - 0.86)	409 / 1984	0.91	(0.90 - 0.93)	152 / 1340	0.87	(0.83 - 0.90)	44 / 270	0.93	(0.93 - 0.94)	576 / 7640
6m	0.77	(0.75 - 0.78)	566 / 1531	0.87	(0.85 - 0.88)	211 / 943	0.82	(0.77 - 0.86)	59 / 187	0.83	(0.82 - 0.84)	139 / 5452
12m	0.66	(0.64 - 0.69)	728 / 816	0.81	(0.79 - 0.84)	254 / 431	0.71	(0.65 - 0.77)	75 / 63	0.68	(0.67 - 0.70)	2079 / 2491
Rivaroxaban												
3m	0.80	(0.79 - 0.81)	850 / 3213	0.89	(0.88 - 0.90)	339 / 2438	0.83	(0.81 - 0.85)	173 / 798	0.92	(0.92 - 0.93)	767 / 8416
6m	0.72	(0.71 - 0.74)	1141 / 2587	0.84	(0.83 - 0.86)	454 / 1716	0.76	(0.73 - 0.78)	244 / 647	0.82	(0.81 - 0.83)	1618 / 6023
12m	0.62	(0.60 - 0.64)	1453 / 1634	0.78	(0.76 - 0.79)	561 / 856	0.67	(0.64 - 0.70)	312 / 451	0.64	(0.64 - 0.66)	2678 / 3338
log-rank test	< 0.001			< 0.001			0.003			< 0.001		

10.4.3. Objective 3

10.4.3.1. Use of DOACs

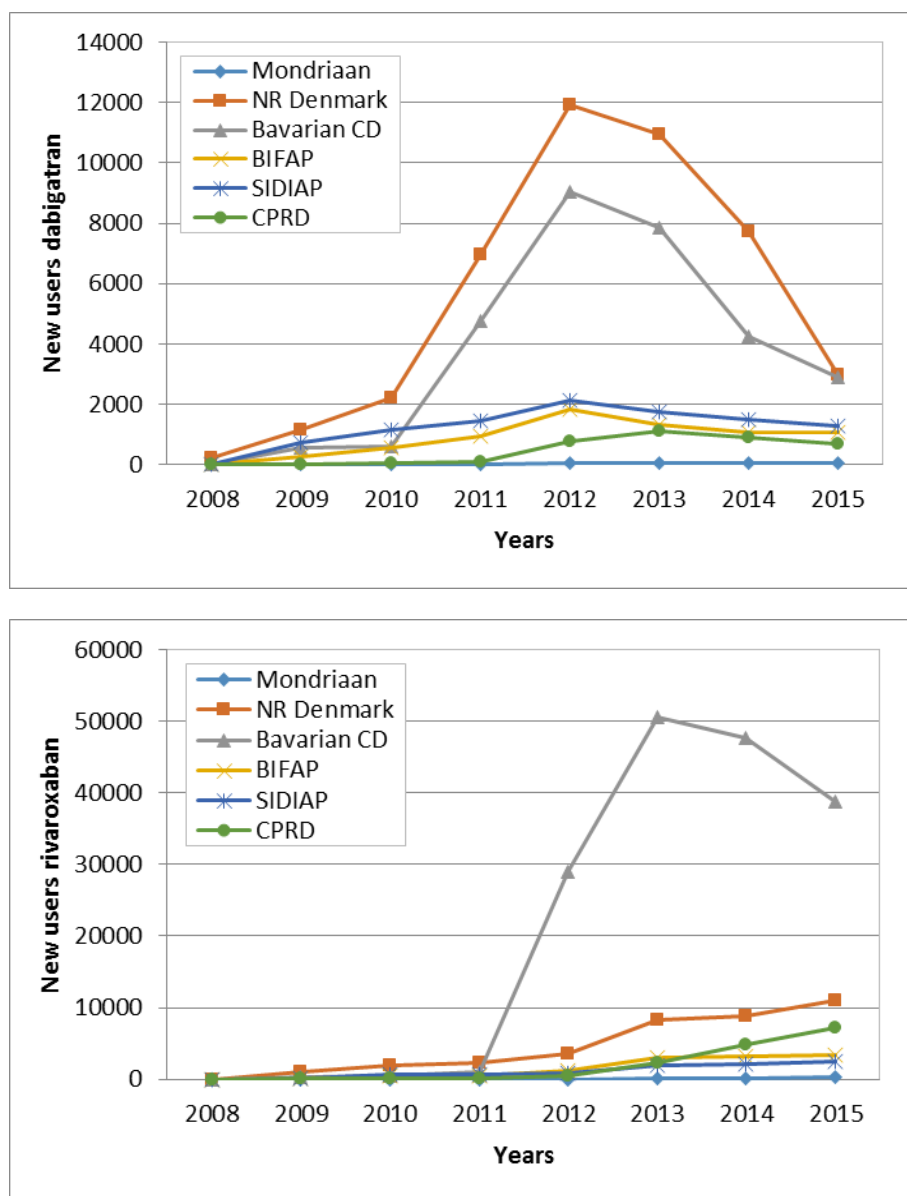
The total number of patients initiating a DOAC increased during the study period in all databases. Comparing new DOAC users for calendar years 2010 and 2015, a 3.2 fold increase was found for SIDIAP whereas the most pronounced increase was found in CPRD (67.1 fold increase). In 2015, highest numbers of new users were found for rivaroxaban in all databases followed by apixaban and dabigatran.

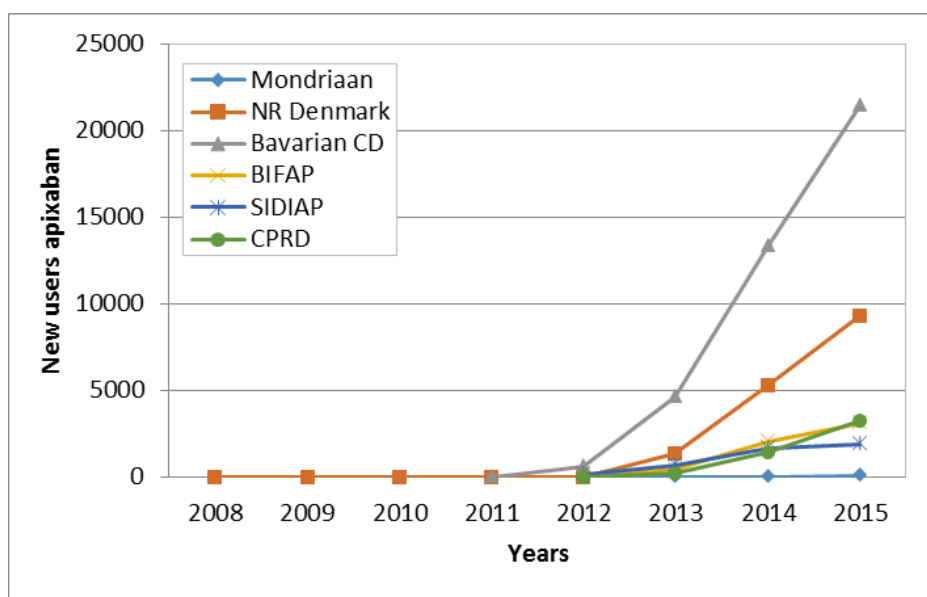
Regarding changes over time, different patterns were found for the three compounds (Table 16, Figure 6). For dabigatran, an increase was found during the study period peaking in 2012 or 2013 followed by a decrease of new users. For rivaroxaban, an increase was found for the whole study period in most databases whereas in the Bavarian database, the number of new users peaked in 2013 followed by a decrease. For apixaban, an increase was found in all databases during the study period.

Table 16. Number of new DOAC users stratified by DOAC compound, database and calendar year

		2008	2009	2010	2011	2012	2013	2014	2015	Total
Dabigatran	Mondriaan	0	0	0	0	51	41	42	52	186
	NR Denmark	242	1176	2208	6967	11936	10969	7750	2971	44219
	Bavarian CD	0	591	600	4782	9037	7876	4260	2901	30047
	BIFAP	2	266	570	960	1853	1352	1063	1061	7127
	SIDIAP	0	719	1157	1467	2117	1758	1519	1311	10048
	CPRD	0	14	42	121	773	1106	930	690	3676
	Total	244	2766	4577	14297	25767	23102	15564	8986	95303
Rivaroxaban	Mondriaan	0	0	0	0	5	53	163	247	468
	NR Denmark	0	1099	1882	2360	3502	8269	8889	11060	37061
	Bavarian CD	0	263	452	946	29030	50646	47665	38833	167835
	BIFAP	0	118	419	530	1276	3070	3210	3425	12048
	SIDIAP	0	176	587	716	827	1906	2081	2402	8695
	CPRD	0	64	123	87	410	2259	4781	7154	14878
	Total	0	1720	3463	4639	35050	66203	66789	63121	240985
Apixaban	Mondriaan	0	0	0	0	0	3	12	88	103
	NR Denmark	0	0	0	0	0	1388	5324	9333	16045
	Bavarian CD	0	0	0	13	614	4654	13315	21386	39982
	BIFAP	0	0	0	0	88	487	2081	3146	5802
	SIDIAP	0	0	0	0	146	700	1665	1907	4418
	CPRD	0	0	0	0	2	239	1467	3230	4938
	Total	0	0	0	13	850	7471	23864	39090	71288
All DOACs	Mondriaan	0	0	0	0	56	97	217	387	757
	NR Denmark	242	2275	4090	9327	15438	20626	21963	23364	97325
	Bavarian CD	0	854	1052	5741	38681	63176	65240	63120	237864
	BIFAP	2	384	989	1490	3217	4909	6354	7632	24977
	SIDIAP	0	895	1744	2183	3090	4364	5265	5620	23161
	CPRD	0	78	165	208	1185	3604	7178	11074	23492
	Total	244	4486	8040	18949	61667	96776	106217	111197	407576

Figure 6. Number of new DOAC users stratified by DOAC compound, database and calendar year





10.4.3.2. Indications for DOAC use

For conditions labelled as therapeutic indication for at least one DOAC, a comparison was made using results for calendar years 2012 (dabigatran, rivaroxaban) or 2013 (apixaban) representing the first calendar year of NVAf SmPC-labelling and calendar year 2015 (end of study period, Table 17).

NVAf was the most common indication in patients initiating DOAC in 2012/2013 and 2015 in most databases. However, in one database (CPRD) 'other/missing' was the most frequent category in new DOAC users. Regarding changes over time (2012/2013 versus 2015), an increase was found in most databases (Mondriaan, BIFSP, SIDIAP, CPRD) for the three DOAC compounds regarding the proportion of patients with NVAf as documented indication whereas in two databases (Bavarian CD, NR Denmark) a slight decrease was found at least for one or two of the three examined DOACs. Considering calendar 2015, the proportion of patients with a recorded diagnosis of NVAf for dabigatran was between 38.9% (Bavarian CD) and 66.6% (BIFAP), for rivaroxaban between 25.3% (Bavarian CD) and 66.4% (Mondriaan) and for apixaban between 36.6% (Bavarian CD) and 72.7% (Mondriaan).

For other indications (e.g., treatment of deep vein thrombosis and pulmonary embolism or prevention of thrombosis after hip/knee replacement) some differences were found between compounds, databases and changes over time (Table 17). Interestingly, there were also some inter-country differences regarding the proportion of patients initiating DOAC with a documented diagnoses of valvular diseases and atrial fibrillation (VAF) reaching highest values in Bavarian CD and SIDIAP. Further results regarding indications stratified by DOAC compound, sex, age group and calendar years of the study period for each database are presented in supplemental files.

Table 17. Number and percentage of new DOAC users stratified for DOAC compound, database, and indication (mutually exclusive categories) for the years 2012 (rivaroxaban, dabigatran) and 2013 (apixaban) in comparison to 2015 (all three DOAC compounds)

Indication*	Database	Dabigatran				Rivaroxaban				Apixaban			
		2012		2015		2012		2015		2013		2015	
		No. new users	%	No. new users	%	No. new users	%	No. new users	%	No. new users	%	No. new users	%
MI	Mondriaan	2	3.9	2	3.8	0	0	15	6.1	1**	33.3	3**	3.4
	NR Denmark	604	5.1	189	6.4	218	6.2	519	4.7	60**	4.3	460*	4.9
	Bavarian CD	267	3.0	99	3.4	873	3.0	1066	2.7	164*	3.5	711*	3.3
	BIFAP	50	2.7	22	2.1	24	1.9	63	1.8	4**	0.8	53**	1.7
	SIDIAP	30	1.4	3	0.2	14	1.7	6	0.2	9**	1.3	5**	0.3
	CPRD	7	0.9	4	0.6	2	0.5	61	0.9	3**	1.3	39**	1.2
PHK	Mondriaan	0	0	0	0	0	0	0	0	0	0	0	0
	NR Denmark	31	0.3	7	0.2	138	3.9	59	0.5	<5	NA	22	0.2
	Bavarian CD	0	0	0	0	0	0	0	0	0	0	0	0
	BIFAP	33	1.8	1	0.1	167	13.1	140	4.1	143	29.4	35	1.1
	SIDIAP	89	4.2	137	10.5	36	4.4	217	9.0	164	23.4	100	5.2
	CPRD	38	4.9	24	3.5	51	12.4	91	1.3	14	5.9	28	0.9
NVAF	Mondriaan	24	47.1	31	59.6	1	20.0	164	66.4	1	33.3	64	72.7
	NR Denmark	4938	41.4	1292	43.5	558	15.9	3105	28.1	689	49.6	4152	44.5
	Bavarian CD	4149	45.9	1129	38.9	8086	27.9	9833	25.3	1617	34.7	7820	36.6
	BIFAP	1088	58.7	707	66.6	526	41.2	2177	63.6	165	33.9	2077	66.0
	SIDIAP	1115	52.7	787	60.0	265	32.0	1440	60.0	157	22.4	1221	64.0
	CPRD	212	27.4	280	40.6	52	12.7	1863	26.0	76	31.8	1305	40.4
DVT-PE	Mondriaan	0	0	0	0	0	0	4	1.6	0	0	0	0
	NR Denmark	129	1.1	67	2.3	282	8.1	1842	16.7	11	0.8	509	5.5
	Bavarian CD	144	1.6	105	3.6	1701	5.9	3642	9.4	65	1.4	1241	5.8
	BIFAP	7	0.4	4	0.4	23	1.8	84	2.5	2	0.4	35	1.1
	SIDIAP	5	0.2	4	0.3	26	3.1	18	0.7	3	0.4	4	0.2
	CPRD	<5	0.4	<5	0.4	14	3.4	678	9.5	<5	0.4	69	2.1
MI + PHK	Mondriaan	0	0	0	0	0	0	0	0	0	0	0	0
	NR Denmark	5	0.0	<5	NA	14	0.4	15	0.1	<5	NA	6	0.1
	Bavarian CD	0	0	0	0	0	0	0	0	0	0	0	0
	BIFAP	0	0	0	0	0	0	0	0	0	0	2	0.1
	SIDIAP	3	0.1	4	0.3	3	0.4	10	0.4	4	0.6	1	0.1
	CPRD	0	0	0	0	<5	0.2	<5	0.0	0	0	0	0
MI + NVAF	Mondriaan	0	0	0	0	0	0	0	0	0	0	0	0
	NR Denmark	1469	12.3	427	14.4	165	4.7	824	7.5	234	16.9	1282	13.7
	Bavarian CD	561	6.2	125	4.3	1104	3.8	1174	3.0	248	5.3	1099	5.1
	BIFAP	32	1.7	15	1.4	11	0.9	60	1.8	3	0.6	58	1.8
	SIDIAP	131	6.2	65	5.0	33	4.0	148	6.2	27	3.9	159	8.3
	CPRD	0	0	0	0	0	0	0	0	0	0	0	0
MI +	Mondriaan	0	0	0	0	0	0	0	0	0	0	0	0

Indication*	Database	Dabigatran				Rivaroxaban				Apixaban			
		2012		2015		2012		2015		2013		2015	
		No. new users	%	No. new users	%	No. new users	%	No. new users	%	No. new users	%	No. new users	%
DVT-PE	NR Denmark	44	0.4	23	0.8	42	1.2	246	2.2	6	0.4	126	1.4
	Bavarian CD	17	0.2	11	0.4	163	0.6	317	0.8	8	0.2	135	0.6
	BIFAP	0	0	0	0	1	0.1	0	0	0	0	0	0
	SIDIAP	0	0	0	0	2	0.2	1	0.0	1	0.1	0	0
	CPRD	<5	0.1	<5	0.1	0	0	5	0.1	0	0	0	0
PHK + NVAF	Mondriaan	0	0	0	0	0	0	0	0	0	0	0	0
	NR Denmark	58	0.5	22	0.7	20	0.6	41	0.4	8	0.6	60	0.6
	Bavarian CD	0	0	0	0	0	0	0	0	0	0	0	0
	BIFAP	1	0.1	6	0.6	6	0.5	7	0.2	4	0.8	3	0.1
	SIDIAP	16	0.8	20	1.5	5	0.6	50	2.1	7	1.0	41	2.1
	CPRD	<5	0.1	<5	0.4	<5	0.5	17	0.2	<5	0.4	15	0.5
PHK + DVT-PE	Mondriaan	0	0	0	0	0	0	0	0	0	0	0	0
	NR Denmark	<5	NA	<5	NA	<5	NA	15	0.1	<5	NA	11	0.1
	Bavarian CD	0	0	0	0	0	0	0	0	0	0	0	0
	BIFAP	0	0	0	0	2	0.2	2	0.1	1	0.2	0	0
	SIDIAP	0	0	1	0.1	0	0	4	0.2	2	0.3	1	0.1
	CPRD	0	0	<5	0.1	1	0.2	15	0.2	0	0	<5	0.0
NVAF + DVT-PE	Mondriaan	0	0	0	0	0	0	0	0	0	0	0	0
	NR Denmark	151	1.3	37	1.2	39	1.1	218	2.0	18	1.3	200	2.1
	Bavarian CD	104	1.2	27	0.9	287	1.0	353	0.9	38	0.8	262	1.2
	BIFAP	5	0.3	1	0.1	3	0.2	15	0.4	2	0.4	8	0.3
	SIDIAP	12	0.6	11	0.8	7	0.8	41	1.7	4	0.6	22	1.2
	CPRD	3	0.4	1	0.1	1	0.2	27	0.4	0	0	6	0.2
VAF	Mondriaan	0**	0	0**	0	0**	0	0**	0	0**	0	0**	0
	NR Denmark	662* *	5.5	173* *	5.8	95**	2.7	496* *	4.5	106* *	7.6	712* *	7.6
	Bavarian CD	1469 **	16.3	419* *	14.4	3145 **	10.8	3461 **	8.9	690* *	14.8	3130 **	14.6
	BIFAP	56**	3.0	52**	4.9	24**	1.9	129* *	3.8	14**	2.9	138* *	4.4
	SIDIAP	217* *	10.3	145* *	11.1	59**	7.1	266* *	11.1	44**	6.3	267* *	14.0
	CPRD	21**	2.7	17**	2.5	5**	1.2	167* *	2.3	7**	2.9	125* *	3.9
Other / Missing	Mondriaan	25**	49.0	19**	36.5	4**	80.0	64**	25.9	1**	33.3	21**	23.9
	NR Denmark	3844 **	32.2	729* *	24.5	1930 **	55.1	3680 **	33.3	251* *	18.1	1793 **	19.2
	Bavarian CD	2326 **	25.7	986* *	34.0	1367 1**	47.1	1898 7**	48.9	1824 **	39.2	6988 **	32.7
	BIFAP	581* *	31.4	253* *	23.8	489* *	38.3	748* *	21.8	149* *	30.6	737* *	23.4
	SIDIAP	499* *	23.6	134* *	10.2	377* *	45.6	202* *	8.4	278* *	39.7	86**	4.5
	CPRD	487* *	63.0	356* *	51.6	281* *	68.5	4229 **	59.1	137* *	57.3	1642 **	50.8

* Indications:

MI: Diagnoses 'Myocardial infarction' and 'angina' were used for defining SmPC indication 'Prevention of atherothrombotic events in adult patients after an acute coronary syndrome with elevated cardiac biomarkers co-administered with acetylsalicylic acid (ASA) alone or with ASA plus clopidogrel or ticlopidine;

PHK: Diagnoses / procedural codes for hip and knee replacement were used for defining SmPC indication 'Primary Prevention of venous thromboembolic events in adult patients you have undergone elective total hip replacement surgery';

NVAF: Diagnosis 'non-valvular atrial fibrillation' was used for defining SmPC indication 'Prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation (NVAF), with one or more risk factors, such as prior stroke or transient ischemic attack (TIA), age \geq 75 years, heart failure (NYHA Class \geq II), diabetes mellitus, hypertension'

DVT-PE: Diagnoses 'Deep vein thrombosis' and 'Pulmonary embolism' were used for defining SmPC indication 'Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults',

VAf: Valvular atrial fibrillation (no labelled indication)** Diagnosis not listed as indication for the respective DOAC (potential off-label use, for single indications only)

10.4.3.3. Contraindications present in new DOAC users

Summarizing all three DOACS, all databases and the whole study period, an overall proportion of 39.0% was revealed for incident DOAC users with at least one contraindication. With regard to the databases, highest proportion of patients with at least 1 contraindication was found in the Bavarian CD (55.7%) followed by Mondriaan (20.3%) whereas lowest values were found in SIDIAP and CPRD (8.2%).

By stratifying this overall measure by the DOAC compound, the respective values for dabigatran, rivaroxaban and apixaban were 32.7%, 42.0% and 37.4% (Table 18). Excluding the Bavarian database (broad definition of renal and hepatic dysfunction by ICD codes, possible inter-country differences in coding behaviour, see limitation section), the respective values for dabigatran, rivaroxaban and apixaban were 18.8%, 13.4%, and 14.1%. Results stratified by database and DOAC compound are given in Table 18.

Table 18. Number and percentage of new DOAC users with at least 1 contraindication (CI) stratified for DOAC compound and database (whole study period)*

	All DOACs			Dabigatran			Rivaroxaban			Apixaban		
	Total	>=1 CI		Total	>=1 CI		Total	>=1 CI		Total	>=1 CI	
	n	n	%	n	n	%	n	n	%	n	n	%
Mondriaan	757	154	20.3	186	28	15.1	468	105	22.4	103	21	20.4
NR Denmark	97325	17591	18.1	44219	9234	20.9	37061	5652	15.3	16045	2705	16.9
Bavarian CD	237864	132548	55.7	30047	18852	62.7	167835	91448	54.5	39982	22248	55.6
BIFAP	24977	4913	19.7	7127	1702	23.9	12048	2254	18.7	5802	957	16.5
SIDIAP	23161	1900	8.2	10048	963	9.6	8695	604	6.9	4418	333	7.5
CPRD	23492	1916	8.2	3676	356	9.7	14878	1163	7.8	4938	397	8.0
Total (all databases)	407576	159022	39.0	95303	31135	32.7	240985	101226	42.0	71288	26661	37.4
Total (excluding Bavarian CD)	169712	26474	15.6	65256	12283	18.8	73150	9778	13.4	31306	4413	14.1

* For NR Denmark, categories with n<5 were imputed as 0 for calculating summarized measures.

Stratifying the aforementioned DOAC-specific summarized measures for contraindications by calendar year (table 19), highest proportions were found in 2012 (all DOACs: 42.9%). With regard to specific compounds, highest proportions were reached for dabigatran (36.5%) and rivaroxaban (47.9%) in 2012 and for apixaban (46.2%) in 2011.

Table 19. Number and percentage of new DOAC users with at least 1 contraindication (CI) stratified for DOAC compound and calendar year (all databases)*

	All DOACs			Dabigatran			Rivaroxaban			Apixaban		
	Total	>=1 CI		Total	>=1 CI		Total	>=1 CI		Total	>=1 CI	
	n	n	%	n	n	%	n	n	%	n	n	%
2008	244	10	4.1	244	10	4.1						
2009	4486	443	9.9	2766	274	9.9	1720	169	9.8			
2010	8040	797	9.9	4577	458	10.0	3463	339	9.8			
2011	18949	5395	28.5	14297	4766	33.3	4639	623	13.4	13	6	46.2
2012	61667	26455	42.9	25767	9415	36.5	35050	16800	47.9	850	240	28.2
2013	96776	41301	42.7	23102	8051	34.8	66203	30386	45.9	7471	2864	38.3
2014	106217	42914	40.4	15564	5215	33.5	66789	28742	43.0	23864	8957	37.5
2015	111197	41707	37.5	8986	2946	32.8	63121	24167	38.3	39090	14594	37.3
Total (all years)	407576	159022	39.0	95303	31135	32.7	240985	101226	42.0	71288	26661	37.4

* For NR Denmark, categories with n<5 were imputed as 0 for calculating summarized measures.

By excluding the Bavarian database (table 20), lower values were revealed for all calendar years reaching the highest value in 2012 (19.2%). With regard to the three compounds, highest values were found for rivaroxaban (17.0%) in 2013, and for dabigatran (22.1%) and apixaban (15.3%) in 2014, respectively.

Table 20. Number and percentage of new DOAC users with at least 1 contraindication (CI) stratified for DOAC compound and calendar year (all databases except Bavarian CD)*

	All DOACs			Dabigatran			Rivaroxaban			Apixaban		
	Total	>=1 CI		Total	>=1 CI		Total	>=1 CI		Total	>=1 CI	
	n	n	%	n	n	%	n	n	%	n	n	%
2008	244	10	4.1	244	10	4.1						
2009	3632	149	4.1	2175	75	3.4	1457	74	5.1			
2010	6988	358	5.1	3977	198	5.0	3011	160	5.3			
2011	13208	1742	13.2	9515	1569	16.5	3693	173	4.7			
2012	22986	4422	19.2	16730	3595	21.5	6020	817	13.6	236	10	4.2
2013	33600	6278	18.7	15226	3223	21.2	15557	2639	17.0	2817	416	14.8
2014	40977	6939	16.9	11304	2495	22.1	19124	2833	14.8	10549	1611	15.3
2015	48077	6576	13.7	6085	1118	18.4	24288	3082	12.7	17704	2376	13.4
Total (all years)	169712	26474	15.6	65256	12283	18.8	73150	9778	13.4	31306	4413	14.1

* For NR Denmark, categories with n<5 were imputed as 0 for calculating summarized measures.

For evaluating time trends of contraindications in more detail (database-specific), a comparison was made using results for calendar years 2012 (dabigatran, rivaroxaban) or 2013 (apixaban) representing the first calendar year of NVAf SmPC-labelling and calendar year 2015 (end of study period, Table 21).

Regarding these calendar years, the proportion of patients with at least one contraindication was between 4.7% (SIDIAF, Apixaban, 2013) and 64.4% (Bavarian CD, Dabigatran, 2012). Regarding changes over time, a decreased proportion of contraindications was found in most databases and for most compounds. In most of the patients with contraindications, only 1 contraindication was present (Table 21).

Table 21. Number and percentage of new DOAC users stratified for DOAC compound, database and number of contraindications (CI) for the years 2012 (rivaroxaban, dabigatran) and 2013 (apixaban) in comparison to 2015 (all three DOAC compounds)*

No. of CI	Database	Dabigatran				Rivaroxaban				Apixaban			
		2012		2015		2012		2015		2013		2015	
		No. new users	%	No. new users	%	No. new users	%	No. new users	%	No. new users	%	No. new users	%
Total (n>1)	Mondriaan	8	15.7	12	23.1	0	0	58	23.5	1	33.3	18	20.5
	NR Denmark	2603	21.8	747	25.1	453	12.9	1810	16.4	281	20.2	1425	15.3
	Bavarian CD	5820	64.4	1828	63.0	1598 3	55.1	2108 5	54.3	2448	52.6	1221 8	57.1
	BIFAP	587	31.7	185	17.4	269	21.1	518	15.1	80	16.4	488	15.5
	SIDIAP	309	14.6	121	9.2	71	8.6	146	6.1	33	4.7	167	8.8
	CPRD	88	11.4	53	7.7	24	5.9	550	7.7	21	8.8	278	8.6
n=1	Mondriaan	7	13.7	6	11.5	0	0	34	13.8	1	33.3	8	9.1
	NR Denmark	2236	18.7	654	22.0	403	11.5	1635	14.8	242	17.4	1200	12.9
	Bavarian CD	2904	32.1	907	31.3	9380	32.3	1263 7	32.5	1455	31.3	7062	33.0
	BIFAP	509	27.5	169	15.9	240	18.8	462	13.5	74	15.2	430	13.7
	SIDIAP	267	12.6	109	8.3	64	7.7	132	5.5	30	4.3	146	7.7
	CPRD	80	10.3	50	7.2	24	5.9	516	7.2	20	8.4	271	8.4
n=2	Mondriaan	1	2.0	4	7.7	0	0	22	8.9	0	0	8	9.1
	NR Denmark	338	2.8	78	2.6	43	1.2	162	1.5	33	2.4	200	2.1
	Bavarian CD	1778	19.7	547	18.9	4461	15.4	5694	14.7	644	13.8	3390	15.9
	BIFAP	68	3.7	14	1.3	28	2.2	52	1.5	5	1.0	52	1.7
	SIDIAP	42	2.0	9	0.7	7	0.8	13	0.5	3	0.4	20	1.0
	CPRD	8	1.0	<5	0.4	0	0	33	0.5	<5	0.4	7	0.2
n≥3	Mondriaan	0	0	2	3.8	0	0	2	0.8	0	0	2	2.3
	NR Denmark	29	0.2	15	0.5	7	0.2	13	0.1	6	0.4	25	0.3
	Bavarian CD	1138	12.6	374	12.9	2142	7.4	2754	7.1	349	7.5	1766	8.3
	BIFAP	10	0.5	2	0.2	1	0.1	4	0.1	1	0.2	6	0.2
	SIDIAP	0	0	3	0.2	0	0	1	0.0	0	0	1	0.1
	CPRD	0	0	0	0	0	0	<5	0.0	0	0	0	0

* For NR Denmark, categories with n<5 were imputed as 0 for calculating summarized measures.

By analysing contraindications in detail, some differences were found between the databases with regard to the three most frequent contraindications for the calendar years mentioned above. Whereas in some databases, concomitant treatment with oral or any anticoagulants was the most common contraindication (BIFAP, SIDIAP, NR Denmark), malignant neoplasm was the most frequent contraindication in other databases (Bavarian CD, CPRD). Other contraindications of relevance in most databases were clinically significant bleeding or vascular aneurysms / major intraspinal / intracerebral vascular abnormalities / concomitant treatment of Acute Coronary Syndrome (ACS) with antiplatelet therapy in patients with a prior stroke or a transient ischaemic attack (TIA). In the Bavarian database and in SIDIAP, renal impairment was of relevance for dabigatran. Hepatic diseases associated with coagulopathy and clinically relevant bleeding risk was relevant in the Bavarian database only.

Comparing the proportion of patients with a particular contraindication some differences were found between the databases. The proportion of patients with a documented diagnosis of malignant neoplasm within 6 months prior to index date, for example, was between 19.3% and 21.3% in the

Bavarian claims database whereas in other databases, this contraindication was of lower importance (CPRD: 1.7% to 3.3%) regarding the two calendar years mentioned before (Table 22). Similar differences were found for renal dysfunction in patients initiating dabigatran for calendar year 2015 (Bavarian claims data: 21.3%; SIDIAP: 3.6%). Comparing the three most common contraindications for the three compounds and analysing changes over time (calendar years mentioned above), no clear pattern was found regarding all databases.

Table 22. Number and percentage of new DOAC users with a contraindication* (TOP 3) stratified by DOAC compound, database for calendar years 2012 (dabigatran, rivaroxaban), 2013 (apixaban) and 2015 (all DOAC compounds)

	Dabigatran		Rivaroxaban		Apixaban	
	2012	2015	2012	2015	2013	2015
Mondriaan	(1) Concomitant treatment with oral anticoagulants (n=5, 9.8%) (2) Malignant neoplasms (n=3, 5.9%) (3) Concomitant treatment with any other anticoagulants (n=2, 3.9%)	(1) Active clinically significant bleeding (n=6, 11.5%) (1) Malignant neoplasms (n=6, 11.5%) (3) intracranial haemorrhage (n=5, 9.6%)	-	(1) Malignant neoplasms (n=18, 7.3%) (2) Intracranial haemorrhage (n=16, 6.5%) (3) Active clinically significant bleeding (n=14, 5.7%)	(1) Concomitant treatment with oral anticoagulants (n=1, 33.3%)	(1) Active clinically significant bleeding (n=9, 10.2%) (2) Intracranial haemorrhage (n=9, 10.2%) (3) Malignant neoplasms (n=7, 8.0%)
NR Denmark	(1) Concomitant treatment with oral anticoagulants (n=1524, 12.8%) (2) Malignant neoplasms (n=320, 2.7%) (3) Vascular aneurysms or major intraspinal or intracerebral vascular abnormalities (n=219, 1.8%)	(1) Concomitant treatment with oral anticoagulants (n=404, 13.6%) (2) Malignant neoplasms (n=125, 4.2%) (3) Vascular aneurysms or major intraspinal or intracerebral vascular abnormalities (n=84, 2.8%)	(1) Concomitant treatment with oral anticoagulants (n=223, 6.4%) (2) Concomitant treatment of Acute Coronary Syndrome (ACS) with antiplatelet therapy in patients with a prior stroke or a transient ischaemic attack (TIA) (n=214, 6.1%) (3) Malignant neoplasms (n=76, 2.2%)	(1) Concomitant treatment of Acute Coronary Syndrome (ACS) with antiplatelet therapy in patients with a prior stroke or a transient ischaemic attack (TIA) (n=782, 7.1%) (2) Concomitant treatment with oral anticoagulants (n=713, 6.4%) (3) Malignant neoplasms (n=483, 4.4%)	(1) Concomitant treatment with oral anticoagulants (n=134, 9.7%) (2) Malignant neoplasms (n=53, 3.8%) (3) Vascular aneurysms or major intraspinal or intracerebral vascular abnormalities (n=37, 2.7%)	(1) Malignant neoplasms (n=392, 4.2%) (2) Concomitant treatment with oral anticoagulants (n=356, 3.8%) (3) Vascular aneurysms or major intraspinal or intracerebral vascular abnormalities (n=315, 3.4%)
Bavarian CD	(1) Severe renal impairment (CrCL< 30 mL/min) / Chronic and acute kidney disease (n=1906, 21.1%) (2) Malignant neoplasms (n=1828, 20.2%) (3) Active clinically significant bleeding (n=1448, 16.0%)	(1) Severe renal impairment (CrCL< 30 mL/min) / chronic and acute kidney disease (n=618, 21.3%) (2) Malignant neoplasms (n=583, 20.1%) (3) Hepatic disease associated with coagulopathy and clinically relevant bleeding risk (n=532, 18.3%)	(1) Malignant neoplasms (n=5990, 20.6%) (2) Hepatic disease associated with coagulopathy and clinically relevant bleeding risk (n=4321, 14.9%) (3) Active clinically significant bleeding (n=4275, 14.7%)	(1) Malignant neoplasms (n=7889, 20.3%) (2) Hepatic disease associated with coagulopathy and clinically relevant bleeding risk (n=7147, 18.4%) (3) Active clinically significant bleeding (n=4891, 12.6%)	(1) Malignant neoplasms (n=898, 19.3%) (2) Hepatic disease associated with coagulopathy and clinically relevant bleeding risk (n=752, 16.2%) (3) Active clinically significant bleeding (n=683, 14.7%)	(1) Malignant neoplasms (n=4553, 21.3%) (2) Hepatic disease associated with coagulopathy and clinically relevant bleeding risk (n=3998, 18.7%) (3) Active clinically significant bleeding (n=3282, 15.3%)
BIFAP	(1) Concomitant treatment with oral anticoagulants (n=277, 14.9%) (2) Concomitant treatment with any other anticoagulants (n=238, 12.8%) (3) Concomitant treatment with systemic ketoconazole, cyclosporine, itraconazole and dronedarone (n=52, 2.8%)	(1) Concomitant treatment with oral anticoagulants (n=78, 7.4%) (2) Concomitant treatment with any other anticoagulants (n=62, 5.8%) (2) Vascular aneurysms or major intraspinal or intracerebral vascular abnormalities (n=19, 1.8%)	(1) Concomitant treatment with any other anticoagulants (n=133, 10.4%) (2) Concomitant treatment with oral anticoagulants (n=115, 9.0%) (3) Active clinically significant bleeding (n=16, 1.3%)	(1) Concomitant treatment with any other anticoagulants (n=202, 5.9%) (2) Concomitant treatment with oral anticoagulants (n=181, 5.3%) (3) Vascular aneurysms or major intraspinal or intracerebral vascular abnormalities (n=71, 2.1%)	(1) Concomitant treatment with any other anticoagulants (n=39, 8.0%) (2) Concomitant treatment with oral anticoagulants (n=27, 5.5%) (3) Active clinically significant bleeding (n=8, 1.6%) (3) Vascular aneurysms or major intraspinal or intracerebral vascular abnormalities (n=8, 1.6%)	(1) Concomitant treatment with any other anticoagulants (n=207, 6.6%) (2) Concomitant treatment with oral anticoagulants (n=144, 4.6%) (3) Vascular aneurysms or major intraspinal or intracerebral vascular abnormalities (n=58, 1.8%)
SIDIAP	(1) Concomitant treatment with any other anticoagulants (n=133, 6.3%) (2) Severe renal impairment	(1) Severe renal impairment (CrCL< 30 mL/min) / chronic and acute kidney disease (n=47, 3.6%) (2) Concomitant treatment	(1) Concomitant treatment with any other anticoagulants (n=40, 4.8%) (2) Vascular aneurysms or major intraspinal or	(1) Concomitant treatment with any other anticoagulants (n=35, 1.5%) (1) Malignant neoplasms (n=35, 1.5%)	(1) Concomitant treatment with any other anticoagulants (n=16, 2.3%) (2) Malignant neoplasms (n=7, 1.0%)	(1) Concomitant treatment with any other anticoagulants (n=35, 1.8%) (2) Vascular aneurysms or major intraspinal or

	(CrCL< 30 mL/min) / chronic and acute kidney disease (n=40, 1.9%) (3) Concomitant treatment with systemic ketoconazole, cyclosporine, itraconazole and dronedarone (n=28, 1.3%) (3) Vascular aneurysms or major intraspinal or intracerebral vascular abnormalities (n=28, 1.3%)	with any other anticoagulants (n=21, 1.6%) (3) Active clinically significant bleeding (n=16, 1.2%)	intracerebral vascular abnormalities (n=11, 1.3%) (3) Malignant neoplasms (n=8, 1.0%)	(3) Vascular aneurysms or major intraspinal or intracerebral vascular abnormalities (n=27, 1.1%)	(3) Vascular aneurysms or major intraspinal or intracerebral vascular abnormalities (n=6, 0.9%)	intracerebral vascular abnormalities (n=32, 1.7%) (3) Active clinically significant bleeding (n=30, 1.6%) (3) Malignant neoplasms (n=30, 1.6%)
CPRD	(1) Prosthetic heart valves requiring anticoagulant treatment (n=26, 3.4%) (2) Malignant neoplasms (n=18, 2.3%) (3) Vascular aneurysms or major intraspinal or intracerebral vascular abnormalities (n=13, 1.7%)	(1) Malignant neoplasms (n=16, 2.3%) (2) Prosthetic heart valves requiring anticoagulant treatment (n=13, 1.9%) (2) Vascular aneurysms or major intraspinal or intracerebral vascular abnormalities (n=13, 1.9%)	(1) Malignant neoplasms (n=7, 1.7%) (2) Arteriovenous malformations (n=4, 1.0%) (3) Active clinically significant bleeding (n=3, 0.7%) (3) Concomitant treatment with any oral anticoagulants (n=3, 0.7%)	(1) Malignant neoplasms (n=195, 2.7%) (2) Vascular aneurysms or major intraspinal or intracerebral vascular abnormalities (n=139, 1.9%) (3) Active clinically significant bleeding (n=83, 1.2%) (3) Arteriovenous malformations (n=83, 1.9%)	(1) Malignant neoplasms (n=8, 3.3%) (2) Active clinically significant bleeding (n=6, 2.5%) (3) Vascular aneurysms or major intraspinal or intracerebral vascular abnormalities (n=5, 2.1%)	(1) Malignant neoplasms (n=86, 2.7%) (2) Vascular aneurysms or major intraspinal or intracerebral vascular abnormalities (n=79, 2.4%) (3) Arteriovenous malformations (n=53, 1.6%)

* Time window for identification of events: Malignant neoplasms: within 6 months prior to index date; Active clinically significant bleeding: within 6 weeks prior to index date; Intracranial haemorrhage: within 6 months prior to index date; Severe renal impairment (CrCL< 30 mL/min) / Chronic and acute kidney disease: within 12 months prior to index date

Detailed results for contraindications for each DOAC stratified by database and calendar year are presented in Tables 23, 24 and 25. Further results (stratifications by sex and age groups) are presented in supplemental files.

Table 23. Number and percentage of new dabigatran users with contraindication stratified by database and calendar year

Table 1: Number and percentage of new adult oral users with contraindications stratified by database and calendar year																																
			Active clinically significant bleeding		Gastro-intestinal ulceration		Malignant neoplasms		Brain or spinal injury		Intra-cranial haemorrhage		Oesophageal varices		Arterio-venous malformations		Vascular aneurysms or major intra-spinal or intra-cerebral vascular abnormalities		Hepatic disease associated with coagulopathy and clinically relevant bleeding risk *		Concomitant treatment with any other anticoagulants		Concomitant treatment with any oral anticoagulants		Severe renal impairment (CrCL< 30 mL/min) / chronic and acute kidney disease		Concomitant treatment with systemic ketocozazole, ciclosporine, itracozazole and drone-darone		Prosthetic heart valves requiring anticoagulant treatment			
Year	Databases	Total	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
2009	Mondrian*	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	
	NR Denmark	1176	<5	NA	<5	NA	6	0.5	<5	NA	<5	NA	<5	NA	<5	NA	8	0.7	12	1.0	<5	NA	7	0.6	<5	NA	<5	NA	<5	NA	<5	NA
	Bavarian CD	591	37	6.3	15	2.5	78	13.2	3	0.5	3	0.5	1	0.2	3	0.5	1	0.2	49	8.3	15	2.5	6	1.0	54	9.1	1	0.2	ND	0.0		
	BIFAP	266	2	0.8	0	0.0	1	0.4	0	0.0	0	0.0	1	0.4	0	0.0	1	0.4	1	0.4	6	2.3	6	2.3	1	0.4	3	1.1	0	0.0		
	SIDIAP	719	2	0.3	0	0.0	2	0.3	0	0.0	0	0.0	0	0.0	0	0.0	1	0.1	0	0.0	2	0.3	0	0.0	3	0.4	0	0.0	0	0.0		
	CPRD	14	1	7.1	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0		
2010	Mondrian*	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	
	NR Denmark	2208	<5	NA	<5	NA	25	1.1	<5	NA	<5	NA	0	0.0	<5	NA	12	0.5	17	0.8	<5	NA	13	0.6	7	0.3	<5	NA	7	0.3		
	Bavarian CD	600	54	9.0	17	2.8	90	15.0	1	0.2	6	1.0	1	0.2	9	1.5	9	1.5	72	12.0	39	6.5	20	3.3	62	10.3	10	1.7		0.0		
	BIFAP	570	4	0.7	0	0.0	6	1.1	0	0.0	0	0.0	0	0.0	3	0.5	5	0.9	0	0.0	26	4.6	16	2.8	1	0.2	2	0.4	2	0.4		
	SIDIAP	1157	2	0.2	0	0.0	6	0.5	2	0.2	2	0.2	0	0.0	2	0.2	5	0.4	0	0.0	12	1.0	1	0.1	10	0.9	9	0.8	0	0.0		
	CPRD	42	0	0.0	0	0.0	2	4.8	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	1	2.4	0	0.0		
2011	Mondrian*	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	
	NR Denmark	6967	79	1.1	38	0.5	131	1.9	21	0.3	25	0.4	6	0.1	32	0.5	95	1.4	71	1.0	47	0.7	76	1.1	56	0.8	41	0.6	72	1.0		
	Bavarian CD	4782	86	18.1	19	4.2	1009	21.1	66	1.4	16	3.4	17	0.4	22	0.6	31	6.6	68	14.4	63	13.2	69	14.5	10	2.2	11	2.4	ND	0.0		

			Active clinically significant bleeding		Gastro-intestinal ulceration		Malignant neoplasms		Brain or spinal injury		Intra-cranial haemorrhage		Oesophageal varices		Arterio-venous malformations		Vascular aneurysms or major intra-spinal or intra-cerebral vascular abnormalities		Hepatic disease associated with coagulopathy and clinically relevant bleeding risk *		Concomitant treatment with any other anticoagulants		Concomitant treatment with any oral anticoagulants		Severe renal impairment (CrCL < 30 mL/min) / chronic and acute kidney disease		Concomitant treatment with systemic ketonazole, ciclosporine, itraconazole and dronedarone		Prosthetic heart valves requiring anticoagulant treatment	
Year	Databas e	Total	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
	BIFAP	960	7	0.7	1	0.1	10	1.0	0	0.0	7	0.7	2	0.2	4	0.4	8	0.8	3	0.3	65	6.8	86	9.0	1	0.1	10	1.0	0	0.0
	SIDIAP	1467	5	0.3	1	0.1	5	0.3	2	0.1	7	0.5	0	0.0	3	0.2	11	0.7	2	0.1	39	2.7	4	0.3	9	0.6	20	1.4	2	0.1
	CPRD	121	3	2.5	0	0.0	1	0.8	0	0.0	0	0.0	0	0.0	2	1.7	3	2.5	0	0.0	0	0.0	16	13.2	1	0.8	2	1.7	3	2.5
2012	Mondriaan	51	0	0.0	0	0.0	3	5.9	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	2	3.9	5	9.8	0	0.0	0	0.0	0	0.0
	NR Denmark	11936	153	1.3	65	0.5	320	2.7	43	0.4	49	0.4	10	0.1	63	0.5	219	1.8	109	0.9	83	0.7	1524	12.8	133	1.1	87	0.7	146	1.2
	Bavarian CD	9037	1448	16.0	384	4.2	1828	20.2	105	1.2	257	2.8	30	0.3	395	4.4	584	6.5	1430	15.8	948	10.5	922	10.2	1906	21.1	150	1.7		0.0
	BIFAP	1853	27	1.5	2	0.1	20	1.1	0	0.0	15	0.8	1	0.1	9	0.5	25	1.3	3	0.2	23	12.8	27	14.7	1	0.1	52	2.8	6	0.3
	SIDIAP	2117	25	1.2	3	0.1	25	1.2	10	0.5	16	0.8	6	0.3	13	0.6	28	1.3	6	0.3	13	6.3	14	0.7	40	1.9	28	1.3	4	0.2
	CPRD	773	9	1.2	2	0.3	18	2.3	1	0.1	4	0.5	0	0.0	12	1.6	13	1.7	0	0.0	0	0.0	8	1.0	0	0.0	7	0.9	26	3.4
2013	Mondriaan	41	0	0.0	0	0.0	2	4.9	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	3	7.3	0	0.0	0	0.0	0	0.0
	NR Denmark	10969	156	1.4	56	0.5	281	2.6	33	0.3	31	0.3	8	0.1	42	0.4	209	1.9	111	1.0	66	0.6	1585	14.4	96	0.9	42	0.4	133	1.2
	Bavarian CD	7876	1201	15.2	294	3.7	1513	19.2	103	1.3	228	2.9	33	0.4	355	4.5	507	6.4	1314	16.7	662	8.4	589	7.5	1588	20.2	101	1.3		0.0
	BIFAP	1352	18	1.3	0	0.0	8	0.6	0	0.0	7	0.5	0	0.0	5	0.4	21	1.6	3	0.2	16	12.3	20	15.4	6	0.4	26	1.9	1	0.1
	SIDIAP	1758	21	1.2	5	0.3	24	1.4	4	0.2	12	0.7	3	0.2	1	0.1	15	0.9	3	0.2	88	5.0	5	0.3	33	1.9	21	1.2	3	0.2
	CPRD	1106	9	0.8	0	0.0	38	3.4	3	0.3	6	0.5	0	0.0	10	0.9	21	1.9	0	0.0	0	0.0	11	1.0	4	0.4	2	0.2	24	2.2
2014	Mondriaan	42	0	0.0	0	0.0	3	7.1	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	1	2.4	0	0.0	0	0.0	0	0.0

			Active clinically significant bleeding		Gastro-intestinal ulceration		Malignant neoplasms		Brain or spinal injury		Intra-cranial haemorrhage		Oesophageal varices		Arterio-venous malformations		Vascular aneurysms or major intra-spinal or intra-cerebral vascular abnormalities		Hepatic disease associated with coagulopathy and clinically relevant bleeding risk *		Concomitant treatment with any other anticoagulants		Concomitant treatment with any oral anticoagulants		Severe renal impairment (CrCL < 30 mL/min) / chronic and acute kidney disease		Concomitant treatment with systemic ketonazole, ciclosporine, itraconazole and dronedarone		Prosthetic heart valves requiring anticoagulant treatment	
Year	Databas e	Total	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
	NR Denmark	7750	97	1.3	30	0.4	24	3.2	23	0.3	14	0.2	8	0.1	46	0.6	16	2.2	89	1.1	39	0.5	12	16	77	1.0	23	0.3	94	1.2
	Bavarian CD	4260	65	15.4	16	4.0	81	19.0	51	1.2	13	3.1	13	0.3	17	4.2	27	6.5	80	18.8	39	9.3	33	7.9	94	22.3	29	0.7		0.0
	BIFAP	1063	17	1.6	1	0.1	22	2.1	0	0.0	6	0.6	1	0.1	6	0.6	20	1.9	2	0.2	10	9.4	12	11	1	0.1	14	1.3	2	0.2
	SIDIAP	1519	10	0.7	2	0.1	22	1.4	2	0.1	4	0.3	1	0.1	6	0.4	18	1.2	2	0.1	57	3.8	5	0.3	37	2.4	10	0.7	11	0.7
	CPRD	930	14	1.5	1	0.1	14	1.5	0	0.0	1	0.1	0	0.0	12	1.3	14	1.5	0	0.0	0	0.0	6	0.6	3	0.3	0	0.0	21	2.3
2015	Mondriaan	52	6	11.5	1	1.9	6	11.5	0	0.0	5	9.6	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	2	3.8	0	0.0	0	0.0	0	0.0
	NR Denmark	2971	54	1.8	20	0.7	12	4.2	18	0.6	9	0.3	5	0.2	19	0.6	84	2.8	32	1.1	18	0.6	40	13.6	23	0.8	<5	NA	44	1.5
	Bavarian CD	2901	45	15.3	11	3.8	58	20.1	41	1.4	88	3.0	17	0.6	13	4.8	21	7.5	53	18.3	28	9.8	19	6.8	61	21.3	13	0.4		0.0
	BIFAP	1061	16	1.5	2	0.2	7	0.7	0	0.0	3	0.3	0	0.0	2	0.2	19	1.8	2	0.2	62	5.8	78	7.4	5	0.5	6	0.6	1	0.1
	SIDIAP	1311	16	1.2	2	0.2	10	0.8	4	0.3	3	0.2	0	0.0	6	0.5	15	1.1	1	0.1	21	1.6	2	0.2	47	3.6	3	0.2	6	0.5
	CPRD	690	4	0.6	0	0.0	16	2.3	2	0.3	1	0.1	0	0.0	4	0.6	13	1.9	0	0.0	0	0.0	2	0.3	2	0.3	0	0.0	13	1.9

* Due to the low number of new dabigatran users, data for Mondriaan are presented for the period 2012-2015 only (ND: Not done)

Table 24. Number and percentage of new rivaroxaban users with contraindication stratified by database and calendar year

			Active clinically significant bleeding		Gastro-intestinal ulceration		Malignant neoplasms		Brain spinal injury or		Intra-cranial haemorrhage		Oesophageal varices		Arterio-venous malformations		Vascular aneurysms or major intraspinal or intra-cerebral vascular abnormalities		Hepatic disease associated with coagulopathy and clinically relevant bleeding risk including cirrhotic patients with Child Pugh B and C		Concomitant treatment with any other anticoagulants		Concomitant treatment with any oral anticoagulants		Concomitant treatment of Acute Coronary Syndrome (ACS) with anti-platelet therapy in patients with a prior stroke or a transient ischaemic attack (TIA)	
Year	Database	Total	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
2009	Mondrian*	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
	NR Denmark	1099	<5	NA	<5	NA	8	0.7	<5	NA	<5	NA	0	0.0	<5	NA	10	0.9	14	1.3	<5	NA	15	1.4	42	3.8
	Bavarian CD	263	23	8.7	9	3.4	45	17.1	1	0.4	2	0.8	0	0.0	4	1.5	4	1.5	28	10.6	14	5.3	5	1.9	ND	ND
	BIFAP	118	2	1.7	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	1	0.8	0	0.0	10	8.5	2	1.7	ND	ND
	SIDIAP	176	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	1	0.6	0	0.0	0	0.0	1	0.6	2	1.1	0	0.0	0	0.0
	CPRD	64	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
2010	Mondrian*	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
	NR Denmark	1882	15	0.8	<5	NA	20	1.1	<5	NA	<5	NA	<5	NA	5	0.3	13	0.7	23	1.2	<5	NA	25	1.3	78	4.1
	Bavarian CD	452	36	8.0	12	2.7	69	15.3	2	0.4	2	0.4	1	0.2	16	3.5	13	2.9	57	12.6	37	8.2	16	3.5	ND	ND
	BIFAP	419	2	0.5	0	0.0	2	0.5	0	0.0	0	0.0	0	0.0	0	0.0	3	0.7	0	0.0	20	4.8	7	1.7	ND	ND
	SIDIAP	587	2	0.3	1	0.2	4	0.7	2	0.3	2	0.3	0	0.0	0	0.0	1	0.2	0	0.0	2	0.3	2	0.3	0	0.0
	CPRD	123	0	0.0	0	0.0	2	1.6	0	0.0	0	0.0	2	1.6	1	0.8	1	0.8	3	2.4	0	0.0	0	0.0	0	0.0
2011	Mondrian*	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
	NR Denmark	2360	14	0.6	8	0.3	17	0.7	<5	NA	0	0.0	<5	NA	5	0.2	31	1.3	19	0.8	6	0.3	24	1.0	89	3.8

			Active clinically significant bleeding		Gastro-intestinal ulceration		Malignant neoplasms		Brain spinal injury or		Intra-cranial haemorrhage		Oesophageal varices		Arterio-venous malformations		Vascular aneurysms or major intraspinal or intra-cerebral vascular abnormalities		Hepatic disease associated with coagulopathy and clinically relevant bleeding risk including cirrhotic patients with Child Pugh B and C		Concomitant treatment with any other anticoagulants		Concomitant treatment with any oral anticoagulants		Concomitant treatment of Acute Coronary Syndrome (ACS) with anti-platelet therapy in patients with a prior stroke or a transient ischaemic attack (TIA)	
Year	Data-base	Total	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
	Bavarian CD	946	117	12.4	39	4.1	165	17.4	16	1.7	17	1.8	3	0.3	30	3.2	28	3.0	120	12.7	91	9.6	62	6.6	ND	ND
	BIFAP	530	1	0.2	0	0.0	5	0.9	0	0.0	0	0.0	0	0.0	1	0.2	5	0.9	1	0.2	22	4.2	9	1.7	ND	ND
	SIDIAP	716	0	0.0	0	0.0	8	1.1	0	0.0	0	0.0	0	0.0	0	0.0	4	0.6	1	0.1	0	0.0	0	0.0	0	0.0
	CPRD	87	0	0.0	0	0.0	2	2.3	0	0.0	1	1.1	0	0.0	0	0.0	1	1.1	0	0.0	0	0.0	0	0.0	0	0.0
2012	Mondrian	5	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
	NR Denmark	3502	39	1.1	22	0.6	76	2.2	14	0.4	9	0.3	<5	NA	18	0.5	40	1.1	36	1.0	31	0.9	223	6.4	214	6.1
	Bavarian CD	29030	4275	14.7	1163	4.0	5990	20.6	325	1.1	534	1.8	106	0.4	1059	3.6	1594	5.5	4321	14.9	3619	12.5	2420	8.3	ND	ND
	BIFAP	1276	16	1.3	1	0.1	12	0.9	0	0.0	5	0.4	0	0.0	4	0.3	13	1.0	N.D.	N.D.	133	10.4	115	9.0	ND	ND
	SIDIAP	827	1	0.1	1	0.1	8	1.0	1	0.1	0	0.0	1	0.1	7	0.8	11	1.3	2	0.2	40	4.8	3	0.4	3	0.4
	CPRD	410	3	0.7	2	0.5	7	1.7	2	0.5	0	0.0	0	0.0	4	1.0	2	0.5	0	0.0	0	0.0	3	0.7	1	0.2
2013	Mondrian	53	1	1.9	0	0.0	2	3.8	0	0.0	1	1.9	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	1	1.9	4	7.5
	NR Denmark	8269	141	1.7	71	0.9	310	3.7	33	0.4	27	0.3	20	0.2	42	0.5	180	2.2	89	1.1	96	1.2	767	9.3	662	8.0
	Bavarian CD	50646	7036	13.9	1953	3.9	10658	21.0	564	1.1	868	1.7	177	0.3	1894	3.7	2967	5.9	8247	16.3	5516	10.9	3537	7.0	ND	ND
	BIFAP	3070	40	1.3	2	0.1	25	0.8	0	0.0	14	0.5	1	0.0	11	0.4	56	1.8	10	0.3	365	11.9	258	8.4	ND	ND
	SIDIAP	1906	11	0.6	5	0.3	28	1.5	5	0.3	2	0.1	2	0.1	6	0.3	19	1.0	2	0.1	104	5.5	6	0.3	15	0.8

			Active clinically significant bleeding		Gastro-intestinal ulceration		Malignant neoplasms		Brain or spinal injury		Intra-cranial haemorrhage		Oesophageal varices		Arterio-venous malformations		Vascular aneurysms or major intraspinal or intra-cerebral vascular abnormalities		Hepatic disease associated with coagulopathy and clinically relevant bleeding risk including cirrhotic patients with Child Pugh B and C		Concomitant treatment with any other anticoagulants		Concomitant treatment with any oral anticoagulants		Concomitant treatment of Acute Coronary Syndrome (ACS) with anti-platelet therapy in patients with a prior stroke or a transient ischaemic attack (TIA)	
Year	Database	Total	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
	CPRD	2259	27	1.2	3	0.1	68	3.0	4	0.2	12	0.5	2	0.1	29	1.3	43	1.9	3	0.1	0	0.0	11	0.5	5	0.2
2014	Mondriaan	163	2	1.2	0	0.0	17	10.4	0	0.0	2	1.2	0	0.0	0	0.0	0	0.0	4	2.5	2	1.2	14	8.6	12	7.4
	NR Denmark	8889	132	1.5	58	0.7	326	3.7	43	0.5	32	0.4	11	0.1	46	0.5	168	1.9	89	1.0	93	1.0	798	9.0	682	7.7
	Bavarian CD	47665	6361	13.3	1787	3.7	10032	21.0	516	1.1	813	1.7	211	0.4	1815	3.8	3019	6.3	8234	17.3	4993	10.5	2884	6.1	ND	ND
	BIFAP	3210	40	1.2	5	0.2	33	1.0	0	0.0	10	0.3	0	0.0	19	0.6	51	1.6	6	0.2	301	9.4	279	8.7	ND	BD
	SIDIAP	2081	17	0.8	3	0.1	19	0.9	1	0.0	2	0.1	1	0.0	5	0.2	26	1.2	2	0.1	74	3.6	7	0.3	17	0.8
	CPRD	4781	47	1.0	8	0.2	136	2.8	11	0.2	11	0.2	5	0.1	61	1.3	87	1.8	10	0.2	0	0.0	35	0.7	9	0.2
2015	Mondriaan	247	14	5.7	1	0.4	18	7.3	0	0.0	16	6.5	0	0.0	0	0.0	0	0.0	5	2.0	3	1.2	6	2.4	12	4.9
	NR Denmark	11060	141	1.3	56	0.5	483	4.4	49	0.4	22	0.2	10	0.1	72	0.7	262	2.4	127	1.1	64	0.6	713	6.4	782	7.1
	Bavarian CD	38833	4891	12.6	1317	3.4	7889	20.3	418	1.1	636	1.6	166	0.4	1512	3.9	2553	6.6	7133	18.4	4428	11.4	2217	5.7	ND	ND
	BIFAP	3425	54	1.6	3	0.1	33	1.0	0	0.0	5	0.1	4	0.1	15	0.4	71	2.1	10	0.3	202	5.9	181	5.3	ND	ND
	SIDIAP	2402	25	1.0	1	0.0	35	1.5	4	0.2	5	0.2	3	0.1	13	0.5	27	1.1		0.0	35	1.5	1	0.0	8	0.3
	CPRD	7154	83	1.2	19	0.3	195	2.7	11	0.2	7	0.1	5	0.1	83	1.2	139	1.9	8	0.1	0	0.0	26	0.4	16	0.2

* Due to the low number of new rivaroxaban users, data for Mondriaan are presented for the period 2012-2015 only (ND: not done)

Table 25. Number and percentage of new apixaban users with contraindication stratified by database and calendar year

			Active clinically significant bleeding		Gastro-intestinal ulceration		Malignant neoplasms		Brain or spinal injury		Intracranial haemorrhage		Oesophageal varices		Arterio-venous malformations		Vascular aneurysms or major intraspinal or intracerebral vascular abnormalities		Hepatic disease associated with coagulopathy and clinically relevant bleeding risk		Concomitant treatment with any other anticoagulants		Concomitant treatment with any oral anticoagulants	
Year	Data-base	Total	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
2012	Mondriaan	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
	NR Denmark	-																						
	Bavarian CD	614	35	5.7	17	2.8	78	12.7	3	0.5	5	0.8	0	0.0	6	1.0	22	3.6	113	18.4	13	2.1	5	0.8
	BIFAP	88	1	1.1	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	6	6.8	1	1.1
	SIDIAP	146	1	0.7	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
	CPRD	2	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
2013	Mondriaan	3	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	1	33.3
	NR Denmark	1388	36	2.6	12	0.9	53	3.8	14	1.0	16	1.2	<5	NA	<5	NA	37	2.7	12	0.9	7	0.5	134	9.7
	Bavarian CD	4654	683	14.7	184	4.0	898	19.3	69	1.5	133	2.9	26	0.6	195	4.2	294	6.3	752	16.2	359	7.7	309	6.6
	BIFAP	487	8	1.6	0	0.0	4	0.8	0	0.0	1	0.2	0	0.0	0	0.0	8	1.6	0	0.0	39	8.0	27	5.5
	SIDIAP	700	1	0.1	0	0.0	7	1.0	0	0.0	1	0.1	1	0.1	1	0.1	6	0.9	1	0.1	16	2.3	2	0.3
	CPRD	239	6	2.5	1	0.4	8	3.3	0	0.0	2	0.8	0	0.0	2	0.8	5	2.1	0	0.0	0	0.0	0	0.0
2014	Mondriaan	12	1	8.3	0	0.0	1	8.3	0	0.0	1	8.3	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
	NR Denmark	5324	144	2.7	53	1.0	195	3.7	35	0.7	44	0.8	8	0.2	32	0.6	172	3.2	63	1.2	37	0.7	374	7.0
	Bavarian CD	13315	1984	14.9	550	4.1	2765	20.8	194	1.5	391	2.9	68	0.5	606	4.6	987	7.4	2274	17.1	1049	7.9	887	6.7
	BIFAP	2081	24	1.2	1	0.0	21	1.0	0	0.0	16	0.8	5	0.2	6	0.3	27	1.3	7	0.3	201	9.7	112	5.4
	SIDIAP	1665	23	1.4	1	0.1	15	0.9	5	0.3	11	0.7	1	0.1	7	0.4	18	1.1	1	0.1	59	3.5	3	0.2
	CPRD	1467	13	0.9	2	0.1	35	2.4	3	0.2	5	0.3	2	0.1	16	1.1	28	1.9	2	0.1	0	0.0	3	0.2
2015	Mondriaan	88	9	10.2	0	0.0	7	8.0	0	0.0	9	10.2	0	0.0	0	0.0	0	0.0	1	1.1	1	1.1	3	3.4

			Active clinically significant bleeding		Gastro-intestinal ulceration		Malignant neoplasms		Brain or spinal injury		Intracranial haemorrhage		Oesophageal varices		Arterio-venous malformations		Vascular aneurysms or major intraspinal or intracerebral vascular abnormalities		Hepatic disease associated with coagulopathy and clinically relevant bleeding risk		Concomitant treatment with any other anticoagulants		Concomitant treatment with any oral anticoagulants	
Year	Data-base	Total	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
	NR Denmark	9333	201	2.2	83	0.9	392	4.2	65	0.7	50	0.5	14	0.2	57	0.6	315	3.4	110	1.2	32	0.3	356	3.8
	Bavarian CD	21386	3282	15.3	886	4.1	4553	21.3	305	1.4	589	2.8	112	0.5	979	4.6	1674	7.8	3998	18.7	2004	9.4	1396	6.5
	BIFAP	3146	55	1.7	3	0.1	41	1.3	0	0.0	19	0.6	3	0.1	12	0.4	58	1.8	10	0.3	207	6.6	144	4.6
	SIDIAP	1907	30	1.6	4	0.2	30	1.6	9	0.5	17	0.9	11	0.6	5	0.3	32	1.7	15	0.8	35	1.8	1	0.1
	CPRD	3230	31	1.0	8	0.2	86	2.7	7	0.2	14	0.4	2	0.1	53	1.6	79	2.4	3	0.1	0	0.0	16	0.5

10.4.3.4. Special warnings / precautions present in new DOAC users

Summarizing all three DOACS, all databases and the whole study period, an overall proportion of 66.5% was revealed for incident DOAC users with at least one special warning / precaution. By stratifying this overall measure by the DOAC compound, the respective values for dabigatran, rivaroxaban and apixaban were 58.0%, 67.4% and 74.5% (Table 26).

With regard to the databases, highest proportion of patients with at least 1 special warning / precaution was found in the Bavarian CD (75.2%) followed by CPRD (67.0%) whereas lowest values were found in Mondriaan (35.8%). Results stratified by database and DOAC compound are given in Table 26.

Table 26. Number and percentage of new DOAC users with at least 1 special warning / precaution (SW/P) stratified for DOAC compound and database (whole study period)

	All DOACs			Dabigatran			Rivaroxaban			Apixaban		
	Total	>=1 SW/P		Total	>=1 SW/P		Total	>=1 SW/P		Total	>=1 SW/P	
	n	n	%	n	n	%	n	n	%	n	n	%
Mondriaan	757	271	35.8	186	62	33.3	468	164	35.0	103	45	43.7
NR Denmark	97325	48069	49.4	44219	20687	46.8	37061	17185	46.4	16045	10197	63.6
Bavarian CD	237864	178842	75.2	30047	22910	76.2	167835	123515	73.6	39982	32417	81.1
BIFAP	24977	16046	64.2	7127	4407	61.8	12048	7526	62.5	5802	4113	70.9
SIDIAP	23161	11936	51.5	10048	4712	46.9	8695	4424	50.9	4418	2800	63.4
CPRD	23492	15734	67.0	3676	2537	69.0	14878	9639	64.8	4938	3558	72.1
Total (all databases)	407576	270898	66.5	95303	55315	58.0	240985	162453	67.4	71288	53130	74.5

Stratifying the aforementioned DOAC-specific summarized measures for special warnings / precautions by calendar year, highest proportion was found in 2015 (all DOACs: 69.8%). With regard to specific compounds, highest proportions were reached for dabigatran (63.9%) in 2015 whereas for rivaroxaban and apixaban highest values were found in 2013 (69.7 %) and 2014 (75.5%), respectively.

Table 27: Number and percentage of new DOAC users with at least 1 special warning / precaution (SW/P) stratified for DOAC compound and calendar year (all databases)

	All DOACs			Dabigatran			Rivaroxaban			Apixaban		
	Total	>=1 SW/P		Total	>=1 SW/P		Total	>=1 SW/P		Total	>=1 SW/P	
	n	n	%	n	n	%	n	n	%	n	n	%
2008	244	84	34.4	244	84	34.4	0	0				
2009	4486	1500	33.4	2766	910	32.9	1720	590	34.3			
2010	8040	2870	35.7	4577	1580	34.5	3463	1290	37.3			
2011	18949	9797	51.7	14297	7990	55.9	4639	1799	38.8	13	8	61.5
2012	61667	39991	64.8	25767	15781	61.2	35050	23811	67.9	850	399	46.9
2013	96776	65365	67.5	23102	13938	60.3	66203	46140	69.7	7471	5287	70.8
2014	106217	73699	69.4	15564	9286	59.7	66789	46406	69.5	23864	18007	75.5
2015	111197	77592	69.8	8986	5746	63.9	63121	42417	67.2	39090	29429	75.3
Total (all years)	407576	270898	66.5	95303	55315	58.0	240985	162453	67.4	71288	53130	74.5

For evaluating time trends of special warnings / precautions in more detail (database-specific), a comparison was made using results for calendar years 2012 (dabigatran, rivaroxaban) or 2013 (apixaban) representing the first calendar year of NVAf SmPC-labelling and calendar year 2015 (end of study period, Table 28).

Regarding these calendar years, the proportion of patients with at least one special warning/precaution was between 28.9% (Mondriaan, dabigatran, 2015) and 82.0% (Bavarian CD, apixaban, 2015). Regarding changes over time, no clear pattern was found for dabigatran whereas for rivaroxaban and apixaban, an increase in the proportion of patients with special warning / precaution was found in most databases (2012/2013 vs. 2015). In most of the patients with special warning/precaution only 1 special warning/precaution was present (Table 28).

Table 28. Number and percentage of new DOAC users stratified for DOAC compound, database and number of special warning/precaution (SW/P) for the years 2012 (rivaroxaban, dabigatran) and 2013 (apixaban) in comparison to 2015 (all three DOAC compounds)

No. (SW/P)	Database	Dabigatran				Rivaroxaban				Apixaban			
		2012		2015		2012		2015		2013		2015	
		No. new users	%	No. new users	%	No. new users	%	No. new users	%	No. new users	%	No. new users	%
Total (n>1)	Mondriaan	20	39.2	15	28.9	2	40.0	90	36.4	0	0	39	44.3
	NR Denmark	5862	49.1	1542	51.9	1441	41.1	5381	48.7	902	65.0	5865	62.8
	Bavarian CD	6963	77.0	2290	78.9	2095 2	72.2	2868 0	73.9	3628	78.0	1753 7	82.0
	BIFAP	1250	67.5	729	68.7	750	58.8	2286	66.7	264	54.2	2287	72.7
	SIDIAP	1145	54.1	693	52.9	411	49.7	1341	55.8	332	47.4	1360	71.3
	CPRD	541	70.0	477	69.1	255	62.2	4639	64.8	161	67.4	2341	72.5
n=1	Mondriaan	18	35.3	10	19.2	2	40.0	74	30.0	0	0	35	39.8
	NR Denmark	5050	42.3	1314	44.2	1168	33.4	4245	38.4	716	51.6	4658	49.9
	Bavarian CD	3633	40.2	1183	40.8	1144 0	39.4	1519 7	39.1	1832	39.4	8346	39.0
	BIFAP	957	51.6	506	47.7	606	47.5	1673	48.8	221	45.4	1721	54.7
	SIDIAP	866	40.9	479	36.5	330	39.9	1032	43.0	258	36.9	949	49.8
	CPRD	312	40.4	266	38.6	170	41.5	3012	42.1	97	40.6	1561	48.3
n=2	Mondriaan	2	3.9	5	9.6	0	0	13	5.3	0	0	4	4.5
	NR Denmark	675	5.7	189	6.4	217	6.2	908	8.2	146	10.5	971	10.4
	Bavarian CD	2252	24.9	760	26.2	6509	22.4	9192	23.7	1238	26.6	6095	28.5
	BIFAP	239	12.9	172	16.2	114	8.9	505	14.7	36	7.4	478	15.2
	SIDIAP	223	10.5	171	13.0	65	7.9	252	10.5	63	9.0	319	16.7
	CPRD	170	22.0	156	22.6	70	17.1	1315	18.4	51	21.3	656	20.3
n≥3	Mondriaan	0	0	0	0	0	0	3	1.2	0	0	0	0
	NR Denmark	137	1.1	39	1.3	56	1.6	228	2.1	40	2.9	236	2.5
	Bavarian CD	1078	11.9	347	12.0	3003	10.3	4291	11.0	558	12.0	3096	14.5
	BIFAP	54	2.9	51	4.8	30	2.4	108	3.2	7	1.4	88	2.8
	SIDIAP	56	2.6	43	3.3	16	1.9	57	2.4	11	1.6	92	4.8
	CPRD	59	7.6	55	8.0	15	3.7	312	4.4	13	5.4	124	3.8

By analysing special warnings / precautions in detail for calendar yaers 2012/2013 versus 2015 (Table 29), age ≥ 75 years was revealed as most frequent special warning in all databases and for all three compounds for the calendar years mentioned above. However, according to the age structure of the population covered by the respective database, the lowest proportion was found in Mondriaan. Whereas in some databases, 'esophagitis, gastritis or gastroesophageal reflux' was the second most frequent special warning (Bavarian CD, BIFAP, CPRD, NR Denmark), there was no clear pattern in the remaining databases.

Comparing the proportion of patients with a particular special warning / precaution some differences were found between the databases regarding the calendar years mentioned above. The proportion of patients with a documented diagnoses of 'esophagitis, gastritis or gastroesophageal reflux', for example, was between 34.8% and 41.9% in the Bavarian claims database whereas in other databases somewhat / distint lower proportions were found.

By analysing changes over time (calendar years mentioned above) for the three most common special warnings / precautions, an increase was found regarding the proportion of new DOAC users for several documented special warning / precaution. Comparing precautions and special warnings for each of the DOACS, no clear pattern was found.

Table 29. Number and percentage of new DOAC users with a special warning/precaution (TOP 3) stratified by DOAC compound, database for calendar years 2012 (dabigatran, rivaroxaban), 2013 (apixaban) and 2015 (all DOAC compounds)

	Dabigatran		Rivaroxaban		Apixaban	
	2012	2015	2012	2015	2013	2015
Mondriaan	(1) Age ≥ 75 years (n=19, 37.3%) (2) Hip fracture surgery (n=3, 5.9%) (3) Major trauma (n=1, 2.0%) (3) Moderate renal impairment (CrCL 30-50 mL/min) (n=1, 2.0%)	(1) Age ≥ 75 years (n=13, 25.0%) (2) Major trauma (n=3, 5.8%) (3) Hip fracture surgery (n=2, 3.8%)	(1) Age ≥ 75 years (n=1, 20.0%) (1) Major trauma (n=1, 20.0%)	(1) Age ≥ 75 years (n=78, 31.6%) (2) Treatment of ACS in patients with a prior stroke or TIA (n=12, 4.9%) (3) Moderate renal impairment (creatinine clearance 30 - 49 ml/min) concomitantly receiving other medicinal products which increase rivaroxaban plasma concentrations with caution (n=11, 4.5%)	-	(1) Age ≥ 75 years (n=35, 39.8%) (2) Major trauma, bacterial endocarditis, bronchiectasis or history of pulmonary bleeding, hip fracture surgery, mild or moderate hepatic impairment (Child Pugh A or B), use of thrombolytic agents for the treatment of acute ischemic stroke (each n=1, 1.1%)
NR Denmark	(1) Age ≥ 75 years (n=5101, 42.7%) (2) Esophagitis, gastritis or gastroesophageal reflux (n=941, 7.9%) (3) Major trauma (n=304, 2.5%)	(1) Age ≥ 75 years (n=1375, 46.3%) (2) Esophagitis, gastritis or gastroesophageal reflux (n=235, 7.9%) (3) Major trauma (n=75, 2.5%)	(1) Age ≥ 75 years (n=1126, 32.2%) (2) Esophagitis, gastritis or gastroesophageal reflux (n=227, 6.5%) (3) Major trauma (n=120, 3.4%)	(1) Age ≥ 75 years (n=4345, 39.3%) (2) Esophagitis, gastritis or gastroesophageal reflux (n=952, 8.6%) (3) Major trauma (n=399, 3.6%)	(1) Age ≥ 75 years (n=799, 57.6%) (2) Esophagitis, gastritis or gastroesophageal reflux (n=141, 10.2%) (3) Major trauma (n=55, 4.0%)	(1) Age ≥ 75 years (n=5184, 55.5%) (2) Esophagitis, gastritis or gastroesophageal reflux (n=859, 9.2%) (3) Major trauma (n=370, 4.0%)
Bavarian CD	(1) Age ≥ 75 years (n=4905, 54.3%) (2) Esophagitis, gastritis or gastroesophageal reflux (n=3172, 35.1%) (3) Congenital or acquired coagulation disorders (n=1668; 18.5%)	(1) Age ≥ 75 years (n=1565, 53.9%) (2) Esophagitis, gastritis or gastroesophageal reflux (n=1216, 41.9%) (3) Congenital or acquired coagulation disorders (n=505, 17.4%)	(1) Age ≥ 75 years (n=12931, 44.5%) (2) Esophagitis, gastritis or gastroesophageal reflux (n=10101, 34.8%) (3) Congenital or acquired coagulation disorders (n=5229, 18.0%)	(1) Age ≥ 75 years (n=17257, 44.4%) (2) Esophagitis, gastritis or gastroesophageal reflux (n=16245, 41.8%) (3) Congenital or acquired coagulation disorders (n=6261, 16.1%)	(1) Age ≥ 75 years (n=2631, 56.5%) (2) Esophagitis, gastritis or gastroesophageal reflux (n=1782, 38.3%) (3) Congenital or acquired coagulation disorders (n=783, 16.8%)	(1) Age ≥ 75 years (n=13060, 61.1%) (2) Esophagitis, gastritis or gastroesophageal reflux (n=8962, 41.9%) (3) Congenital or acquired coagulation disorders (n=3900, 18.2%)
BIFAP	(1) Age ≥ 75 years (n=1119, 60.4%) (2) Esophagitis, gastritis or gastroesophageal reflux (n=197, 10.6%) (3) Congenital or acquired coagulation disorders (n=130, 7.0%)	(1) Age ≥ 75 years (n=625, 58.9%) (2) Esophagitis, gastritis or gastroesophageal reflux (n=121, 11.4%) (3) Congenital or acquired coagulation disorders (n=117, 11.0%)	(1) Age ≥ 75 years (n=646, 50.6%) (2) Esophagitis, gastritis or gastroesophageal reflux (n=121, 9.5%) (3) Congenital or acquired coagulation disorders (n=77, 6.0%)	(1) Age ≥ 75 years (n=2012, 58.7%) (2) Esophagitis, gastritis or gastroesophageal reflux (n=406, 11.9%) (3) Congenital or acquired coagulation disorders (n=374, 10.9%)	(1) Age ≥ 75 years (n=235, 48.3%) (2) Esophagitis, gastritis or gastroesophageal reflux (n=47, 9.7%) (3) Congenital or acquired coagulation disorders (n=14, 2.9%)	(1) Age ≥ 75 years (n=2090, 66.4%) (2) Esophagitis, gastritis or gastroesophageal reflux (n=376, 12.0%) (3) Congenital or acquired coagulation disorders (n=252, 8.0%)
SIDIAP	(1) Age ≥ 75 years (n=1045, 49.4%) (2) Moderate renal impairment (CrCL 30-50 mL/min) (n=164, 7.7%) (3) Low body weight (n=94, 4.4%)	(1) Age ≥ 75 years (n=624, 47.6%) (2) Moderate renal impairment (CrCL 30-50 mL/min) (n=139, 10.6%) (3) Low body weight (e.g. < 50 kg/60 kg) (n=69, 5.3%)	(1) Age ≥ 75 years (n=361, 43.7%) (2) Low body weight (n=46, 5.6%) (3) Severe renal impairment (creatinine clearance 15 - 29 ml/min) (n=22, 2.7%)	(1) Age ≥ 75 years (n=1192, 49.6%) (2) Low body weight < 50 kg/60 kg (n=159, 6.6%) (3) Bronchiectasis or history of pulmonary bleeding (n=88, 3.7%)	(1) Age ≥ 75 years (n=275, 39.3%) (2) Mild or moderate hepatic impairment (Child Pugh A or B) (n=42, 6.0%) (3) Severe renal impairment (creatinine clearance 15-29 ml/min) (n=19, 2.7%)	(1) Age ≥ 75 years (n=1214, 63.7%) (2) Low body weight (n=170, 8.9%) (3) Severe renal impairment (creatinine clearance 15-29 ml/min) (n=127, 6.7%)
CPRD	(1) Age ≥ 75 years (n=397, 51.4%) (2) Esophagitis, gastritis or gastroesophageal reflux	(1) Age ≥ 75 years (n=374, 54.2%) (2) Esophagitis, gastritis or gastroesophageal reflux	(1) Age ≥ 75 years (n=191, 46.6%) (2) Esophagitis, gastritis or gastroesophageal reflux	(1) Age ≥ 75 years (n=3552, 49.7%) (2) Esophagitis, gastritis or gastroesophageal reflux	(1) Age ≥ 75 years (n=129, 54.0%) (2) Esophagitis, gastritis or gastroesophageal reflux	(1) Age ≥ 75 years (n=1916, 59.3%) (2) Esophagitis, gastritis or gastroesophageal reflux

	(n=198, 25.6%) (3) Moderate renal impairment (CrCL 30-50 mL/min) (n=159, 20.6%)	(n=184, 26.7%) (3) Moderate renal impairment (CrCL 30-50 mL/min) (n=130, 18.8%)	(n=96, 23.4%) (3) Moderate renal impairment (creatinine clearance 30 - 49 ml/min) concomitantly receiving other medicinal products which increase rivaroxaban plasma concentrations with caution (n=17, 4.1%)	(n=1852, 25.9%) (3) Bronchiectasis or history of pulmonary bleeding (n=409, 5.7%)	(n=71, 29.7%) (3) Bronchiectasis or history of pulmonary bleeding (n=18, 7.5%)	(849, 26.3%) (3) Bronchiectasis or history of pulmonary bleeding (n=178, 5.5%)
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* Time window for identification of events: Hip fracture surgery: 6 months prior to index date; Major trauma: 6 months prior to index date; Moderate renal impairment (CrCL 30-50 mL/min): 12 months prior to index date; Treatment of ACS in patients with a prior stroke or TIA: 6 months prior to index date); Moderate renal impairment (creatinine clearance 30 - 49 ml/min) concomitantly receiving other medicinal products which increase rivaroxaban plasma concentrations with caution: 12 months prior to index date; Bacterial endocarditis: 6 months prior to index date; use of thrombolytic agents for the treatment of acute ischemic stroke: 6 months prior to index date; Severe renal creatinine clearance 15 - 29 ml/min with caution: 12 months prior to index date.

Detailed results for special warnings/precautions for each DOAC stratified by database and calendar year are presented in Tables 30, 31 and 32. Further results (stratifications by sex and age groups) are presented in supplemental files.

Table 30. Number and percentage of new dabigatran users with special warnings/precautions stratified by database and calendar year

			Age ≥ 75 years		Low body weight		Congenital or acquired coagulation disorders		Thrombocytopenia		Major trauma		Bacterial endocarditis		Esophagitis, gastritis or gastro-esophageal reflux		Vascular retinopathy		Bronchiectasis or history of pulmonary bleeding		Hip fracture surgery		Moderate renal impairment (12 months prior to index date)	
Calendar year	Database	Total	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
2009	Mondriaan *	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
	NR Denmark	1176	262	22.3	ND	ND	7	0.6	0	0	23	2.0	0	0	70	6.0	0	0	5	0.4	15	1.3	ND	ND
	Bavarian CD	591	95	16.1	ND	ND	35	5.9	7	1.2	36	6.1	0	0	95	16.1	24	4.1	0	0	13	2.2	ND	ND
	BIFAP	266	70	26.3	1	0.4	2	0.8	1	0.4	5	1.9	0	0.0	30	11.3	0	0.0	5	1.9	8	3.0	6	2.3
	SIDIAP	719	192	26.7	14	1.9	5	0.7	0	0.0	16	2.2	0	0.0	13	1.8	0	0.0	4	0.6	0	0.0	19	2.6
	CPRD	14	2	14.3	0	0.0	1	7.1	0	0.0	0	0.0	0	0.0	3	21.4	0	0.0	0	0.0	0	0.0	0	0.0
2010	Mondriaan *	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
	NR Denmark	2208	496	22.5	ND	ND	12	0.5	0	0.0	61	2.8	0	0.0	172	7.8	0	0.0	15	0.7	38	1.7	ND	ND
	Bavarian CD	600	143	23.8	ND	ND	44	7.3	3	0.5	45	7.5	0	0.0	153	25.5	27	4.5	2	0.3	18	3.0	ND	ND
	BIFAP	570	163	28.6	1	0.2	12	2.1	1	0.2	4	0.7	0	0.0	65	11.4	0	0.0	13	2.3	8	1.4	18	3.2
	SIDIAP	1157	279	24.1	26	2.2	13	1.1	1	0.1	36	3.1	0	0.0	27	2.3	0	0.0	11	1.0	1	0.1	44	3.8
	CPRD	42	11	26.2	0	0.0	0	0.0	0	0.0	1	2.4	0	0.0	10	23.8	0	0.0	1	2.4	1	2.4	4	9.5
2011	Mondriaan *	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
	NR Denmark	6967	2768	39.7	ND	ND	128	1.8	6	0.1	137	2.0	5	0.1	531	7.6	<5	NA	78	1.1	52	0.7	ND	ND
	Bavarian CD	4782	2525	52.8	ND	ND	989	20.7	78	1.6	457	9.6	8	0.2	1489	31.1	355	7.4	7	0.1	116	2.4	ND	ND
	BIFAP	960	403	42.0	5	0.5	51	5.3	8	0.8	9	0.9	0	0.0	102	10.6	0	0.0	21	2.2	14	1.5	53	5.5
	SIDIAP	1467	484	33.0	60	4.1	21	1.4	1	0.1	29	2.0	0	0.0	29	2.0	0	0.0	20	1.4	0	0.0	72	4.9
	CPRD	121	51	42.1	1	0.8	0	0.0	0	0.0	2	1.7	0	0.0	27	22.3	0	0.0	4	3.3	2	1.7	22	18.2
2012	Mondriaan	51	19	37.3	0	0.0	0	0.0	0	0.0	1	2.0	0	0.0	0	0.0	0	0.0	0	0.0	3	5.9	1	2.0

			Age ≥ 75 years		Low body weight		Congenital or acquired coagulation disorders		Thrombocytopenia		Major trauma		Bacterial endocarditis		Esophagitis, gastritis or gastro-esophageal reflux		Vascular retinopathy		Bronchiectasis or history of pulmonary bleeding		Hip fracture surgery		Moderate renal impairment (12 month prior to index date)	
Calendar year	Database	Total	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
	NR Denmark	11936	5101	42.7	ND	ND	190	1.6	5	0.0	304	2.5	9	0.1	941	7.9	<5	NA	146	1.2	121	1.0	ND	ND
	Bavarian CD	9037	4905	54.3	ND	ND	1668	18.5	146	1.6	810	9.0	6	0.1	3172	35.1	661	7.3	42	0.5	208	2.3	ND	ND
	BIFAP	1853	1119	60.4	13	0.7	130	7.0	14	0.8	8	0.4	0	0.0	197	10.6	0	0.0	34	1.8	5	0.3	90	4.9
	SIDIAP	2117	1045	49.4	94	4.4	34	1.6	2	0.1	35	1.7	0	0.0	51	2.4	0	0.0	60	2.8	0	0.0	164	7.7
	CPRD	773	397	51.4	11	1.4	9	1.2	0	0.0	11	1.4	0	0.0	198	25.6	0	0.0	45	5.8	6	0.8	159	20.6
2013	Mondriaan	41	17	41.5	0	0.0	0	0.0	0	0.0	1	2.4	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	1	2.4
	NR Denmark	10969	4481	40.9	ND	ND	176	1.6	5	0.0	277	2.5	<5	NA	768	7.0	<5	NA	138	1.3	126	1.1	ND	ND
	Bavarian CD	7876	4425	56.2	ND	ND	1403	17.8	113	1.4	706	9.0	6	0.1	2833	36.0	578	7.3	32	0.4	168	2.1	ND	ND
	BIFAP	1352	793	58.7	14	1.0	109	8.1	14	1.0	6	0.4	0	0.0	146	10.8	1	0.1	21	1.6	5	0.4	70	5.2
	SIDIAP	1758	865	49.2	95	5.4	25	1.4	1	0.1	15	0.9	0	0.0	42	2.4	0	0.0	45	2.6	0	0.0	135	7.7
	CPRD	1106	637	57.6	13	1.2	14	1.3	2	0.2	9	0.8	0	0.0	264	23.9	0	0.0	58	5.2	7	0.6	259	23.4
2014	Mondriaan	42	11	26.2	0	0.0	0	0.0	0	0.0	1	2.4	1	2.4	0	0.0	1	2.4	0	0.0	1	2.4	1	2.4
	NR Denmark	7750	3338	43.1	ND	ND	112	1.4	<5	NA	191	2.5	<5	NA	630	8.1	<5	NA	95	1.2	83	1.1	ND	ND
	Bavarian CD	4260	2381	55.9	ND	ND	764	17.9	68	1.6	403	9.5	3	0.1	1740	40.8	338	7.9	21	0.5	106	2.5	ND	ND
	BIFAP	1063	616	57.9	11	1.0	91	8.6	11	1.0	8	0.8	1	0.1	107	10.1	0	0.0	27	2.5	2	0.2	67	6.3
	SIDIAP	1519	711	46.8	92	6.1	19	1.3	2	0.1	10	0.7	0	0.0	39	2.6	0	0.0	48	3.2	3	0.2	129	8.5
	CPRD	930	487	52.4	13	1.4	11	1.2	0	0.0	9	1.0	0	0.0	234	25.2	0	0.0	40	4.3	7	0.8	163	17.5
2015	Mondriaan	52	13	25.0	0	0.0	0	0.0	0	0.0	3	5.8	0	0.0	0	0.0	0	0.0	0	0.0	2	3.8	1	1.9
	NR Denmark	2971	1375	46.3	ND	ND	49	1.6	<5	NA	75	2.5	<5	NA	235	7.9	0	0.0	55	1.9	20	0.7	ND	ND
	Bavarian CD	2901	1565	53.9	ND	ND	505	17.4	36	1.2	250	8.6	1	0.0	1216	41.9	197	6.8	10	0.3	51	1.8	ND	ND
	BIFAP	1061	625	58.9	11	1.0	117	11.0	9	0.8	7	0.7	0	0.0	121	11.4	0	0.0	23	2.2	2	0.2	94	8.9
	SIDIAP	1311	624	47.6	69	5.3	25	1.9	3	0.2	15	1.1	0	0.0	36	2.7	0	0.0	42	3.2	3	0.2	139	10.6

			Age ≥ 75 years		Low body weight		Congenital or acquired coagulation disorders		Thrombocytopenia		Major trauma		Bacterial endocarditis		Esophagitis, gastritis or gastro-esophageal reflux		Vascular retinopathy		Bronchiectasis or history of pulmonary bleeding		Hip fracture surgery		Moderate renal impairment (12 month prior to index date)	
Calendar year	Database	Total	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
	CPRD	690	374	54.2	7	1	10	1.4	0	0	8	1.2	0	0.0	184	26.7	0	0	33	4.8	3	0.4	130	18.8

* Due to the low number of new dabigatran users, data for Mondriaan are presented for the period 2012-2015 only

Table 31. Number and percentage of new rivaroxaban users with special warnings/precautions stratified by database and calendar year

			Age ≥ 75 years		Low body weight		Congenital or acquired coagulation disorders		Thrombocytopenia		Major trauma		Bacterial endocarditis		Esophagitis, gastritis or gastroesophageal reflux		Vascular retinopathy		Bronchiectasis or history of pulmonary bleeding		Hip fracture surgery		Severe renal creatinine clearance 15 - 29 ml/min with caution		Moderate renal impairment concomitantly receiving other medicinal products which increase rivaroxaban plasma concentrations with caution		Contra-indicated for the treatment of ACS in patients with a prior stroke or TIA	
Calendar year	Database	Total	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
2009	Mondriaan *	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
	NR Denmark	1099	284	25.8	ND	ND	<5	NA	0	0	21	1.9	0	0	51	4.6	0	0	11	1.0	14	1.3	ND	ND	ND	ND	6	0.5
	Bavarian CD	263	80	30.4	ND	ND	18	6.8	0	0.0	20	7.6	0	0.0	56	21.3	23	8.7	0	0.0	9	3.4	ND	ND	ND	ND	ND	ND
	BIFAP	118	23	19.5	0	0.0	1	0.8	0	0.0	2	1.7	0	0.0	11	9.3	0	0.0	1	0.8	3	2.5	0	0.0	0	0.0	ND	ND
	SIDIAP	176	35	19.9	3	1.7	1	0.6	0	0.0	4	2.3	0	0.0	4	2.3	0	0.0	3	1.7	0	0.0	0	0.0	0	0.0	0	0.0
	CPRD	64	16	25.0	2	3.1	1	1.6	0	0.0	1	1.6	0	0.0	13	20.3	0	0.0	1	1.6	1	1.6	0	0.0	0	0.0	0	0.0
2010	Mondriaan *	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
	NR Denmark	1882	487	25.9	ND	ND	10	0.5	0	0.0	55	2.9	0	0.0	137	7.3	0	0.0	27	1.4	30	1.6	ND	ND	ND	ND	5	0.3
	Bavarian CD	452	148	32.7	ND	ND	39	8.6	5	1.1	35	7.7	0	0.0	123	27.2	33	7.3	1	0.2	17	3.8	ND	ND	ND	ND	ND	ND
	BIFAP	419	102	24.3	0	0.0	3	0.7	2	0.5	5	1.2	0	0.0	34	8.1	0	0.0	8	1.9	6	1.4	1	0.2	0	0.0	ND	ND
	SIDIAP	587	153	26.1	15	2.6	4	0.7	1	0.2	18	3.1	0	0.0	14	2.4	0	0.0	7	1.2	4	0.7	4	0.7	0	0.0	0	0.0
	CPRD	123	38	30.9	0	0.0	0	0.0	0	0.0	1	0.8	0	0.0	32	26.0	0	0.0	5	4.1	1	0.8	1	0.8	1	0.8	0	0.0
2011	Mondriaan *	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
	NR Denmark	2360	598	25.3	ND	ND	17	0.7	<5	NA	61	2.6	0	0.0	122	5.2	0	0.0	22	0.9	35	1.5	ND	ND	ND	ND	10	0.4

			Age ≥ 75 years		Low body weight		Congenital or acquired coagulation disorders		Thrombocytopenia		Major trauma		Bacterial endocarditis		Esophagitis, gastritis or gastroesophageal reflux		Vascular retinopathy		Bronchiectasis or history of pulmonary bleeding		Hip fracture surgery		Severe renal creatinine clearance 15 - 29 ml/min with caution		Moderate renal impairment concomitantly receiving other medicinal products which increase rivaroxaban plasma concentrations with caution		Contraindicated for the treatment of ACS in patients with a prior stroke or TIA	
	Bavarian CD	946	34.4	36.4	ND	ND	12.9	13.6	16	1.7	99	10.5	0	0.0	31.1	32.9	56	5.9	1	0.1	26	2.7	ND	ND	ND	ND	ND	ND
	BIFAP	530	11.6	21.9	1	0.2	1	0.2	1	0.2	4	0.8	0	0.0	61	11.5	0	0.0	7	1.3	13	2.5	0	0.0	1	0.2	ND	ND
	SIDIAP	716	14.8	20.7	16	2.2	8	1.1	1	0.1	20	2.8	0	0.0	21	2.9	0	0.0	10	1.4	0	0.0	6	0.8	0	0.0	0	0.0
	CPRD	87	25	28.7	0	0.0	1	1.1	0	0.0	0	0.0	0	0.0	18	20.7	0	0.0	3	3.4	0	0.0	0	0.0	2	2.3	0	0.0
2012	Mondriaan	5	1	20.0	0	0.0	0	0.0	0	0.0	1	20.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
	NR Denmark	3502	11.26	32.2	ND	ND	86	2.5	<5	NA	12.0	3.4	<5	NA	22.7	6.5	0	0.0	35	1.0	64	1.8	ND	ND	ND	ND	62	1.8
	Bavarian CD	29030	12.931	44.5	ND	ND	52.29	18.0	50.0	1.7	28.36	9.8	27	0.1	10.101	34.8	18.54	6.4	11.3	0.4	71.0	2.4	ND	ND	ND	ND	ND	ND
	BIFAP	1276	64.6	50.6	17	1.3	77	6.0	7	0.5	15	1.2	0	0.0	12.1	9.5	1	0.1	18	1.4	12	0.9	2	0.2	11	0.9	ND	ND
	SIDIAP	827	36.1	43.7	46	5.6	19	2.3	3	0.4	20	2.4	0	0.0	16	1.9	0	0.0	17	2.1	1	0.1	22	2.7	1	0.1	3	0.4
	CPRD	410	19.1	46.6	8	2.0	12	2.9	0	0.0	8	2.0	0	0.0	96	23.4	0	0.0	16	3.9	3	0.7	4	1.0	17	4.1	2	0.5
2013	Mondriaan	53	11	20.8	0	0.0	0	0.0	0	0.0	12	22.6	0	0.0	0	0.0	1	1.9	0	0.0	1	1.9	0	0.0	1	1.9	4	7.5
	NR Denmark	8269	32.52	39.3	ND	ND	23.9	2.9	<5	NA	31.7	3.8	<5	NA	68.5	8.3	<5	NA	10.8	1.3	14.7	1.8	ND	ND	ND	ND	24.0	2.9
	Bavarian CD	50646	23.599	46.6	ND	ND	87.08	17.2	73.7	1.5	50.31	9.9	26	0.1	19.240	38.0	32.08	6.3	18.0	0.4	13.84	2.7	ND	ND	ND	ND	ND	ND
	BIFAP	3070	18.18	59.2	31	1.0	21.8	7.1	20	0.7	18	0.6	0	0.0	31.3	10.2	1	0.0	59	1.9	12	0.4	10	0.3	22	0.7	ND	ND
	SIDIAP	1906	10.18	53.4	10.9	5.7	50	2.6	1	0.1	29	1.5	0	0.0	50	2.6	0	0.0	58	3.0	2	0.1	72	3.8	3	0.2	15	0.8

			Age ≥ 75 years		Low body weight		Congenital or acquired coagulation disorders		Thrombocytopenia		Major trauma		Bacterial endocarditis		Esophagitis, gastritis or gastroesophageal reflux		Vascular retinopathy		Bronchiectasis or history of pulmonary bleeding		Hip fracture surgery		Severe renal creatinine clearance 15 - 29 ml/min with caution		Moderate renal impairment concomitantly receiving other medicinal products which increase rivaroxaban plasma concentrations with caution		Contraindicated for the treatment of ACS in patients with a prior stroke or TIA	
	CPRD	2259	11 56	51. 2	38	1.7	51	2.3	0	0.0	38	1.7	1	0.0	56 5	25. 0	0	0.0	97	4.3	23	1.0	20	0.9	12 7	5.6	7	0.3
2014	Mondriaan	163	50	30. 7	0	0.0	0	0.0	0	0.0	3	1.8	2	1.2	0	0.0	3	1.8	3	1.8	0	0.0	0	0.0	2	1.2	12	7.4
	NR Denmark	8889	37 08	41. 7	ND	ND	25 8	2.9	<5	NA	37 7	4.2	<5	NA	72 2	8.1	0	0.0	11 2	1.3	16 1	1.8	ND	ND	ND	ND	20 8	2.3
	Bavarian CD	4766 5	22 11 5	46. 4	ND	ND	80 54	16. 9	72 1	1.5	47 46	10. 0	27	0.1	19 01 8	39. 9	27 03	5.7	21 0	0.4	12 80	2.7	ND	ND	ND	ND	ND	ND
	BIFAP	3210	18 82	58. 6	27	0.8	28 1	8.8	28	0.9	30	0.9	0	0.0	37 1	11. 6	2	0.1	68	2.1	13	0.4	12	0.4	30	0.9	ND	ND
	SIDIAP	2081	10 09	48. 5	12 2	5.9	42	2.0	5	0.2	22	1.1	0	0.0	69	3.3	0	0.0	58	2.8	2	0.1	70	3.4	8	0.4	17	0.8
	CPRD	4781	24 00	50. 2	72	1.5	83	1.7	2	0.0	67	1.4	2	0.0	11 85	24. 8	0	0.0	23 4	4.9	44	0.9	60	1.3	26 8	5.6	17	0.4
2015	Mondriaan	247	78	31. 6	0	0.0	0	0.0	0	0.0	7	2.8	1	0.4	0	0.0	3	1.2	1	0.4	3	1.2	0	0.0	11	4.5	12	4.9
	NR Denmark	1106 0	43 45	39. 3	ND	ND	27 4	2.5	7	0.1	39 9	3.6	10	0.1	95 2	8.6	0	0.0	14 8	1.3	14 4	1.3	ND	ND	ND	ND	25 8	2.3
	Bavarian CD	3883 3	17 25 7	44. 4	ND	ND	62 61	16. 1	62 9	1.6	38 94	10. 0	22	0.1	16 24 5	41. 8	20 89	5.4	16 6	0.4	11 19	2.9	ND	ND	ND	ND	ND	ND
	BIFAP	3425	20 12	58. 7	46	1.3	37 4	10. 9	32	0.9	28	0.8	0	0.0	40 6	11. 9	0	0.0	65	1.9	11	0.3	13	0.4	31	0.9	ND	ND
	SIDIAP	2402	11 92	49. 6	15 9	6.6	69	2.9	7	0.3	30	1.2	0	0.0	74	3.1	0	0.0	88	3.7	5	0.2	82	3.4	1	0.0	8	0.3
	CPRD	7154	35 52	49. 7	10 5	1.5	12 0	1.7	5	0.1	99	1.4	1	0	18 52	25. 9	0	0	40 9	5.7	57	0.8	90	1.3	31 3	4.4	26	0.4

* Due to the low number of new rivaroxaban users. data for Mondriaan are presented for the period 2012-2015 only

Table 32. Number and percentage of new apixaban users with special warnings/precautions stratified by database and calendar year

Year	Data-base	Total	Age ≥ 75 years		Low body weight		Congenital or acquired coagulation disorders		Thrombocytopenia		Major trauma		Bacterial endocarditis		Esophagitis, gastritis or gastroesophageal reflux		Vascular retinopathy		Bronchiectasis or history of pulmonary bleeding		Hip fracture surgery		Severe renal impairment (creatinine clearance 15-29 mL/min)		Mild or moderate hepatic impairment (Child Pugh A or B) *		Elevated liver enzymes ALT/AST >2 x ULN or total bilirubin ≥ 1.5 x ULN		Use of thrombolytic agents for the treatment of acute ischemic stroke		Prosthetic heart valves	
			n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
2012	Mondriaan	0	0		0		0		0		0		0		0		0		0		0		0		0						0	
	NR Denmark	-																														
	Bavarian CD	614	124	20.2	N D	N D	37	6.0	4	0.7	44	7.2	1	0.2	20	3.2	24	3.9	1	0.2	15	2.4	N D	N D	N D	N D	N D	N D	N D	N D	N D	N D
	BIFAP	88	27	30.7	1	1.1	0	0.0	0	0.0	0	0.0	0	0.0	9	10.2	0	0.0	1	1.1	0	0.0	0	0.0	0	0.0	N D	N D	N D	N D	0	0.0
	SIDIAP	146	43	29.5	1	0.7	1	0.7	0	0.0	4	2.7	0	0.0	11	7.5	0	0.0	2	1.4	0	0.0	0	0.0	0	0.0	N D	N D	0	0.0	0	0.0
	CPRD	2	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	1	50.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
2013	Mondriaan	3	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	N D	N D	0	0.0	0	0.0
	NR Denmark	1388	799	57.6	N D	N D	46	3.2	0	0.0	55	4.0	<5	NA	14	1.2	<5	NA	24	1.7	18	1.3	N D	N D	16	1.2	N D	N D	0	0.0	26	1.9
	Bavarian CD	4654	2631	56.5	N D	N D	78	16.8	62	1.3	44	9.5	8	0.2	17	3.8	27	5.9	23	0.5	11	2.4	N D	N D	N D	N D	N D	N D	N D	N D	N D	N D
	BIFAP	487	235	48.3	5	1.0	14	2.9	2	0.4	2	0.4	0	0.0	47	9.7	0	0.0	3	0.6	2	0.4	3	0.6	1	0.2	N D	N D	N D	N D	1	0.2
	SIDIAP	700	275	39.3	32	4.6	10	1.4	0	0.0	14	2.0	0	0.0	7	1.0	0	0.0	16	2.3	1	0.1	19	2.7	42	6.0	N D	N D	0	0.0	1	0.1
	CPRD	239	129	54.0	4	1.7	4	1.7	1	0.4	2	0.8	0	0.0	71	29.7	0	0.0	18	7.5	2	0.8	7	2.9	0	0.0	0	0.0	0	0.0	2	0.8
2014	Mondriaan	12	6	50.0	1	8.3	0	0.0	0	0.0	1	8.3	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	N D	N D	0	0.0	0	0.0
	NR Denmark	5324	3062	57.5	N D	N D	11	2.9	5	0.1	20	3.9	5	0.1	50	9.6	<5	NA	99	1.9	82	1.5	N D	N D	64	1.2	N D	N D	0	0.0	93	1.7
	Bavarian CD	13315	82	62.8	N D	N D	24	18.2	20	1.5	13	10.2	14	1.1	53	40.2	92	6.9	53	0.4	36	2.7	N D	N D	N D	N D	N D	N D	N D	N D	N D	N D
	BIFAP	2081	1390	66.8	24	1.6	16	8.1	20	1.2	21	1.0	1	0.0	23	11.3	0	0.0	47	2.3	13	0.6	17	0.8	4	0.2	N D	N D	N D	N D	1	0.0
	SIDIAP	1665	913	54.8	14	8.5	38	2.3	6	0.4	22	1.3	0	0.0	51	3.1	0	0.0	57	3.4	4	0.2	61	3.7	93	5.6	N D	N D	0	0.0	2	0.1
	CPRD	1467	861	58.7	29	2.0	20	1.4	2	0.1	13	0.9	0	0.0	41	28.3	1	0.1	71	4.8	8	0.5	25	1.7	26	1.8	0	0.0	0	0.0	21	1.4
2015	Mondriaan	88	35	39.8	0	0.0	0	0.0	0	0.0	1	1.1	1	1.1	0	0.0	0	0.0	1	1.1	1	1.1	0	0.0	1	1.1	N D	N D	1	1.1	0	0.0
	NR Denmark	9333	5184	55.5	N D	N D	20	2.6	10	0.1	37	4.0	9	0.1	85	9.2	0	0.0	15	1.7	12	1.4	N D	N D	14	1.5	N D	N D	0	0.0	18	2.0

			Age ≥ 75 years		Low body weight		Congenital or acquired coagulation disorders		Thrombocytopenia		Major trauma		Bacterial endocarditis		Esophagitis, gastritis or gastroesophageal reflux		Vascular retinopathy		Bronchiectasis or history of pulmonary bleeding		Hip fracture surgery		Severe renal impairment (creatinine clearance 15-29 mL/min)		Mild or moderate hepatic impairment (Child Pugh A or B) *		Elevated liver enzymes ALT/AST >2 x ULN or total bilirubin ≥ 1.5 x ULN		Use of thrombolytic agents for the treatment of acute ischemic stroke		Prosthetic heart valves		
	Bavarian CD	21386	13060	61.1	N D	N D	3900	18.2	348	1.6	2347	11.0	210.1	8962	41.9	1375	6.4	129	0.6	637	3.0	N D	N D	N D	N D	N D	N D	N D	N D	N D	N D	N D	
	BIFAP	3146	2090	66.4	39	1.2	252	8.0	29	0.9	38	1.2	00.0	376	12.0	00.0	00.0	78	2.5	16	0.5	23	0.7	5	0.2	N D	N D	N D	N D	N D	N D	9	0.3
	SIDIAP	1907	1214	63.7	170	8.9	51	2.7	3	0.2	34	1.8	00.0	62	3.3	00.0	00.0	73	3.8	7	0.4	127	6.7	118	6.2	N D	N D	0	0.0	11	0.6		
	CPRD	3230	1916	59.3	44	1.4	49	1.5	4	0.1	40	1.2	10	849	26.3	10	0	178	5.5	19	0.6	56	1.7	51	1.6	0	0.0	0	0.0	53	1.6		

10.4.3.5. Potential interactions present in new DOAC users

Summarizing all three DOACS, all databases and the whole study period, an overall proportion of 44.1% was revealed for incident DOAC users with at least one potential interaction. By stratifying this overall measure by the DOAC compound, the respective values for dabigatran, rivaroxaban and apixaban were 51.1%, 43.4% and 37.3% (Table 33).

With regard to the databases, highest proportion of patients with at least 1 potential interaction was found in NR Denmark (59.8%) followed by BIFAP (54.1%) whereas distinct lower (and similar) values were found in Mondriaan (23.2%), CPRD (23.0%), and SIDIAP (22.4%). Results stratified by database and DOAC compound are given in Table 33.

Table 33. Number and percentage of new DOAC users with at least 1 potential interaction (PI) stratified for DOAC compound and database (whole study period)

	All DOACs			Dabigatran			Rivaroxaban			Apixaban		
	Total	>=1 PI		Total	>=1 PI		Total	>=1 PI		Total	>=1 PI	
	n	n	%	n	n	%	n	n	%	n	n	%
Mondriaan	757	176	23.2	186	51	27.4	468	115	24.6	103	10	9.7
NR Denmark	97325	47565	48.9	44219	25692	58.1	37061	16671	45.0	16045	5202	32.4
Bavarian CD	237864	108068	45.4	30047	14559	48.5	167835	76418	45.5	39982	17091	42.7
BIFAP	24977	13502	54.1	7127	4387	61.6	12048	6439	53.4	5802	2676	46.1
SIDIAP	23161	5189	22.4	10048	2593	25.8	8695	1713	19.7	4418	883	20.0
CPRD	23492	5402	23.0	3676	1390	37.8	14878	3264	21.9	4938	748	15.1
Total (all databases)	407576	179902	44.1	95303	48672	51.1	240985	104620	43.4	71288	26610	37.3

Stratifying the aforementioned DOAC-specific summarized measures by calendar year (table 34), a decrease was found between 2013 and 2015 (period with available data for all three DOACs in all databases) regarding the proportion of potential interactions. In 2015, the respective values for dabigatran, rivaroxaban, and apixaban were 39.8%, 37.6%, and 34.9%, respectively.

Table 34. Number and percentage of new DOAC users with at least 1 potential interaction (PI) stratified for DOAC compound and calendar year (all databases)

	All DOACs			Dabigatran			Rivaroxaban			Apixaban		
	Total	>=1 PI		Total	>=1 PI		Total	>=1 PI		Total	>=1 PI	
	n	n	%	n	n	%	n	n	%	n	n	%
2008	244	193	79.1	244	193	79.1						
2009	4486	1915	42.7	2766	1156	41.8	1720	759	44.1			
2010	8040	3086	38.4	4577	1721	37.6	3463	1365	39.4			
2011	18949	10555	55.7	14297	7930	55.5	4639	2618	56.4	13	7	53.8
2012	61667	32900	53.4	25767	14387	55.8	35050	18022	51.4	850	491	57.8
2013	96776	45357	46.9	23102	11953	51.7	66203	30167	45.6	7471	3237	43.3
2014	106217	44939	42.3	15564	7753	49.8	66789	27945	41.8	23864	9241	38.7
2015	111197	40957	36.8	8986	3579	39.8	63121	23744	37.6	39090	13634	34.9
Total (all years)	407576	179902	44.1	95303	48672	51.1	240985	104620	43.4	71288	26610	37.3

For evaluating time trends of potential interactions in more detail (database-specific), a comparison was made using results for calendar years 2012 (dabigatran, rivaroxaban) or 2013 (apixaban) representing the first calendar year of NVAf SmPC-labelling and calendar year 2015 (end of study period, Table 35).

The proportion of patients with at least one potential interaction was between 11.4% (Mondriaan, apixaban, 2015) and 72.8% (NR Denmark, rivaroxaban, 2012). Regarding changes over time, a decreased proportion of potential interactions was found in most databases and for most compounds. In most of the patients with potential interaction only one potential interaction was present (Table 35). Respective results for other calendar years of the study period are part of the supplemental files.

Table 35. Number and percentage of new DOAC users stratified for DOAC compound, database and number of potential interactions (PI) for the years 2012 (rivaroxaban, dabigatran) and 2013 (apixaban) in comparison to 2015 (all three DOAC compounds).

No. of PI	Database	Dabigatran				Rivaroxaban				Apixaban			
		2012		2015		2012		2015		2013		2015	
		No. new users	%	No. new users	%	No. new users	%	No. new users	%	No. new users	%	No. new users	%
Total (n>1)	Mondriaan	13	25.5	15	28.9	1	20.0	46	18.6	0	0	10	11.4
	NR Denmark	7586	63.6	1255	42.2	2548	72.8	3152	28.5	637	45.9	2524	27.0
	Bavarian CD	4398	48.7	1330	45.8	1435	49.4	1742	44.9	2132	45.8	8925	41.7
	BIFAP	1253	66.6	490	46.2	822	64.4	1387	40.5	300	61.6	1243	39.5
	SIDIAP	812	38.4	275	21.0	200	24.2	399	16.6	99	14.1	333	17.5
	CPRD	325	42.0	214	31.0	100	24.4	1333	18.6	69	28.9	599	18.5
n=1	Mondriaan	9	17.6	13	25.0	1	20.0	33	13.4	0	0	10	11.4
	NR Denmark	4253	35.6	708	23.8	1175	33.6	2128	19.2	349	25.1	1409	15.1
	Bavarian CD	3418	37.8	1067	36.8	1191	41.1	1487	38.3	1871	39.9	7502	35.1
	BIFAP	763	41.2	379	35.7	613	48.0	1131	33.0	221	45.4	1011	32.1
	SIDIAP	488	23.1	213	16.3	135	16.3	326	13.6	76	10.9	276	14.5
	CPRD	239	30.9	178	25.8	85	20.7	1221	17.1	61	25.5	499	15.4
n=2	Mondriaan	2	3.9	1	1.9	0	0	13	5.3	0	0	0	0
	NR Denmark	2132	17.9	357	12.0	370	10.6	863	7.8	221	15.9	842	9.0
	Bavarian CD	866	9.6	232	8.0	2294	7.9	2439	6.3	245	5.2	1345	6.3
	BIFAP	372	20.1	101	9.5	184	14.4	236	6.9	69	14.2	212	6.7
	SIDIAP	226	10.7	60	4.6	53	6.4	66	2.8	16	2.3	50	2.6
	CPRD	76	9.8	30	4.3	13	3.2	105	1.5	6	2.5	92	2.8
n≥3	Mondriaan	2	3.9	1	1.9	0	0	0	0	0	0	0	0
	NR Denmark	1201	10.1	190	6.4	1003	28.6	161	1.5	67	4.8	273	2.9
	Bavarian CD	114	1.3	31	1.1	138	0.5	112	0.3	16	0.3	78	0.4
	BIFAP	118	6.4	10	0.9	25	2.0	20	0.6	10	2.1	20	0.6
	SIDIAP	98	4.6	2	0.2	12	1.5	7	0.3	7	1.0	7	0.4
	CPRD	10	1.3	6	0.9	2	0.5	7	0.1	2	0.8	8	0.2

By analysing potential interactions in detail (Table 36), some differences were found between the databases regarding the three most frequent contraindications. Whereas in most databases (Mondriaan, Bavarian CD, and BIFAP) concomitant treatment with NSAIDs was the most common potential interaction, a somewhat different pattern was found in CPRD, SIDIAP, and NR Denmark. Other relevant potential interacting compounds were the category 'Anticoagulants and antiplatelets, dextran, sulfinpyrazone' and regarding single compounds, ASA, amiodarone, and SSRIs/SNRIs were most frequent.

Comparing the proportion of patients with a particular potential interaction some differences were found between the databases, for example for concomitant NSAID use. With regard to calendar years mentioned above, the highest proportion of concomitant NSAID use was found in new DOAC users in BIFAP (apixaban, 2013: 46.8%). With regard to changes over time (comparing results for calendar years mentioned above), different patterns were found for particular potential interacting compounds. For most DOAC compounds and most database, a decrease in concomitant NSAID prescriptions were found which was particularly pronounced in the Spanish (BIFAP), in the Catalan database (SIDIAP), and in the Danish database (NR Denmark).

Table 36. Number and percentage of new DOAC users with a potential interaction* (TOP 3) stratified by DOAC compound, database for calendar years 2012 (dabigatran, rivaroxaban), 2013 (apixaban) and 2015 (all DOAC compounds)

	Dabigatran		Rivaroxaban		Apixaban	
	2012	2015	2012	2015	2013	2015
Mondriaan	(1) NSAID (n=9, 17.6%) (2) Anticoagulants and antiplatelets, dextran, sulfinpyrazone (n=3, 5.9%) (3) Amiodarone (n=2, 3.9%)	(1) NSAID (n=6, 11.5%) (2) SSRI/SNRI (n=3, 5.8%) (3) Amiodarone, verapamil, (anticoagulants and antiplatelets, dextran, sulfinpyrazone), ASA (each n=2, 3.8%)	(1) NSAID (n=1, 20%)	(1) NSAID (n=21, 8.5%) (2) Anticoagulants and antiplatelets, dextran, sulfinpyrazone (n=12, 4.9%) (3) Verapamil (n=10, 4.0%)	-	(1) NSAID (n=3, 3.4%) (1) Verapamil (n=3, 3.4%) (1) Amiodarone (n=3, 3.4%)
NR Denmark	(1) Anticoagulants and antiplatelets, dextran, sulfinpyrazone (n=5288, 44.3%) (2) NSAID (n=3326, 27.9%) (3) ASA (n=2046, 17.1%)	(1) Anticoagulants and antiplatelets, dextran, sulfinpyrazone (n=1237, 41.6%) (2) ASA (n=320, 10.8%) (3) SSRI/SNRI (n=269, 9.1%)	(1) NSAID (n=1036, 29.6%) (2) Anticoagulants and antiplatelets, dextran, sulfinpyrazone (n=979, 28.0%) (3) ASA (n=346, 9.9%) NSAID (n=673, 19.2%)	(1) Anticoagulants and antiplatelets, dextran, sulfinpyrazone (n=3180, 28.8%) (2) NSAID (n=1239, 11.2%) (3) ASA (n=701, 6.3%)	(1) Anticoagulants and antiplatelets, dextran, sulfinpyrazone (n=629, 45.3%) (2) NSAID (n=239, 17.2%) (3) ASA (n=187, 13.5%)	(1) Anticoagulants and antiplatelets, dextran, sulfinpyrazone (n=3469, 37.2%) (2) ASA (n=757, 8.1%) (3) NSAID (n=696, 7.5%)
Bavarian CD	(1) Anticoagulants and antiplatelets, dextran, sulfinpyrazone (n=2406, 26.6%) (2) NSAID (n=1496, 16.6%) (3) SSRI/SNRI (n=659, 7.3%)	(1) Anticoagulants and antiplatelets, dextran, sulfinpyrazone (n=704, 24.3%) (2) NSAID (n=531; 18.3%) (3) ASA (n=190, 6.5%)	(1) NSAID (n=7556; 26.0%) (2) Anticoagulants and antiplatelets, dextran, sulfinpyrazone (n=7217, 24.9%) (3) ASA (n=1435, 4.9%)	(1) NSAID (n=9816; 25.3%) (2) Anticoagulants and antiplatelets, dextran, sulfinpyrazone (n=8339, 21.5%) (3) ASA (n=1936, 5.0%)	(1) NSAID (n=1173; 25.0%) (2) Anticoagulants and antiplatelets, dextran, sulfinpyrazone (n=974, 20.8%) (3) ASA (n=289, 6.2%)	(1) Anticoagulants and antiplatelets, dextran, sulfinpyrazone (n=5276, 24.7%) (2) NSAID (n=3570; 16.7%) (3) ASA (n=1728; 8.1%)
BIFAP	(1) Anticoagulants and antiplatelets, dextran, sulfinpyrazone (n=673, 36.3%) (2) NSAID (n=592, 31.9%) (3) SSRI/SNRI (n=283, 15.3%)	(1) Anticoagulants and antiplatelets, dextran, sulfinpyrazone (n=228, 21.5%) (2) NSAID (n=132, 12.4%) (3) SSRI/SNRI (n=124, 11.7%)	(1) NSAID (n=493, 38.6%) (2) Anticoagulants and antiplatelets, dextran, sulfinpyrazone (n=401, 31.4%) (3) ASA (n=165, 12.9%)	(1) Anticoagulants and antiplatelets, dextran, sulfinpyrazone (n=716, 20.9%) (2) NSAID (n=583, 17.0%) (3) ASA (n=346, 10.1%)	(1) NSAID (n=228, 46.8%) (2) Anticoagulants and antiplatelets, dextran, sulfinpyrazone (n=108, 22.2%) (3) ASA (n=55, 11.3%)	(1) Anticoagulants and antiplatelets, dextran, sulfinpyrazone (n=654, 20.8%) (2) NSAID (n=455, 14.5%) (3) ASA (n=306, 9.7%)
SIDIAP	(1) NSAID (n=369, 17.4%) (2) SSRI/SNRI (n=299, 14.1%) (3) Anticoagulants and antiplatelets, dextran, sulfinpyrazone (n=275, 13.0%)	(1) SSRI/SNRI (n=107, 8.2%) (2) Amiodarone (n=91, 6.9%) (3) Anticoagulants and antiplatelets, dextran, sulfinpyrazone (n=60, 4.6%)	(1) NSAID (n=110, 13.3%) (2) Anticoagulants and antiplatelets, dextran, sulfinpyrazone (n=81, 9.8%) (3) Amiodarone (n=52, 6.3%)	(1) Amiodarone (n=196, 8.2%) (2) Anticoagulants and antiplatelets, dextran, sulfinpyrazone (n=120, 5.9%) (3) NSAID (n=97, 4.0%)	(1) NSAID (n=49, 7.0%) (2) Anticoagulants and antiplatelets, dextran, sulfinpyrazone (n=35, 5.0%) (3) Amiodarone (n=27, 3.9%)	(1) Amiodarone (n=149, 7.8%) (2) Anticoagulants and antiplatelets, dextran, sulfinpyrazone (n=119, 6.2%) (3) NSAID (n=94, 4.9%)
CPRD	(1) Anticoagulants and antiplatelets, dextran, sulfinpyrazone (n=143, 3.9%) (2) ASA (n=116, 15.0%) (3) SSRI/SNRI (n=88, 2.4%)	(1) Anticoagulants and antiplatelets, dextran, sulfinpyrazone (n=88, 2.4%) (2) ASA (n=71, 10.3%) (3) SSRI/SNRI (n=65, 1.8%)	(1) NSAID (n=45, 11.0%) (2) Anticoagulants and antiplatelets, dextran, sulfinpyrazone (n=40, 9.8%) (3) ASA (n=35, 8.5%)	(1) Anticoagulants and antiplatelets, dextran, sulfinpyrazone (n=729, 10.2%) (2) ASA (n=537, 7.5%) (3) NSAID (n=269, 3.8%)	(1) Anticoagulants and antiplatelets, dextran, sulfinpyrazone (n=30, 12.6%) (2) ASA (n=22, 9.2%) (3) NSAID (n=15, 6.3%)	(1) Anticoagulants and antiplatelets, dextran, sulfinpyrazone (n=340, 10.5%) (2) ASA (n=250, 7.7%) (3) Amiodarone (n=147, 4.6%)

* ASA: Acetylsalicylic acid, NSAID: Nonsteroidal antiinflammatory drug, SNRI: Serotonin and norepinephrine reuptake inhibitors, SSRI: Selective Serotonin Reuptake Inhibitors

Detailed results for potential interactions for each DOAC stratified by database and calendar year are presented in Tables 37, 38 and 39. Further results (stratifications by sex and age groups) are presented in supplemental files.

Table 37. Number and percentage of new dabigatran users with potential interactions stratified by database and calendar year - part 1

			Systemic ketoconazole		Ciclosporine		Itraconazole		Dronedarone		Tacrolimus		Amiodarone		Posaconazole		Quinidine		Verapamil		Ticagrelor	
Year	Database	Total	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
2009	Mondriaan *	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
	NR Denmark	1176	0	0	0	0	<5	NA	0	0	0	0	<5	NA	0	0	0	0	6	0.5	0	0
	Bavarian CD	591	0	0.0	1	0.2	0	0.0	0	0.0	0	0.0	2	0.3	0	0.0		0	9	1.5	0	0.0
	BIFAP	266	1	0.4	0	0.0	2	0.8	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	2	0.8	0	0.0
	SIDIAP	719	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	1	0.1	0	0.0	0	0.0	0	0.0	0	0.0
	CPRD	14	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
2010	Mondriaan *	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
	NR Denmark	2208	0	0	0	0	<5	NA	0	0	0	0	<5	NA	0	0	0	0	10	0.5	0	0
	Bavarian CD	600	0	0.0	1	0.2	0	0.0	9	1.5	0	0.0	5	0.8	0	0.0	0	0	7	1.2	0	0.0
	BIFAP	570	0	0.0	0	0.0	1	0.2	1	0.2	0	0.0	8	1.4	0	0.0	0	0.0	6	1.1	0	0.0
	SIDIAP	1157	1	0.1	0	0.0	1	0.1	7	0.6	0	0.0	8	0.7	0	0.0	0	0.0	2	0.2	0	0.0
	CPRD	42	0	0.0	0	0.0	0	0.0	1	2.4	1	2.4	1	2.4	0	0.0	0	0.0	0	0.0	0	0.0
2011	Mondriaan *	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
	NR Denmark	6967	<5	NA	0	0	10	0.1	32	0.5	0	0	273	3.9	0	0	0	0	370	5.3	14	0.2
	Bavarian CD	4782	0	0.0	0	0.0	2	0.0	112	2.3	1	0.0	191	4.0	0	0.0	0	0	122	2.6	6	0.1
	BIFAP	960	1	0.1	0	0.0	1	0.1	8	0.8	1	0.1	39	4.1	0	0.0	0	0.0	14	1.5	0	0.0
	SIDIAP	1467	2	0.1	1	0.1	0	0.0	18	1.2	1	0.1	50	3.4	0	0.0	0	0.0	10	0.7	0	0.0
	CPRD	121	0	0.0	0	0.0	0	0.0	2	1.7	0	0.0	4	3.3	0	0.0	0	0.0	4	3.3	1	0.8
2012	Mondriaan	51	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	2	3.9	0	0.0	0	0.0	0	0.0	0	0.0
	NR Denmark	11936	0	0	0	0	31	0.3	56	0.5	0	0	613	5.1	0	0	0	0	678	5.7	36	0.3
	Bavarian CD	9037	0	0.0	6	0.1	6	0.1	138	1.5	0	0.0	426	4.7	0	0.0	0	0	219	2.4	17	0.2
	BIFAP	1853	0	0.0	5	0.3	8	0.4	39	2.1	1	0.1	190	10.3	0	0.0	0	0.0	48	2.6	0	0.0
	SIDIAP	2117	1	0.0	0	0.0	5	0.2	22	1.0	0	0.0	178	8.4	0	0.0	0	0.0	21	1.0	1	0.0
	CPRD	773	0	0.0	0	0.0	1	0.1	6	0.8	0	0.0	48	6.2	0	0.0	0	0.0	7	0.9	0	0.0

Year	Database	Total	Systemic ketoconazole		Ciclosporine		Itraconazole		Dronedarone		Tacrolimus		Amiodarone		Posaconazole		Quinidine		Verapamil		Ticagrelor	
			n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
2013	Mondriaan	41	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	1	2.4	0	0.0	0	0.0	1	2.4	0	0.0
	NR Denmark	1096	0	0	<5	NA	23	0.2	18	0.2	0	0	670	6.1	0	0	0	0	493	4.5	33	0.3
	Bavarian CD	7876	0	0.0	1	0.0	6	0.1	95	1.2	2	0.0	352	4.5	0	0.0	0	0.0	176	2.2	18	0.2
	BIFAP	1352	0	0.0	0	0.0	3	0.2	23	1.7	1	0.1	119	8.8	0	0.0	0	0.0	20	1.5	0	0.0
	SIDIAP	1758	1	0.1	0	0.0	1	0.1	19	1.1	0	0.0	191	10.9	0	0.0	0	0.0	20	1.1	0	0.0
	CPRD	1106	0	0.0	0	0.0	0	0.0	2	0.2	1	0.1	71	6.4	0	0.0	0	0.0	16	1.4	1	0.1
2014	Mondriaan	42	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	3	7.1	0	0.0
	NR Denmark	7750	0	0	<5	NA	16	0.2	5	0.1	0	0	458	5.9	0	0	0	0	306	3.9	25	0.3
	Bavarian CD	4260	0	0.0	0	0.0	0	0.0	29	0.7	2	0.0	182	4.3	0	0.0	0	0.0	75	1.8	12	0.3
	BIFAP	1063	0	0.0	0	0.0	2	0.2	12	1.1	3	0.3	119	11.2	0	0.0	0	0.0	24	2.3	0	0.0
	SIDIAP	1519	0	0.0	2	0.1	1	0.1	9	0.6	0	0.0	157	10.3	0	0.0	0	0.0	9	0.6	0	0.0
	CPRD	930	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	48	5.2	0	0.0	0	0.0	13	1.4	0	0.0
2015	Mondriaan	52	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	2	3.8	0	0.0	0	0.0	2	3.8	0	0.0
	NR Denmark	2971	0	0	0	0	<5	NA	<5	NA	0	0	130	4.4	0	0	0	0	94	3.2	<5	NA
	Bavarian CD	2901	0	0.0	0	0.0	1	0.0	12	0.4	0	0.0	97	3.3	1	0.0	0	0.0	45	1.6	10	0.3
	BIFAP	1061	0	0.0	0	0.0	0	0.0	6	0.6	2	0.2	92	8.7	0	0.0	0	0.0	14	1.3	2	0.2
	SIDIAP	1311	0	0.0	0	0.0	0	0.0	3	0.2	0	0.0	91	6.9	0	0.0	0	0.0	10	0.8	0	0.0
	CPRD	690	0	0	0	0	0	0	0	0	0	0	33	4.8	0	0.0	0	0.0	9	1.3	2	0.3

* Due to the low number of new dabigatran users, data for Mondriaan are presented for the period 2012-2015 only

Table 37. Number and percentage of new dabigatran users with potential interactions stratified by database and calendar year - part 2

			Rifampicin		Carbamazepine		Phenytoin		Hypericum perforatum		Ritonavir		Anticoagulants/ Anti-platelets		ASA		Clopidogrel		NSAID		Clarithromycin		SSRI/ SNRI	
Year	Database	Total	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
2009	Mondriaan *	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
	NR Denmark	1176	<5	NA	0	0	0	0	0	0	0	0	389	33.1	232	19.7	8	0.7	326	27.7	<5	NA	67	5.7
	Bavarian CD	591	2	0.3	2	0.3	0	0.0	0	0.0	0	0.0	35	5.9	12	2.0	1	0.2	353	59.7	3	0.5	11	1.9
	BIFAP	266	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	34	12.8	19	7.1	3	1.1	155	58.3	0	0.0	21	7.9
	SIDIAP	719	1	0.1	0	0.0	0	0.0	0	0.0	0	0.0	3	0.4	1	0.1	0	0.0	20	2.8	0	0.0	3	0.4
	CPRD	14	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	2	14.3	2	14.3	0	0.0	1	7.1	0	0.0	2	14.3
2010	Mondriaan *	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
	NR Denmark	2208	<5	NA	<5	NA	<5	NA	0	0	0	0	457	20.7	192	8.7	15	0.7	632	28.6	7	0.3	105	4.8
	Bavarian CD	600	0	0.0	2	0.3	0	0.0	0	0.0	0	0.0	74	12.3	20	3.3	7	1.2	344	57.3	4	0.7	26	4.3
	BIFAP	570	2	0.4	1	0.2	1	0.2	0	0	0	0	91	16.0	48	8.4	2	0.4	277	48.6	2	0.4	48	8.4
	SIDIAP	1157	5	0.4	0	0.0	0	0.0	0	0	0	0	33	2.9	21	1.8	3	0.3	60	5.2	6	0.5	33	2.9
	CPRD	42	1	2.4	0	0.0	0	0.0	0	0	0	0	3	7.1	3	7.1		0.0	9	21.4	1	2.4	2	4.8
2011	Mondriaan *	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
	NR Denmark	6967	6	0.1	10	0.1	6	0.1	0	0	0	0	2660	38.2	1138	16.3	173	2.5	2190	31.5	116	1.7	759	10.9
	Bavarian CD	4782	3	0.1	15	0.3	4	0.1	0	0.0	0	0.0	1527	31.9	282	5.9	189	4.0	1009	21.1	41	0.9	311	6.5
	BIFAP	960	1	0.1	1	0.1	4	0.4	0	0	0	0	254	26.5	125	13.0	13	1.4	381	39.7	7	0.7	111	11.6
	SIDIAP	1467	1	0.1	4	0.3	1	0.1	0	0	0	0	96	6.5	52	3.5	14	1.0	146	10.0	11	0.7	94	6.4
	CPRD	121	0	0.0	0	0.0	0	0.0	0	0	0	0	19	15.7	13	10.7	5	4.1	24	19.8	6	5.0	10	8.3
2012	Mondriaan	51	0	0.0	1	2.0	0	0.0	0	0	0	0	3	5.9	1	2.0	1	2.0	9	17.6	0	0.0	1	2.0
	NR Denmark	11936	10	0.1	37	0.3	5	0.0	0	0	0	0	5288	44.3	2046	17.1	377	3.2	3326	27.9	186	1.6	1361	11.4
	Bavarian CD	9037	3	0.0	49	0.5	3	0.0	0	0.0	1	0.0	2406	26.6	592	6.6	327	3.6	1496	16.6	71	0.8	659	7.3
	BIFAP	1853	5	0.3	4	0.2	6	0.3	0	0	0	0	673	36.3	237	12.8	45	2.4	592	31.9	35	1.9	283	15.3
	SIDIAP	2117	5	0.2	4	0.2	5	0.2	0	0	0	0	275	13.0	124	5.9	19	0.9	369	17.4	35	1.7	299	14.1
	CPRD	773	1	0.1	5	0.6	2	0.3	0	0.0	0	0.0	143	18.5	116	15.0	41	5.3	61	7.9	58	7.5	88	11.4

			Rifampicin		Carbamazepine		Phenytoin		Hypericum perforatum		Ritonavir		Anticoagulants/ Anti-platelets		ASA		Clopidogrel		NSAID		Clarithromycin		SSRI/ SNRI	
Year	Database	Total	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
2013	Mondriaan	41	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	3	7.3	0	0.0	8	19.5	0	0.0	0	0.0
	NR Denmark	10969	<5	NA	47	0.4	6	0.1	0	0	0	0	4714	43.0	1506	13.7	355	3.2	2764	25.2	138	1.3	1095	10.0
	Bavarian CD	7876	9	0.1	30	0.4	1	0.0	0	0.0	0	0.0	1739	22.1	441	5.6	296	3.8	1275	16.2	71	0.9	491	6.2
	BIFAP	1352	2	0.1	4	0.3	4	0.3	0	0.0	0	0.0	475	35.1	175	12.9	30	2.2	359	26.6	18	1.3	206	15.2
	SIDIAP	1758	0	0.0	6	0.3	1	0.1	0	0.0	0	0.0	157	8.9	65	3.7	12	0.7	238	13.5	17	1.0	223	12.7
	CPRD	1106	0	0.0	2	0.2	6	0.5	0	0.0	0	0.0	181	16.4	133	12.0	57	5.2	79	7.1	106	9.6	123	11.1
2014	Mondriaan	42	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	6	14.3	36	85.7	0	0.0	5	11.9	0	0.0	1	2.4
	NR Denmark	7750	5	0.1	21	0.3	<5	NA	0	0	0	0	3493	45.1	1056	13.6	329	4.2	1443	18.6	104	1.3	784	10.1
	Bavarian CD	4260	2	0.0	10	0.2	5	0.1	0	0.0	0	0.0	1067	25.0	299	7.0	234	5.5	719	16.9	42	1.0	258	6.1
	BIFAP	1063	2	0.2	2	0.2	3	0.3	0	0.0	0	0.0	310	29.2	119	11.2	23	2.2	260	24.5	11	1.0	141	13.3
	SIDIAP	1519	2	0.1	3	0.2	0	0.0	0	0.0	0	0.0	110	7.2	45	3.0	9	0.6	145	9.5	12	0.8	167	11.0
	CPRD	930	0	0.0	2	0.2	0	0.0	0	0.0	0	0.0	119	12.8	96	10.3	26	2.8	51	5.5	53	5.7	101	10.9
2015	Mondriaan	52	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	2	3.8	2	3.8	0	0.0	6	11.5	0	0.0	3	5.8
	NR Denmark	2971	0	0	9	0.3	<5	NA	0	0	0	0	1237	41.6	320	10.8	166	5.6	246	8.3	22	0.7	269	9.1
	Bavarian CD	2901	1	0.0	17	0.6	2	0.1	0	0.0	1	0.0	704	24.3	190	6.5	157	5.4	531	18.3	22	0.8	182	6.3
	BIFAP	1061	1	0.1	4	0.4	3	0.3	0	0.0	0	0.0	228	21.5	99	9.3	13	1.2	132	12.4	3	0.3	124	11.7
	SIDIAP	1311	0	0.0	3	0.2	3	0.2	0	0.0	0	0.0	60	4.6	38	2.9	2	0.2	55	4.2	5	0.4	107	8.2
	CPRD	690	0	0.0	2	0.3	0	0	0	0.0	0	0.0	88	12.8	71	10.3	16	2.3	34	4.9	23	3.3	65	9.4

* Due to the low number of new dabigatran users, data for Mondriaan are presented for the period 2012-2015 only

ASA: acetylsalicylic acid, NSAID: non steroidal antiinflammatory drug, SNRI: Serotonin and norepinephrine reuptake inhibitors, SSRI: Selective Serotonin Reuptake Inhibitors

Table 38. Number and percentage of new rivaroxaban users with potential interactions stratified by database and calendar year – part 1

Year	Database	Total	Systemic keto-conazole		Ciclosporine		Itraconazole		Dronedarone		Tacrolimus		Amiodarone		Posaconazole		Quinidine		Verapamil		Ticagrelor		Rifampicin	
			n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
2009	Mondriaan *	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
	NR Denmark	1099	0	0	0	0	0	0	0	0	0	0	<5	NA	0	0	0	0	7	0.6	0	0	<5	NA
	Bavarian CD	263	0	0.0	0	0.0		0.0	0	0.0	0	0.0	4	1.5	0	0.0		0	4	1.5	0	0.0	0	0.0
	BIFAP	118	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0	0	0	0	0.0	0	0.0	3	2.5
	SIDIAP	176	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0	0	0	0	0.0	0	0.0	2	1.1
	CPRD	64	0	0.0	0	0.0	1	1.6	0	0.0	0	0.0	0	0.0	0	0	0	0	0	0.0	0	0.0	1	1.6
2010	Mondriaan *	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
	NR Denmark	1882	0	0	0	0	<5	NA	0	0	0	0	<5	NA	0	0	0	0	13	0.7	0	0	<5	NA
	Bavarian CD	452	0	0.0	0	0.0		0.0	2	0.4	0	0.0	2	0.4	0	0.0	0	0	6	1.3	0	0.0	1	0.2
	BIFAP	419	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	2	0.5	0	0	0	0	1	0.2	0	0.0	2	0.5
	SIDIAP	587	0	0.0	0	0.0	1	0.2	0	0.0	0	0.0	3	0.5	0	0	0	0	0	0.0	0	0.0	1	0.2
	CPRD	123	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	1	0.8	0	0	0	0	0	0.0	0	0.0	1	0.8
2011	Mondriaan *	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
	NR Denmark	2360	<5	NA	<5	NA	<5	NA	0	0	0	0	<5	NA	0	0	0	0	21	0.9	<5	NA	7	0.3
	Bavarian CD	946	0	0.0	1	0.1		0.0	6	0.6	0	0.0	23	2.4	0	0.0	0	0	21	2.2	0	0.0	1	0.1
	BIFAP	530	0	0.0	1	0.2	0	0.0	0	0.0	1	0.2	3	0.6	0	0	0	0	2	0.4	0	0.0	4	0.8
	SIDIAP	716	0	0.0	0	0.0	0	0.0	1	0.1	0	0.0	0	0.0	0	0	0	0	1	0.1	0	0.0	0	0.0
	CPRD	87	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0	0	0	0	0.0	0	0.0	0	0.0
2012	Mondriaan	5	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0	0	0	0	0.0	0	0.0	0	0.0
	NR Denmark	3502	0	0	0	0	7	0.2	10	0.3	0	0	85	2.4	0	0	0	0	72	2.1	5	0.1	5	0.1
	Bavarian CD	29030	0	0.0	12	0.0	23	0.1	321	1.1	13	0.0	991	3.4	1	0.0	0	0	541	1.9	33	0.1	26	0.1
	BIFAP	1276	0	0.0	3	0.2	3	0.2	15	1.2	2	0.2	91	7.1	0	0	0	0	28	2.2	0	0.0	4	0.3
	SIDIAP	827	0	0.0	0	0.0	0	0.0	9	1.1	0	0.0	52	6.3	0	0	0	0	2	0.2	0	0.0	0	0.0

			Systemic keto-conazole		Ciclosporine		Itraconazole		Drone-darone		Tacrolimus		Amiodarone		Posaconazole		Quinidine		Verapamil		Ticagrelor		Rifampicin	
Year	Database	Total	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
	CPRD	410	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	12	2.9	0	0	0	0	4	1.0	0	0.0	0	0.0
2013	Mondriaan	53	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	1	1.9	0	0	0	0	1	1.9	0	0.0	0	0.0
	NR Denmark	8269	0	0	<5	NA	20	0.2	7	0.1	0	0	234	2.8	0	0	0	0	245	3.0	18	0.2	17	0.2
	Bavarian CD	50646	0	0.0	32	0.1	17	0.0	424	0.8	20	0.0	1573	3.1	2	0.0	0	0	930	1.8	75	0.1	61	0.1
	BIFAP	3070	1	0.0	0	0.0	13	0.4	46	1.5	3	0.1	228	7.4	0	0	0	0	68	2.2	0	0.0	6	0.2
	SIDIAP	1906	2	0.1	0	0.0	2	0.1	17	0.9	1	0.1	152	8.0	0	0	0	0	22	1.2	0	0.0	3	0.2
	CPRD	2259	0	0.0	0	0.0	3	0.1	7	0.3	2	0.1	75	3.3	0	0	0	0	30	1.3	0	0.0	1	0.0
2014	Mondriaan	163	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	2	1.2	0	0	0	0	9	5.5	0	0.0	0	0.0
	NR Denmark	8889	0	0	<5	NA	13	0.1	8	0.1	0	0	176	2.0	0	0	0	0	226	2.5	11	0.1	7	0.1
	Bavarian CD	47665	0	0.0	23	0.0	18	0.0	270	0.6	13	0.0	1251	2.6	0	0.0	0	0	749	1.6	67	0.1	63	0.1
	BIFAP	3210	0	0.0	1	0.0	8	0.2	38	1.2	5	0.2	215	6.7	0	0	0	0	54	1.7	1	0.0	3	0.1
	SIDIAP	2081	0	0.0	1	0.0	4	0.2	17	0.8	5	0.2	182	8.7	0	0	0	0	14	0.7	1	0.0	1	0.0
	CPRD	4781	0	0.0	0	0.0	3	0.1	8	0.2	0	0.0	159	3.3	0	0	0	0	56	1.2	6	0.1	3	0.1
2015	Mondriaan	247	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	4	1.6	0	0	0	0	10	4.0	1	0.4	0	0.0
	NR Denmark	11060	0	0	0	0	7	0.1	<5	NA	0	0	276	2.5	0	0	0	0	253	2.3	11	0.1	<5	NA
	Bavarian CD	38833	0	0.0	24	0.1	10	0.0	140	0.4	17	0.0	981	2.5	3	0.0	0	0	495	1.3	48	0.1	60	0.2
	BIFAP	3425	0	0.0	1	0.0	3	0.1	27	0.8	4	0.1	235	6.9	0	0	0	0	57	1.7	2	0.1	4	0.1
	SIDIAP	2402	0	0.0	3	0.1	0	0.0	17	0.7	4	0.2	196	8.2	0	0	0	0	21	0.9	0	0.0	1	0.0
	CPRD	7154	0	0	0	0	3	0.0	8	0.1	1	0.0	201	2.8	0	0	0	0	89	1.2	5	0.1	1	0.0

* Due to the low number of new rivaroxaban users, data for Mondriaan are presented for the period 2012-2015 only

Table 38. Number and percentage of new rivaroxaban users with potential interactions stratified by database and calendar year – part 2

			Carbama- zepine		Phenytoin		Hypericum perforatum		Ritonavir		Anticoagu- lants/ Anti- platelets		ASA		Clopidogrel		NSAID		Vorico- nazole		Erythro- mycin		Fluco- nazole	
Year	Database	Total	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
2009	Mondriaan *	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
	NR Denmark	1099	<5	NA	<5	NA	0	0	0	0	324	29.5	176	16.0	<5	NA!	317	28.8	0	0	<5	NA	5	0.5
	Bavarian CD	263	2	0.8	0	0.0	0	0.0	0	0.0	29	11.0	8	3.0	3	1.1	132	50.2	0	0.0	0	0.0	0	0.0
	BIFAP	118	0	0.0	0	0.0	0	0	0	0	19	16.1	9	7.6	0	0.0	88	74.6	0	0	0	0.0	1	0.8
	SIDIAP	176	0	0.0	0	0.0	0	0	0	0	2	1.1	1	0.6	1	0.6	4	2.3	0	0	1	0.6	1	0.6
	CPRD	64	0	0.0	0	0.0	0	0	0	0	7	10.9	7	10.9	0	0.0	18	28.1	0	0	0	0.0	0	0.0
2010	Mondriaan *	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
	NR Denmark	1882	<5	NA	0	0	0	0	0	0	393	20.9	157	8.39	15	0.8	542	28.8	0	0	9	0.5	14	0.7
	Bavarian CD	452	0	0.0	0	0.0	0	0.0	0	0.0	67	14.8	18	4.0	6	1.3	249	55.1	0	0.0	0	0.0	0	0.0
	BIFAP	419	0	0.0	1	0.2	0	0	0	0	60	14.3	33	7.9	3	0.7	254	60.6	0	0	1	0.2	0	0.0
	SIDIAP	587	0	0.0	0	0.0	0	0	0	0	9	1.5	3	0.5	1	0.2	13	2.2	0	0	0	0.0	0	0.0
	CPRD	123	0	0.0	0	0.0	0	0	0	0	14	11.4	12	9.8	2	1.6	32	26.0	0	0	0	0.0	0	0.0
2011	Mondriaan	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
	NR Denmark	2360	<5	NA	0	0	0	0	0	0	481	20.4	198	8.4	26	1.1	931	39.4	0	0	10	0.4	11	0.5
	Bavarian CD	946	3	0.3	2	0.2	0	0.0	0	0.0	187	19.8	48	5.1	8	0.8	472	49.9	0	0.0	0	0.0	0	0.0
	BIFAP	530	1	0.2	0	0.0	0	0	0	0	66	12.5	32	6.0	5	0.9	314	59.2	0	0	2	0.4	0	0.0
	SIDIAP	716	1	0.1	0	0.0	0	0	0	0	7	1.0	5	0.7	1	0.1	13	1.8	0	0	0	0.0	0	0.0
	CPRD	87	0	0.0	0	0.0	0	0	0	0	7	8.0	6	6.9	1	1.1	22	25.3	0	0	0	0.0	0	0.0
2012	Mondriaan	5	0	0.0	0	0.0	0	0	0	0	0	0.0	0	0.0	0	0.0	1	20.0	0	0	0	0.0	0	0.0
	NR Denmark	3502	21	0.6	<5	NA	0	0	0	0	979	28.0	346	9.9	72	2.9	103 6	29.6	0	0	29	0.8	76	2.2
	Bavarian CD	2903 0	154	0.5	26	0.1	0	0.0	3	0.0	721 7	24.9	143 5	4.9	708	2.4	755 6	26.0	0	0.0	7	0.0	0	0.0
	BIFAP	1276	3	0.2	1	0.1	0	0	0	0	401	31.4	165	12.9	30	2.4	493	38.6	0	0	6	0.5	10	0.8
	SIDIAP	827	4	0.5	2	0.2	0	0	0	0	81	9.8	43	5.2	4	0.5	110	13.3	0	0	1	0.1	5	0.6
	CPRD	410	2	0.5	1	0.2	0	0	0	0	40	9.8	35	8.5	10	2.4	45	11.0	0	0	9	2.2	4	1.0

			Carbama- zepine		Phenytoin		Hypericum perforatum		Ritonavir		Anticoagu- lants/ Anti- platelets		ASA		Clopidogrel		NSAID		Vorico- nazole		Erythro- mycin		Fluco- nazole	
Year	Database	Total	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
2013	Mondriaan	53	0	0.0	0	0.0	0	0	0	0	4	7.5	2	3.8	0	0.0	12	22.6	0	0	0	0.0	0	0.0
	NR Denmark	8269	33	0.4	9	0.1	0	0	0	0	287 9	34.8	103 4	12.5	232	2.8	186 8	22.6	0	0	49	0.6	274	3.3
	Bavarian CD	5064 6	227	0.4	43	0.1	0	0.0	6	0.0	113 70	22.4	250 4	4.9	134 1	2.6	119 80	23.7	0	0.0	24	0.0	0	0.0
	BIFAP	3070	13	0.4	8	0.3	0	0	0	0	942	30.7	376	12.2	68	2.2	104 8	34.1	0	0	17	0.6	24	0.8
	SIDIAP	1906	2	0.1	4	0.2	0	0	0	0	192	10.1	81	4.2	22	1.2	286	15.0	0	0	3	0.2	13	0.7
	CPRD	2259	6	0.3	14	0.6	0	0	0	0	274	12.1	204	9.0	90	4.0	173	7.7	0	0	59	2.6	37	1.6
2014	Mondriaan	163	1	0.6	0	0.0	0	0	0	0	12	7.4	6	3.7	5	3.1	28	17.2	0	0	0	0.0	2	1.2
	NR Denmark	8889	29	0.3	7	0.1	0	0	0	0	282 7	31.8	882	9.9	250	2.8	171 7	19.3	<5	NA	45	0.5	293	3.3
	Bavarian CD	4766 5	179	0.4	22	0.0	0	0.0	5	0.0	988 4	20.7	217 8	4.6	116 3	2.4	113 18	23.7	0	0.0	18	0.0	0	0.0
	BIFAP	3210	8	0.2	8	0.2	0	0	0	0	890	27.7	368	11.5	58	1.8	887	27.6	0	0	6	0.2	22	0.7
	SIDIAP	2081	3	0.1	2	0.1	0	0	0	0	191	9.2	98	4.7	22	1.1	206	9.9	0	0	1	0.0	13	0.6
	CPRD	4781	21	0.4	22	0.5	0	0	0	0	566	11.8	446	9.3	167	3.5	275	5.8	0	0	89	1.9	79	1.7
2015	Mondriaan	247	0	0.0	0	0.0	0	0	0	0	12	4.9	6	2.4	3	1.2	21	8.5	0	0	0	0.0	2	0.8
	NR Denmark	1106 0	34	0.3	9	0.1	0	0	0	0	318 0	28.8	701	6.3	259	2.3	123 9	11.2	0	0	25	0.2	200	1.8
	Bavarian CD	3883 3	121	0.3	23	0.1	0	0.0	3	0.0	833 9	21.5	193 6	5.0	966	2.5	981 6	25.3	0	0.0	13	0.0	0	0.0
	BIFAP	3425	7	0.2	3	0.1	0	0	0	0	716	20.9	346	10.1	69	2.0	583	17.0	0	0	4	0.1	18	0.5
	SIDIAP	2402	1	0.0	2	0.1	0	0	0	0	120	5.0	84	3.5	9	0.4	97	4.0	0	0	1	0.0	4	0.2
	CPRD	7154	12	0.2	21	0.3	0	0	0	0	729	10.2	537	7.5	235	3.3	269	3.8	0	0	64	0.9	47	0.7

* Due to the low number of new rivaroxaban users, data for Mondriaan are presented for the period 2012-2015 only

ASA: acetylsalicylic acid, NSAID: non steroidal antiinflammatory drug

Table 39. Number and percentage of new apixaban users with potential interactions stratified by database and calendar year – part 1

			Systemic keto-conazole		Ciclosporine		Itraconazole		Dronedarone		Tacrolimus		Amiodarone		Posaconazole		Quinidine		Verapamil		Ticagrelor		Rifampicin	
Year	Database	Total	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
2012	Mondriaan	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
	NR Denmark	-																						
	Bavarian CD	614	0	0.0	0	0.0	0	0.0	1	0.2	0	0.0	0	0.0	0	0.0	0	0	6	1.0	0	0.0	2	0.3
	BIFAP	88	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0	0	0	0	0.0	0	0.0	1	1.1
	SIDIAP	146	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0	0	0	0	0.0	0	0.0	0	0.0
	CPRD	2	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0	0	0	0	0.0	0	0.0	0	0.0
2013	Mondriaan	3	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0	0	0	0	0.0	0	0.0	0	0.0
	NR Denmark	1388	0	0	0	0	<5	NA	<5	NA	0	0	86	6.2	0	0	0	0	80	5.8	5	0.4	0	0
	Bavarian CD	4654	0	0.0	3	0.1	1	0.0	57	1.2	4	0.1	216	4.6	0	0.0	0	0	0	0.0	10	0.2	4	0.1
	BIFAP	487	0	0.0	1	0.2	2	0.4	4	0.8	1	0.2	21	4.3	0	0	0	0	9	1.8	0	0.0	1	0.2
	SIDIAP	700	0	0.0	0	0.0	0	0.0	6	0.9	1	0.1	27	3.9	0	0	0	0	4	0.6	0	0.0	0	0.0
	CPRD	239	0	0.0	0	0.0	0	0.0	4	1.7	0	0.0	15	6.3	0	0	0	0	10	4.2	0	0.0	0	0.0
2014	Mondriaan	12	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0	0	0	0	0.0	0	0.0	0	0.0
	NR Denmark	5324	0	0	<5	NA	16	0.3	8	0.2	0	0	381	7.2	0	0	0	0	275	5.2	8	0.2	<5	NA
	Bavarian CD	13315	0	0.0	9	0.1	5	0.0	146	1.1	8	0.1	630	4.7	0	0.0	0	0	255	1.9	35	0.3	11	0.1
	BIFAP	2081	0	0.0	2	0.1	1	0.0	32	1.5	4	0.2	172	8.3	0	0	0	0	49	2.4	1	0.0	1	0.0
	SIDIAP	1665	1	0.1	0	0.0	0	0.0	12	0.7	5	0.3	179	10.8	0	0	0	0	18	1.1	0	0.0	1	0.1
	CPRD	1467	0	0.0	0	0.0	0	0.0	13	0.9	0	0.0	83	5.7	0	0	0	0	27	1.8	1	0.1	0	0.0
2015	Mondriaan	88	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	3	3.4	0	0	0	0	3	3.4	0	0.0	0	0.0
	NR Denmark	9333	0	0	<5	NA	13	0.1	<5	NA	0	0	474	5.1	0	0	0	0	286	3.1	9	0.1	5	0.1
	Bavarian CD	21386	0	0.0	10	0.0	9	0.0	153	0.7	12	0.1	897	4.2	0	0.0	0	0	347	1.6	55	0.3	19	0.1
	BIFAP	3146	0	0.0	3	0.1	3	0.1	37	1.2	9	0.3	215	6.8	0	0	0	0	68	2.2	1	0.0	2	0.1
	SIDIAP	1907	0	0.0	0	0.0	0	0.0	9	0.5	1	0.1	149	7.8	0	0	0	0	15	0.8	0	0.0	0	0.0
	CPRD	3230	0	0.0	0	0.0	1	0.0	14	0.4	0	0.0	147	4.6	0	0	0	0	45	1.4	3	0.1	3	0.1

Table 39. Number and percentage of new apixaban users with potential interactions stratified by database and calendar year – part 2

			Carbama- zepine		Phenytoin		Hypericum perforatum		Ritonavir		Anticoagu- lants/ Anti- platelets		ASA		Clopidogrel		NSAID		Vorico- nazole		Naproxen	
Year	Database	Total	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
2012	Mondriaan	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
	NR Denmark	-																				
	Bavarian CD	614	1	0.2	0	0.0	0	0.0	0	0.0	28	4.6	13	2.1	3	0.5	406	66.1		0.0	3	0.5
	BIFAP	88	0	0.0	0	0.0	0	0	0	0	15	17.0	8	9.1	0	0.0	51	58.0	0	0	3	3.4
	SIDIAP	146	0	0.0	0	0.0	0	0	0	0	0	0.0	0	0.0	0	0.0	3	2.1	0	0	0	0.0
	CPRD	2	0	0.0	0	0.0	0	0	0	0	0	0.0	0	0.0	0	0.0	1	50.0	0	0	0	0.0
2013	Mondriaan	3	0	0.0	0	0.0	0	0	0	0	0	0.0	0	0.0	0	0.0	0	0.0	0	0	0	0.0
	NR Denmark	1388	<5	NA	<5	NA	0	0	0	0	629	45,3	187	13,5	60	4,35	239	17,2	<5	NA	12	0,9
	Bavarian CD	4654	21	0.4	3	0.1	0	0.0	0	0.0	974	20.8	289	6.2	171	3.6	117 3	25.0	0	0.0	0	0.0
	BIFAP	487	2	0.4	0	0.0	0	0	0	0	108	22.2	55	11.3	5	1.0	228	46.8	0	0	14	2.9
	SIDIAP	700	1	0.1	1	0.1	0	0	0	0	35	5.0	15	2.1	4	0.6	49	7.0	0	0	8	1.1
	CPRD	239	1	0.4	2	0.8	0	0	0	0	30	12.6	22	9.2	8	3.3	15	6.3	0	0	2	0.8
2014	Mondriaan	12	0	0.0	0	0.0	0	0	0	0	0	0.0	0	0.0	0	0.0	0	0.0	0	0	0	0.0
	NR Denmark	5324	18	0,3	5	0,1	0	0	0	0	224 4	42,1	591	11,1	174	3,3	665	12,5	0	0	44	0,8
	Bavarian CD	1331 5	47	0.4	11	0.1	0	0.0	0	0.0	296 8	22.3	924	6.9	590	4.4	239 3	18.0		0.0	54	0.4
	BIFAP	2081	3	0.1	4	0.2	0	0	0	0	534	25.7	246	11.8	39	1.9	554	26.6	0	0	51	2.5
	SIDIAP	1665	4	0.2	2	0.1	0	0	0	0	146	8.8	78	4.7	14	0.8	178	10.7	0	0	35	2.1
	CPRD	1467	8	0.5	4	0.3	0	0	0	0	194	13.2	140	9.5	66	4.5	89	6.1	0	0	54	3.7
2015	Mondriaan	88	0	0.0	0	0.0	0	0	0	0	1	1.1	0	0.0	0	0.0	3	3.4	0	0	0	0.0
	NR Denmark	9333	26	0,3	7	0,1	0	0	0	0	346 9	37,2	757	8,12	349	3,72	696	7,5	0	0	44	0,5
	Bavarian CD	2138 6	69	0.3	12	0.1	0	0.0	0	0.0	527 6	24.7	172 8	8.1	107 9	5.0	357 0	16.7		0.0	84	0.4
	BIFAP	3146	6	0.2	6	0.2	0	0	0	0	654	20.8	306	9.7	78	2.5	455	14.5	0	0	37	1.2
	SIDIAP	1907	1	0.1	1	0.1	0	0	0	0	119	6.2	71	3.7	14	0.7	94	4.9	0	0	21	1.1
	CPRD	3230	7	0.2	6	0.2	0	0	0	0	340	10.5	250	7.7	116	3.6	96	3.0	0	0	43	1.3

ASA: acetylsalicylic acid, NSAID: non steroidal antiinflammatory drug

10.5. Other analyses

10.5.1. Objective 1

10.5.1.1. Multiple imputations CPRD

We conducted multiple imputation techniques to impute missing data on BMI and smoking, but this had no effect on adjusted risk estimates.

10.5.1.2. Primary non adherence and exposure misclassification (BIFAP and SIDIAP)

To assess the degree of drug exposure misclassification a study on primary non-adherence was performed analyzing the proportion on patients that received a prescription for a DOAC and also got it dispensed during the study from the pharmacy. This analysis was performed in the BIFAP and SIDIAP databases on a sample where both prescriptions and dispensing could be linked (14.4% of all prescriptions in the BIFAP database). The percentages of primary non-adherence ranged from 9.2% for apixaban in the BIFAP database to 15% for rivaroxaban in the SIDIAP database.

More detailed information is included in the excel file for objective 2 BIFAP and SIDIAP.

10.5.1.3 Prescriber type DK database (pending)

Pending

10.5.2. Objective 2

As the DOACs can be prescribed for other indications than NVAf, a sensitivity analysis was performed where all patients with other DOAC indications than NVAf in a +/- 3 month period around the first DOAC were excluded. When comparing these results with those of the main analysis, the total number of patients treated with DOAC slightly decreased, but the proportions of the individual DOAC were stable. Regarding the renal function at baseline and the dose adjustment the numbers were quite similar than in the principal analysis except in the EGB where the percentages of CKD and dose adjustment were slightly lower respect to the principal analysis. The analysis showed few differences. The percentage of concomitant medications increased in the SIDIAP database both in all DOAC analyses and in the analyses by individual DOAC. The percentage of previous cardiovascular events decreased in SIDIAP and EGB databases for all individual DOAC and it only decreased for rivaroxaban in the other databases.

10.6. Adverse events/adverse reactions

NA

11. Discussion

11.1. Key results

11.1.1. Objective 1

Results of the association study showed that age & sex and fully adjusted hazard ratios for current use of DOACs vs. VKA for risk of major bleeding were comparable between three of the four data sources with estimates around unity and a reduced risk in the Danish data. For individual DOACs, rivaroxaban showed a 21-27% increased risk of major bleeding versus VKAs in both AOK NORDWEST and CPRD, whereas the HR in BIFAP was 1.02 (95% CI 0.91-1.13) and 0.94 (95% CI 0.890-1.09) in Denmark. Apixaban and dabigatran consistently yielded lower risk estimates in all data sources. DOACs were associated with an increased risk of gastrointestinal bleeding compared VKA use with statistically significant adjusted HRs around 1.3-1.4 in all data sources except Denmark. These effects were driven by dabigatran and rivaroxaban. The incidence of intracranial bleeding was low in all data sources and point estimates were below 1.0 in all data sources, except for a statistically significant increased risk for rivaroxaban in CPRD (adjusted HR 2.37, 95% CI 1.19-4.71). When expanding the outcome to any stroke or transient ischemic attack, HRs for current use of DOACs vs. VKA were 1.53 for dabigatran and 2.16 for apixaban. In BIFAP (adjusted HRs 1.1-1.2) and AOK NORDWEST (adjusted HRs 0.64-0.99), such increased risks were not found.

There were some differences with respect to comorbidities, especially the proportion of patients with a history of cardiovascular diseases was substantially higher in the German database, which might be related to differences in coding requirements between the data sources. However, this was consistent with regard to the proportion of patients receiving cardiovascular medication. In contrast, the prevalence of antiplatelet drug use was lower in the German data sources, which could be explained by the fact that low dose aspirin is distributed differently compared to CPRD and BIFAP (more often over-the-counter in Germany).

Stratification into clinically relevant subgroups showed no major differences between males and females, but a higher risk in patients aged 75 years and older in both CPRD and BIFAP. The number of events among patients in extreme weight categories or having severe renal failure were generally very low.

11.1.2. Objective 2

A total of 186,405 of new DOAC users (≥ 18 years) (e.g. can have prior use of OACs) with non-valvular atrial fibrillation (NVAf) were identified in eight databases representing six different European countries in the period 2008-2015 with different contributing times for the different databases. During the study period the overall incidence of new DOAC users increased except in the Bavarian CD, and the individual DOAC with the highest incidence percentage increase was apixaban followed by rivaroxaban. The striking figure for percentage increase in EGB is due to the fact that apixaban use was minimum in 2013. For 2013-2012 for apixaban it was maximum in EGB (10,550.0) and minimum in Bavarian CD (218.61) while the values for 2015-2014 were maximum in Mondriaan (868.5) and minimum in SIDIAP (35.1). In 2015, the incidence of DOAC use ranged from 8.5 per 10,000 in SIDIAP (Spain) to 27.6 per 10,000 in NRD (Denmark), with a higher incidence in men than in women.

The largest group of users was 75 years or younger in all databases. The mean age ranged from 69.3 years in the Mondriaan database to 75.7 years in the BIFAP database (SD11.3; 10.4, respectively).

Male users were more frequent than female in all databases, except in the AOK NORDWEST and Bavarian databases. The percentage of comorbidities ranged from 31.1% (Mondriaan) to 87.3% (AOK), being previous cardiovascular events the most frequent comorbidity. The unexpected high percentage of chronic kidney disease observed at baseline in the Bavarian and AOK databases may

be related to their high proportion of overall comorbidities and specifically of cardiovascular diseases. Impaired cardiovascular function may affect renal function as well. The proportion of patients who have received a concomitant interacting drug at baseline and during the follow up ranged from 16.4% in SIDIAP to 70.5% in EGB databases. Concomitant treatment with any other anticoagulant drug was present in variable proportions but in an important number of patients in several databases (the two German databases, BIFAP and EGB). However, some of this use could be related to switching to anticoagulant therapy.

Concomitant use of contraindicated anticoagulants varied between 0.4% (CPRD), and 24.3% (EGB). NSAIDs varied from 4.3% (Mondriaan) to 26.0% (Bavarian CD) and antiplatelet drugs from 1% in SIDIAP to 18.1% in EGB respectively. The most frequent concomitant interacting drugs were heparins in AOK, BIFAP, Bavarian CD (8.4%, 10.44%, 12.0% respectively), amiodarone in EGB, NRD, and SIDIAP databases (42.2%, 6.2% and 5.7% respectively) and verapamil in Mondriaan (4.1%). Among selective serotonin reuptake inhibitors, potential interacting drugs only for dabigatran, the highest proportion was observed in the CPRD and NRD (9.1% and 5.3% respectively). There were some differences between databases in the same country, in Spain, between SIDIAP (16%) and BIFAP (48%). This could be related to the different database characteristics: SIDIAP is a prescription linked to dispensing database covering 80% of the catalan population while BIFAP is a prescription database which covers a sample of the Spanish population. The differences found in the overall proportion of patients who have received a concomitant medication between SIDIAP and EGB claims databases could be due to different prescriber behaviors as well as the characteristics of the respective databases EGB is a representative sample of the total population and SIDIAP includes about 80% of the total population. The registry of laboratory values in Mondriaan, BIFAP, SIDIAP and CPRD identified patients with moderate reduced kidney function from 3.9% of patients in Mondriaan to 22.6% in CPRD. The information of dose adjustment was available in BIFAP, SIDIAP, CPRD and EGB, its proportions varied from 4.6% in SIDIAP to 15.6% in EGB. The proportion of dose adjustment related to a change in renal function or to a change in age was less of 1% in the three databases. In the Mondriaan database this proportion was always 0. AOK NORDWEST and the Bavarian databases do not have this information registered.

The highest percentage of switchers was observed in the AOK NORDWEST database (16%) and the lowest one in the Mondriaan database (2.4%). The highest percentage of discontinuers was observed in the Bavarian CD (79.4%) and the lowest one in the CPRD 17.7%.

Regarding the Kaplan-Meier figures for all DOACs, the CPRD was the database that showed the highest probability of survival at 12 months and the lowest one was observed in the Mondriaan database. Apixaban had the highest survival probability at 12 months when compared to the other DOACs (maximum in CPRD) except in the Mondriaan and AOK NORDWEST databases, dabigatran showed the lowest survival probabilities at 12 months (minimum in Mondriaan), except in AOK NORDWEST database. The differences between each individual DOAC curves were statistically significant (log-rank test p values < 0.05) in all databases.

11.1.3. Objective 3

Regarding changes over time of new DOAC users, an increase was found for rivaroxaban and apixaban whereas for dabigatran the number of new users peaked within the study period followed by a decrease. Despite methodological differences, similar patterns were found for these three DOAC compounds in other studies (Barnes et al., 2015; Weitz et al., 2015).

According to changes in labelling for the three DOACS within the study period, some time-dependent differences regarding documented indications were found. During the first years of the study period, prophylaxis of thrombosis after hip or knee replacement was of particular importance for dabigatran and rivaroxaban whereas at the end of the study period, NVAF was the most common indication for all three DOACs. Due to a substantial number of patients with 'missing /

other indications' found in most databases which is probably related to coding issues (see limitations section), analyses regarding off-label usage (see supplemental material) should be interpreted very carefully. Even in rivaroxaban patients with a documented "indication" MI (which is an off-label use according to the SmPC), one should abstain from considering all those patients as "off-label" treated due to the fact that time windows were used for defining comorbidities as e.g. MI. In addition, there are some uncertainties (in some databases) in distinguishing indications from comorbidities which may also limit our analyses of "indications".

Regarding contraindications in incident DOAC users, an overall proportion of 39.0% was found combining all three DOACS and databases. Between the compounds, some differences were found reaching highest values for rivaroxaban (42.0%) followed by apixaban (37.4%) and dabigatran (32.7%). Excluding the Bavarian database (broad definition of renal and hepatic dysfunction leading to overestimation, possible inter-country differences in coding behaviour, see limitations section), somewhat lower proportions of contraindications were found (overall: 15.6%, dabigatran: 18.8%, rivaroxaban: 13.4%, and apixaban: 14.1%). However, even after exclusion of the Bavarian database, there was a substantial range between the databases with regard to the proportion of incident users with present contraindication (CPRD and SIDIAP: 8.2%, Mondriaan: 20.3%).

For special warnings and precautions, an overall proportion in incident DOAC users was estimated with 66.5%. Comparing the compounds, highest values were found for apixaban (74.5%) followed by rivaroxaban (67.4%), and dabigatran (58.0%). Highest values were found for the Bavarian database (75.2%) followed by CPRD (67.0%). A much lower proportion was found in Mondriaan (35.8%). In the Bavarian database, renal and liver function were not mapped due to explicit criteria focussing on lab values (in contrast to the analysis of contraindications where the SmPC is somewhat vague).

With regard to potential interactions, an overall proportion of 46.8% was revealed for incident DOAC users. For the three DOAC compounds, highest value was found for dabigatran (55.3%), followed by rivaroxaban (44.9%) and apixaban (41.6%). Comparing the databases, the highest value was found in NR Denmark (59.8%) followed by BIFAP (54.1%) and Bavarian CD (45.4%) whereas somewhat lower values were found for the remaining databases.

Regarding the overall measures for the aforementioned issues, one should keep in mind that combining all databases for revealing summarized measures might be somewhat misleading due to differences between the databases (GP versus Claims database, documentation of lab values, coding behaviour). In addition, large databases will influence the overall measure to a higher extent than smaller databases. However, for a first interpretation, such overall measures for contraindications, special warnings/precautions, and potential interactions might be of some help. Regarding indications, we abstained from calculating such measures due to the large number of patients in category "missing / other indications".

11.2. Limitations

11.2.1. Limitations related to the data source

A major limitation is related to data availability and completeness within each data source. There was a high percentage of missing data on laboratory values of renal function based (ranging from 3.4 in CPRD database to 77.9 in the BIFAP database). However, most of the databases have information on disease codes related to renal function. Information on the indication associated with the drug prescription might also be incomplete.

Regarding defining the indications, differences between databases have to be considered. For example, a definite linkage between compound and indication is lacking in some databases (e.g., Bavarian CD, AOK NORDWEST). In addition, indication might have been documented before the study period which is probably the main reason for the high proportion of patients in the indication category 'other / missing'. Furthermore, by analyzing data from the primary care sector, hip or knee replacement as indication is probably underestimated due to lacking coding of these surgical procedures usually conducted in hospitals. In addition, a clear, medically meaningful definition of non-valvular versus valvular atrial fibrillation is lacking and may have some impact on the numbers of patients revealed for the respective categories.

Regarding contraindications and precautions / special warnings, mapping of the respective SmPC terms to the coding systems is difficult at least for some terms. For example, a clear definition of 'malignancies with an increased bleeding risk' or 'major trauma' is lacking and in this study, a broad definition was used to avoid an underestimation of contraindications and precautions/special warnings. However, those broad definitions will lead to a substantial overestimation. On the other hand, some interventional procedures were not clearly defined or were not available in most of the databases used for analysis (e.g. ophthalmic surgery, biopsy, spinal anaesthesia, invasive procedures) leading to a (probably slight) underestimation of contraindications and special warnings / precautions.

In some databases, no lab values were documented but codes for renal dysfunction were used. However, similar to the coding issues described above, a broad definition (including somewhat non-specific renal dysfunction codes) were used in this study explaining to some extent the high proportion of patients with renal dysfunction found in some databases. Furthermore, a clear definition of the time window (prior to the index date) for considering conditions as contraindication or special warning/precaution is missing in SmPCs. Again, an overestimation might be also related to this issue.

Regarding potential interactions, lacking documentation of OTC might be relevant in particular for NSAIDs, low-dose ASA (mainly pharmacodynamics interactions) and St. John's wort (pharmacokinetic interaction).

11.2.2. Limitations related to methodology

Potential limitations of this observational pharmacoepidemiological study arise due to (i) possible misclassification of the exposure status, e.g., unknown exposure status during hospitalization and incorrect calculation of the treatment duration, missing data. The type of exposure data was not homogeneous across the databases. Misclassification of the exposure is a potential concern in pharmacoepidemiological studies using databases since we used prescription, dispensing or reimbursing data and they did not have complete information on the actual drug intake. In addition, drugs prescribed by physicians other than GPs could be missed when using prescribing databases as these are commonly general practice databases. It could be that, especially in frail patients, treatment with DOAC is initiated and maintained by medical specialists which will then be unobserved in the study cohorts using data from primary care or only become visible when the GP takes over at some point.

To assess the degree of drug exposure misclassification a study on primary non-adherence has been performed analyzing the proportion on patients that got a DOAC dispensed during the study period from all the patients that had an initial prescription of DOACs. This analysis was performed in the BIFAP and SIDIAP databases that contain information on both prescriptions and dispensing. The percentages of primary non-adherence ranged from 9.2% for apixaban in the BIFAP database to 15% for rivaroxaban in the SIDIAP database.

There were difficulties in assessing concomitant interacting drugs in the time period before the index date in some databases, therefore its assessment was restricted to the index date and follow-up periods.

Dose adjustment related to change in renal function and age was only assessed if a change in dose paralleled a change in renal function or in age but we did not assess if any change in these two categories was followed by a change in dose. In addition, a dose adjustment was defined as switching from one active principle contained in each tablet to another strength of the same active principle. This definition precludes to assess posology changes that may have happened without changing to another strength of the same active principle. Prescription data on posology were not taken into account in the prescription databases and the claims databases do not have this information available. There might also be differences in the relation between the strength change and the associated renal function change across the databases since each one of them may have a different time schedule/frame of registering this information.

In this study a major bleeding event was defined as a bleeding in any critical area or organ. This definition is not completely in line with the definition given by the ISTH, because there is no clinical information available on hemoglobine level or any blood transfusions given. The data sources used for the association studies were different with respect to the coding systems used. Although a stringent harmonization procedure was used to ensure all sources measured the outcome events in the same way, we cannot exclude that some degree of misclassification was possible due to incompatibility of relevant codes. CPRD and BIFAP are based on primary care data, while AOK NORDWEST uses outcome data from hospital admissions only. In sensitivity analyses restricted to CPRD hospital admission events only, more or less similar results were obtained compared to the main analysis. In BIFAP, GI hospital admission were identified using an algorithm in combination with manual review. The adjusted HRs for current DOAC use was 1.13, thus lower compared to the main analysis including all events. It could be argued that the outcome definition used involves diagnostic codes where it is debatable whether the bleeding event is really major, like hematuria, melena and rectal bleeding. Additional sensitivity analyses are proposed to exclude such events from the primary outcome definition. Although traumatic intracranial bleeding events have an external cause, such events were included as the propensity of having a bleeding event during trauma might be higher due the anticoagulant effect. Although intracranial bleeding were assessed, the incidence of such bleeding events was low. In practice, coding of stroke events is often not specific into hemorrhagic and ischemic strokes. Therefore, we also used any stroke as separate outcome event, but we also included TIAs into this definition, which given its ischemic nature might not be relevant in the context of this study. In a additional analysis, we excluded TIAs in the stroke analysis, but the impact on risk estimates was marginal.

In our analyses, we compared current use of DOACs with current use of VKAs. Between the countries there is variation in the type of VKA used. Warfarin is predominantly used in the UK, while in Spain and Germany acenocoumarol is used. If there would be a difference in bleeding risk between warfarin and acenocoumarol, this could influence the comparison between CPRD and the other two data sources, but there seems no direct head-to-head comparison conducted, except the notion that genetic polymorphisms might have some effect, which is something we do not have available in our studies (Beinema 2008).

Regarding definition of indication, some limitations have to be considered. Whereas some indications listed in chapter 4.1 of the respective DOAC SmPCs could be covered by the coding systems of the databases quite well (e.g. deep vein thrombosis and pulmonary embolism), some

other indications could be covered to a much lesser extent. For example, the approved indication for rivaroxaban 'prevention of atherothrombotic events in adult patients after an acute coronary syndrome (ACS) with elevated cardiac biomarkers co-administered with acetylsalicylic acid (ASA) alone or with ASA plus clopidogrel or ticlopidine' were covered by ICD-codes for 'myocardial infarction / angina' due to difficulties in an exact matching of the exact indication using the databases and coding systems available. In addition, cardiac biomarkers (e.g. troponin test) is not available in most databases and is primarily measured in patients admitted to hospitals for angina / MI receiving cardiac interventions (e.g. PTCA). To avoid a misleading presentation and incorrect detailedness, the diagnoses actually coded (see table A1.4 of the protocol) were stated in tables presenting indications (objective 3) instead of the exact SmPC indication (see table A1.3 of the protocol). Furthermore, we did not consider tablet strength for analysis of indication due to some overlap in indications treated with a particular tablet strength and potential recommended dose reduction due to e.g. renal dysfunction. In addition, all indications listed in at least one DOAC SmPC at the point of time of study protocol development were used for the indication related analysis. Hence, even indications not listed for a respective DOAC compound (e.g. 'prevention of atherothrombotic events in adult patients after an acute coronary syndrome (ACS) with elevated cardiac biomarkers co-administered with acetylsalicylic acid (ASA) alone or with ASA plus clopidogrel or ticlopidine' covered by the codes angina/myocardial infarction were considered in incident dabigatran and incident apixaban users).

In our analysis of the association study, we did not take different strengths of DOACs into account. During protocol development and discussion with EMA this was not something that was addressed, although it was part of the descriptive studies. Although interesting to see whether the risk of bleeding differs between different strength of DOACs, such stratification would underpower the analysis of relevant patient subgroups more.

11.3. Interpretation

Overall the results on incidence appear to be quite consistent across the different databases. The NRD, AOK NORDWEST and Bavarian DB databases presented the highest standardized incidence in 2015. The differences in incidence across countries might be explained by the presence of a higher proportion of older women in the AOK NORDWEST and Bavarian databases compared to the other which may have led to a higher prevalence of cardiovascular diseases and NVAf in the German population. The NRD also has a high prevalence of cardiovascular disease. Besides the application of different treatment guidelines and marketing and regulatory policies across the different countries may help explain these differences.

The German Bavarian and AOK NORDWEST databases had the highest proportion of comorbidities being the databases with most frequent previous cardiovascular events as well as a higher proportion of patients using cardiovascular drugs.

As the data on laboratory values of renal function was scarce (missing data for renal failure up to 77.9%) it is difficult to draw conclusions on that. However, we guess that most of these unregistered values indicate not severely affected renal function, otherwise they probably would have been registered. Besides the information on dose adjustment related to change in renal function could not be assessed confidently.

There was variability across the databases in the proportion of concomitant interacting drugs, being the reimbursed EGB database with the highest percentage of patients with concomitant interacting drugs and SIDIAP the database with the lowest percentage. As this is constant for all DOACs and for individual DOACs these differences can be explained by the different physician behavior or differences in the health system (country guidelines on prescription) as well as intrinsic database characteristics. The patients in Bavarian and AOK NORDWEST database had also higher percentage of patients with comorbidities that could explain the high proportion on concomitant drugs. Dabigatran users had higher proportion of concomitant interacting drugs than the other

DOAC, the higher number of potential interacting drugs of widespread utilization described for dabigatran compared to the other DOAC can help explain that result.

Mondriaan was the database with the lowest percentages of switchers except in the case of apixaban where SDIAP had the lowest, and AOK NORTHWEST is the one with the highest percentages. The high percentage of comorbidities in AOK NORTHWEST could lead to more problems with the anticoagulant treatment and justify the treatments changes.

Dabigatran was the DOAC with the highest percentage of discontinuers in all databases except in the Bavarian where rivaroxaban had the highest proportion of discontinuers. In the same sense dabigatran showed the lowest survival probabilities, the log-rank test showed differences between individual DOAC, being apixaban the DOAC with lowest discontinuation probability.

The association study across four European databases showed that the overall hazard ratios of major bleeding risk for DOACs versus VKAs ranged between 0.84 (Denmark) and 1.13 (UK CPRD). When stratifying according to the type of bleeding event, the risk of gastrointestinal bleeding was statistically significantly increased by 48-67% in users of dabigatran users and 30-50% for rivaroxaban users compared to VKA users in all data sources except for Denmark. Compared to VKAs, apixaban was not associated with an increased risk of GI bleeding in all data sources and seemed to be associated with the lowest risk of major bleeding events compared to dabigatran and rivaroxaban. In contrast, the risk of intracranial bleeding was lower for DOACs compared to VKAs in all databases, except for rivaroxaban in CPRD, which showed a significantly higher risk compared to VKAs although the number of events was low. When stratifying according to clinically relevant subgroups, we found no remarkable differences between males and females and generally higher risk of major bleeding among DOAC users aged ≥ 75 years when compared to younger users, which seemed to be driven by the higher risk of rivaroxaban in CPRD. This finding could suggest that the benefit-risk balance of especially rivaroxaban might be different for an older patient population. As the incidence of AF increases with older age, this is important information. Due to low numbers in patients with extreme low or high weight and impaired renal function we could not identify differences in benefit-risk balance for these subgroup of patients. From a clinical perspective it seems reassuring that physicians do not seem to prescribe DOACs to such vulnerable patients in daily clinical practice.

The higher risk for rivaroxaban on bleeding risk in CPRD is an interesting observation. We assessed whether characteristics of rivaroxaban users were different compared to those of dabigatran and apixan, but found no striking differences in that respect. Rivaroxaban was the most commonly used DOAC during the study period in the UK. The difference found for rivaroxaban might be explained by a selected prescribing of this drug to a group of patients with higher stroke and bleeding risk. Although we have corrected for confounders in the analysis, possible unobserved confounding could still be present. However, for all analyses there was no large difference between the crude and adjusted risk estimates. The finding of a higher risk for rivaroxaban was also found in a propensity weighted nationwide cohort study in Denmark that rivaroxaban is associated with higher risk of major bleeding (Larsen 2016). This finding is not restricted to Europe: in a study by Lip et al. in a US claims database they also found that rivaroxaban had a worse safety profile than dabigatran and rivaroxaban (Lip 2016).

In CPRD we found an increased risk of stroke associated with current use of DOACs, especially for apixaban. A possible explanation could be that apixaban was introduced later than dabigatran and rivaroxaban, and was marketed as potentially safer with respect to gastrointestinal bleeding. This might cause channeling bias in which apixaban was prescribed to a more fragile patient population with higher stroke and bleeding risk. However, this was not reflected in the risks found for bleeding events for apixaban, which were generally lower compared to the other DOACs. It remains unclear why the risk of stroke in CPRD is higher compared to the two other data sources. Restricting events to hospitalised stroke events yielded similar results.

11.4. Generalisability

The use of a common study protocol, with the use of harmonized diagnoses and drug codes codes and with the network having experience of conducting these type of studies supports the interpretation and comparability of results across the selected countries.

There are differences in population coverage among the databases, while Bavarian and SIDIAP had a population coverage of 84% and 80% respectively, the other databases had a lower coverage ranging from 24% in the two German regions covered by the AOK NORDWEST to 3% in Mondriaan. The EGB is a representative sample of a wider database that covers 97% of the French population. Furthermore there are differences in the type of data being BIFAP, SIDIAP, Mondriaan and CPRD a general practice database with prescription drug data (although prescribing and dispensing data is available for a sample in BIFAP and complete in SIDIAP), Bavarian, AOK NORDWEST and EGB are claims database. These differences have been assessed with the primary non-adherence study in BIFAP and SIDIAP.

The definition of the inclusion criteria ensures the generalisability of the results as all the new users with a diagnosis of NVAf were included. The only exclusion criteria in the main analysis were a) to have valid information on the database and b) patients with a history of valvular atrial fibrillation on index date or prior to initiating DOACs. In addition the performance of a sensitivity analysis where patients with multiple DOAC indications have been excluded, that gave similar results for most of the main variables, ensures the validity and generalisability of the results.

12. Other information

N/A

13. Conclusion

Prescribing of the DOAC has changed over time and is currently most commonly being prescribed to treat NVAf, while during the first years dabigatran and rivaroxaban were more often prescribed as prophylaxis of thrombosis after hip or knee replacement. The DOACs are being prescribed to a varying proportion of patients with at least one contraindication, ranging from around 5-32%. Also, 29-73% of patients that are prescribed DOACs have a special warning. Further, 11-68% of patients had at least one potential interaction identified for their DOAC therapy.

For those having an indication for NVAf, the largest group of users was 75 years or younger. More males than females were being treated, except in the German databases. Comorbidities were frequent in the study population, ranging from 31.1% in the Netherlands to 87.3% in Germany. The most common comorbidity were previous cardiovascular events. Many were using concomitant interacting drugs in the first treatment episode the DOAC, ranging from 16.4% in Spain to 70.5% in France.

In general, the largest bleeding risk in our study was found for rivaroxaban. For individual DOACs, rivaroxaban showed a 21-27% increased risk of major bleeding versus VKAs in both Germany and the UK databases, whereas the HR in the Spanish population was 1.02 (95% CI 0.91-1.13). Apixaban and dabigatran consistently yielded lower risk estimates in all data sources. DOACs were associated with an increased risk of gastrointestinal bleeding compared VKA use with statistically significant adjusted HRs around 1.3-1.4 in all data sources. These effects were driven by dabigatran and rivaroxaban. The incidence of intracranial bleeding was low in all data sources and point estimates were below 1.0 in all data sources, except for a statistically significant increased risk for rivaroxaban in CPRD (adjusted HR 2.37, 95% CI 1.19-4.71).

14. References

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Larsen TB, Skjoth F, Nielsen PB, Kjaeldgaard JN, Lip GY. Comparative effectiveness and safety of non-vitamin K antagonist oral anticoagulants and warfarin in patients with atrial fibrillation: propensity weighted nationwide cohort study. *BMJ* 2016 Jun 16;353:i3189.

Lip GY, Keshishian A, Kamble S, Pan X, Mardekian J, Horblyuk R, et al. Real-world comparison of major bleeding risk among non-valvular atrial fibrillation patients initiated on apixaban, dabigatran, rivaroxaban, or warfarin. *Thromb Haemost* 2016;115(05):975-986.

Please see study protocol for relevant references related to the study methods.

Annex 1. List of stand-alone documents

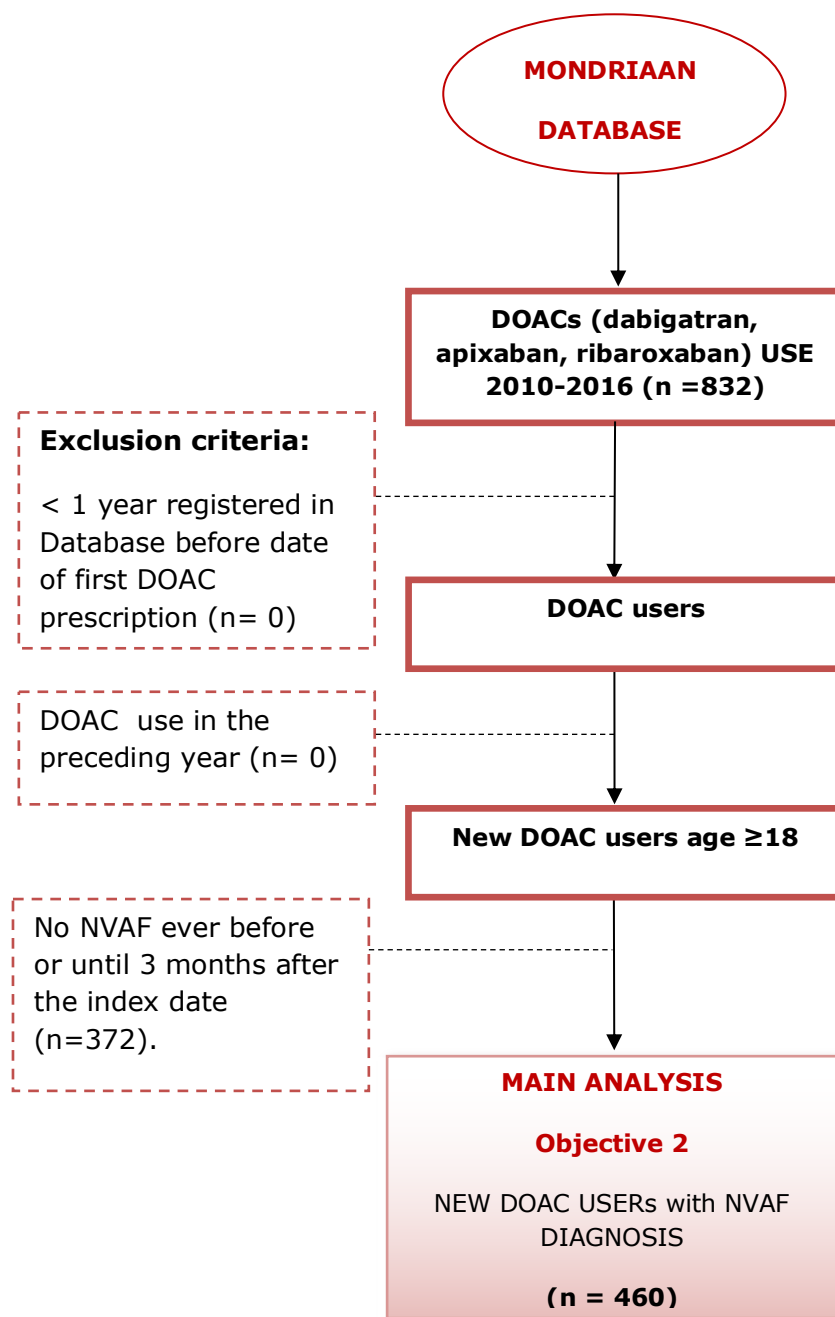
Number	Document reference number	Date	Title
Annex 2	Version 3.0, EUPAS 16014	1 June 2018	Study protocol (amended)
Annex 3		October 2018	Detailed results for each objective and database (for list see Annex 3)
Annex 4		October 2018	Flowcharts Study population
Annex 5		1 June 2018	Answers to questions from EMA and FDA
Annex 6		October 2018	Response to EMA reviewers' questions

Annex 2. Study protocol (see separate document)

Annex 3. Detailed results for each cohort

Results files finalreport DOAC – EUPAS 16014	
Cohort	
AOK NORDWEST	
Annex_III_obj1_AOKnordwest.xlsx	Obj 1
Annex_III_obj2_AOKnordwest.xlsx	Obj 2
Annex_III_obj2_AOKnordwest_KMdrug	Obj 2
Annex_III_obj2_AOKnordwest_KMdrugsex	Obj 2
Annex_III_obj2_AOKnordwest_KMdrugage	Obj 2
Annex_III_obj2_AOKnordwest_KMdrughepatic	Obj 2
Annex_III_obj2_AOKnordwest_KMdrugckd	Obj 2
Bavarian	
Annex_III_obj2_Bavarian.xlsx	Obj 2
Annex_III_obj3_Bavarian.xlsx	Obj 3
BIFAP	
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Annex_III_obj2_BIFAP.xlsx	Obj 2
Annex_III_obj3_BIFAP.xlsx	Obj 3
CPRD	
Annex_III_obj1_CPRD.xlsx	Obj 1
Annex_III_obj2_CPRD.xlsx	Obj 2
Annex_III_obj2_CPRD_KMcurves.pdf	Obj 2
Annex_III_obj3_CPRD.xlsx	Obj 3
NDR	
Annex_III_obj1_NDR.xlsx	Obj 1
Annex_III_obj2_NDR.xlsx	Obj 2
Annex_III_obj3_NDR.xlsx	Obj 3
EGB	
Annex_III_obj2_EGB.xlsx	Obj 2
Mondriaan	
Annex_III_obj2_Mondriaan.xlsx	Obj 2
Annex_III_obj3_Mondriaan.xlsx	Obj 3
SIDIAP	
Annex_III_obj2_SIDIAP.xlsx	Obj 2
Annex_III_obj3_SIDIAP.xlsx	Obj 3

Annex 4. Flowcharts objective 1&2



Sensitivity analysis not applicable, none of the patients have any other indication than NVAF.

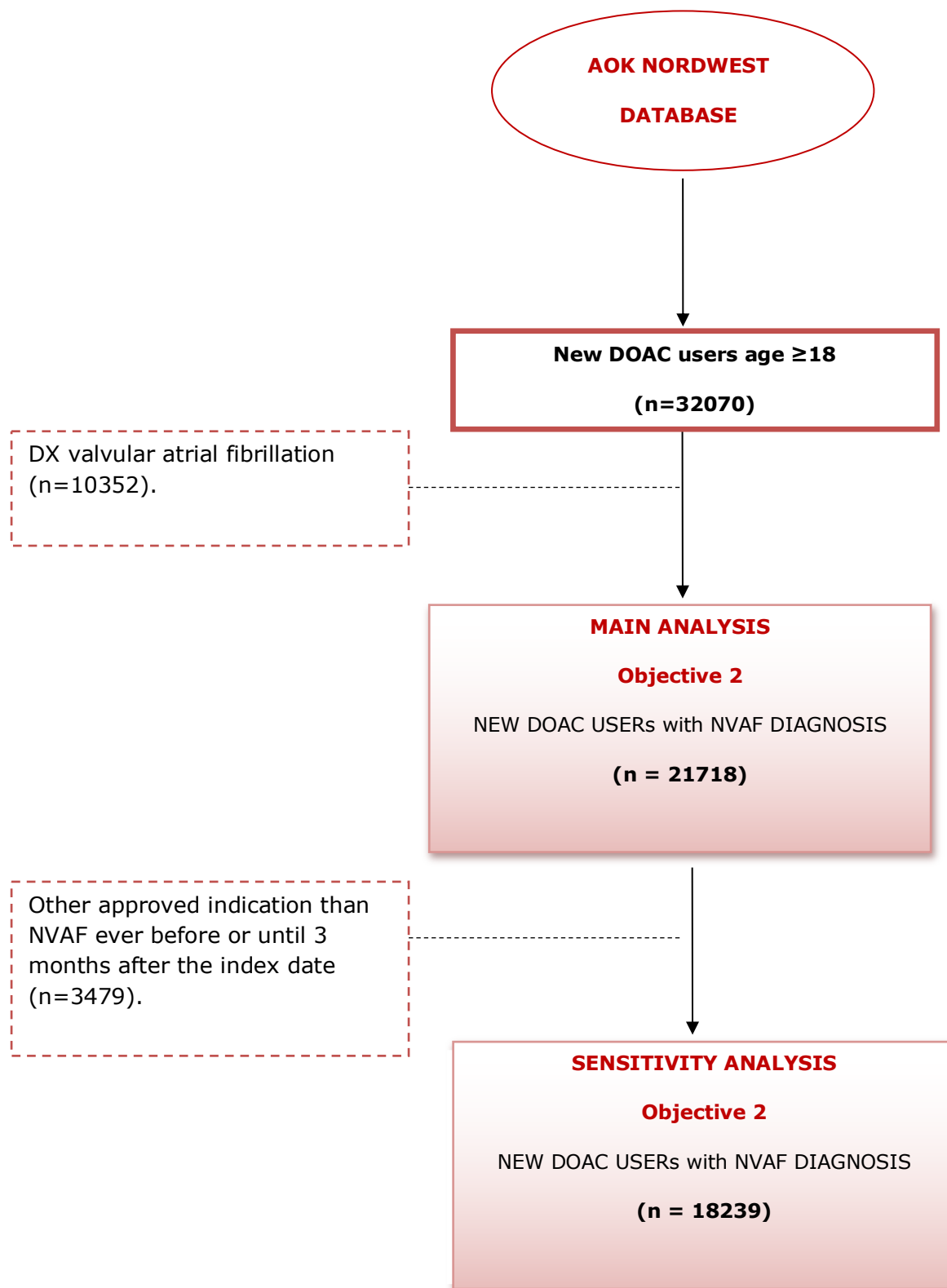


Figure 1. Flow chart patients selection in BIFAP

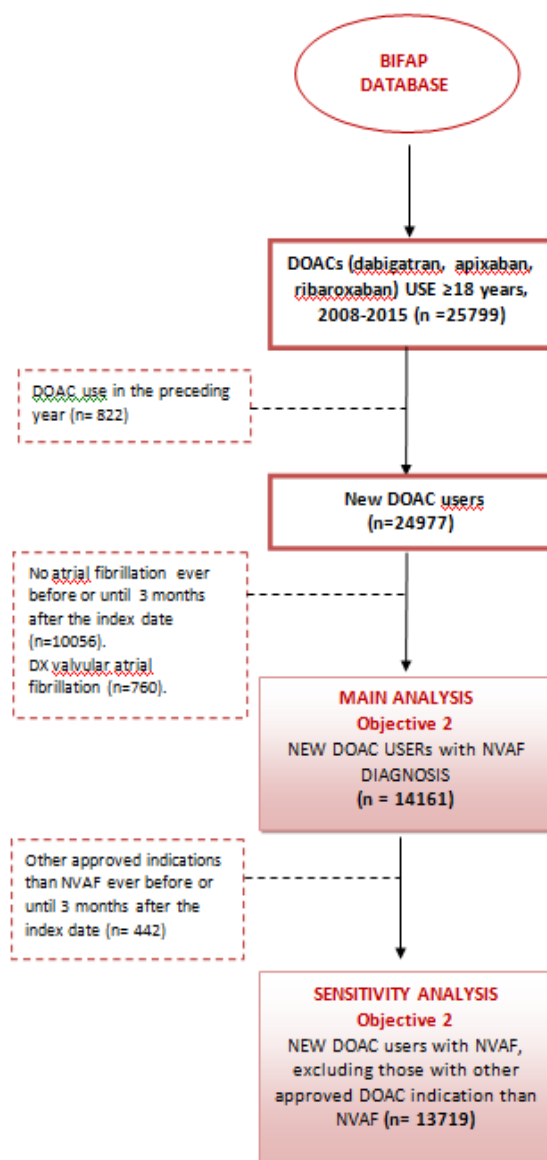
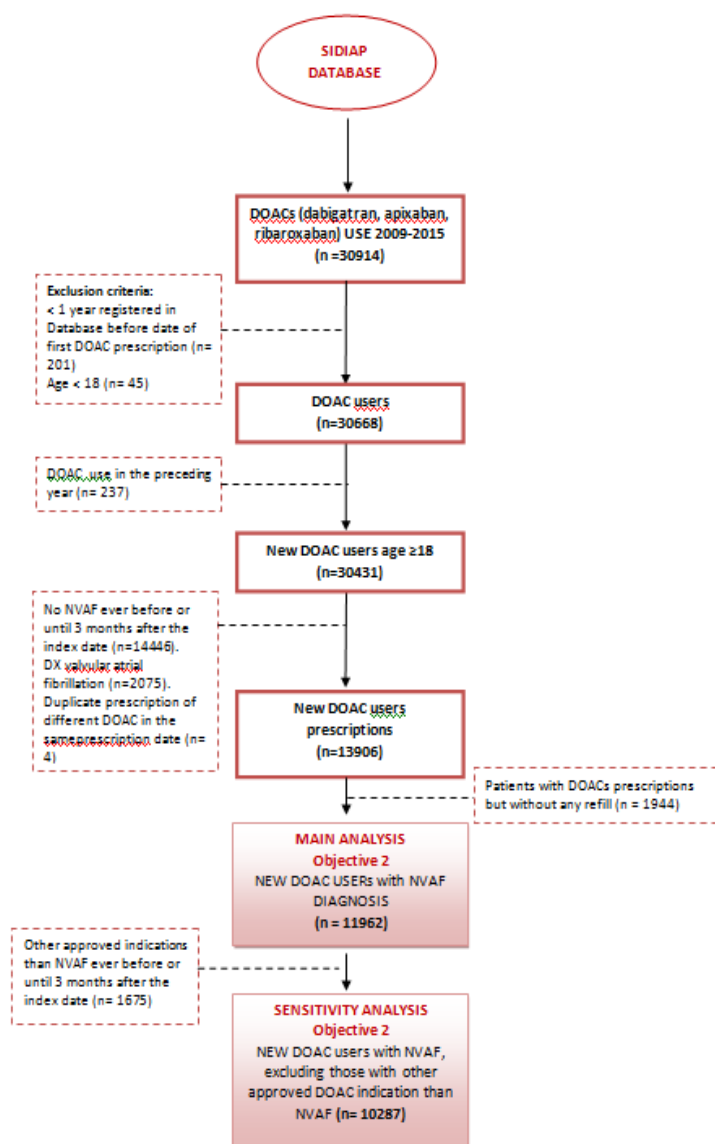


Figure 1. Flow chart patients selection in SIDIAP



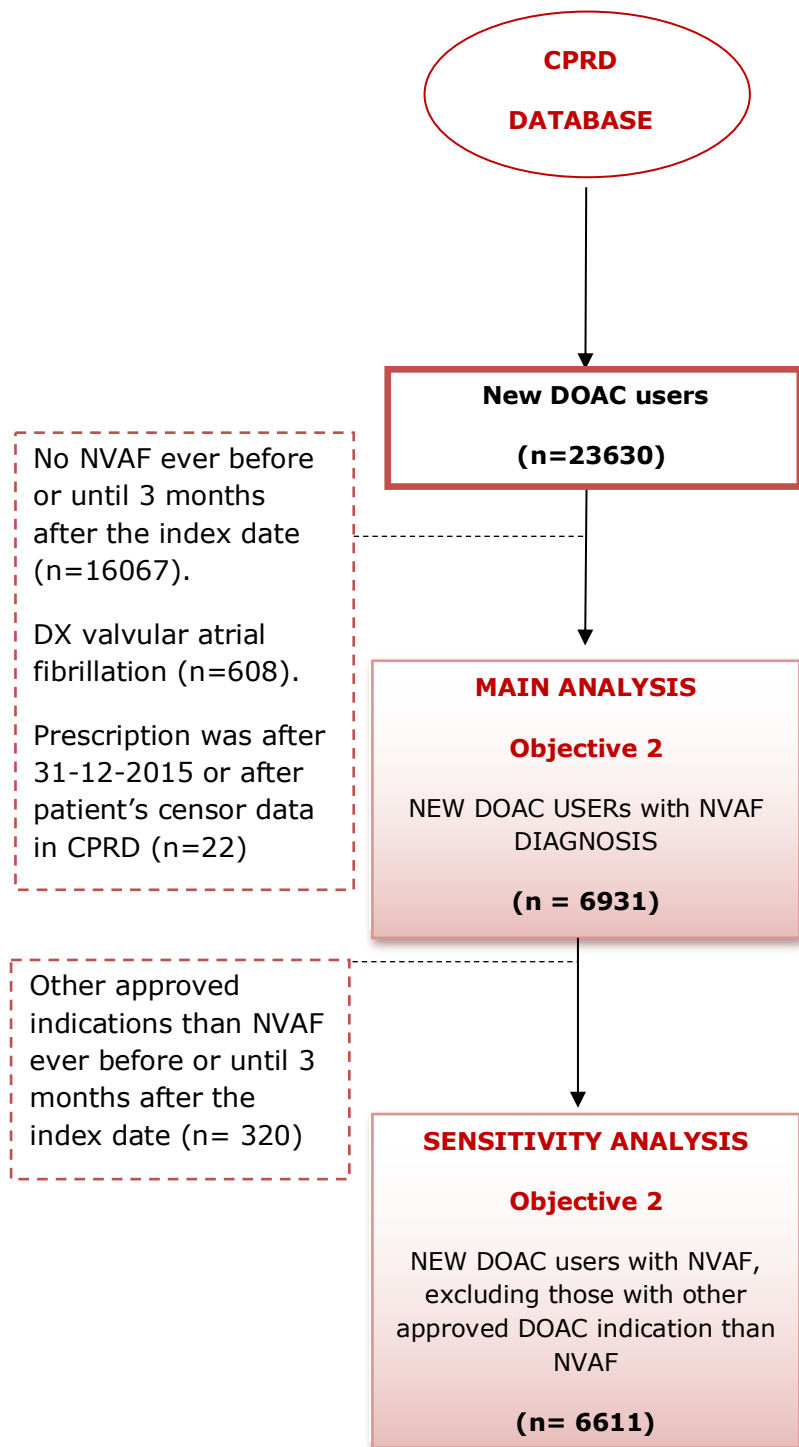
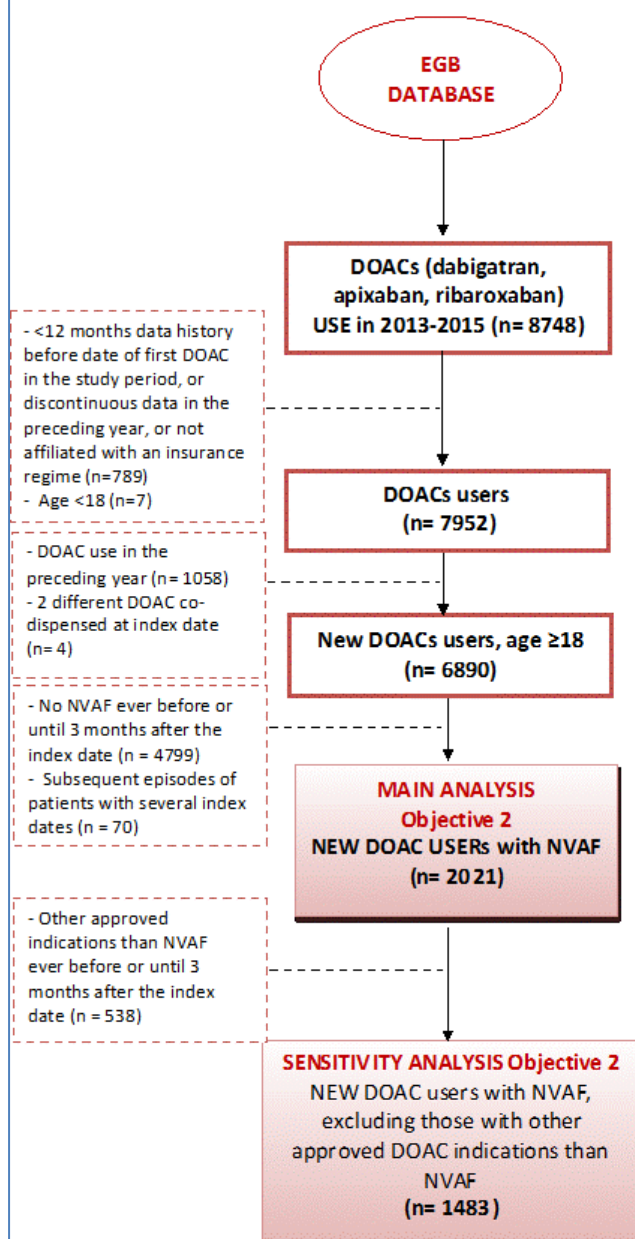
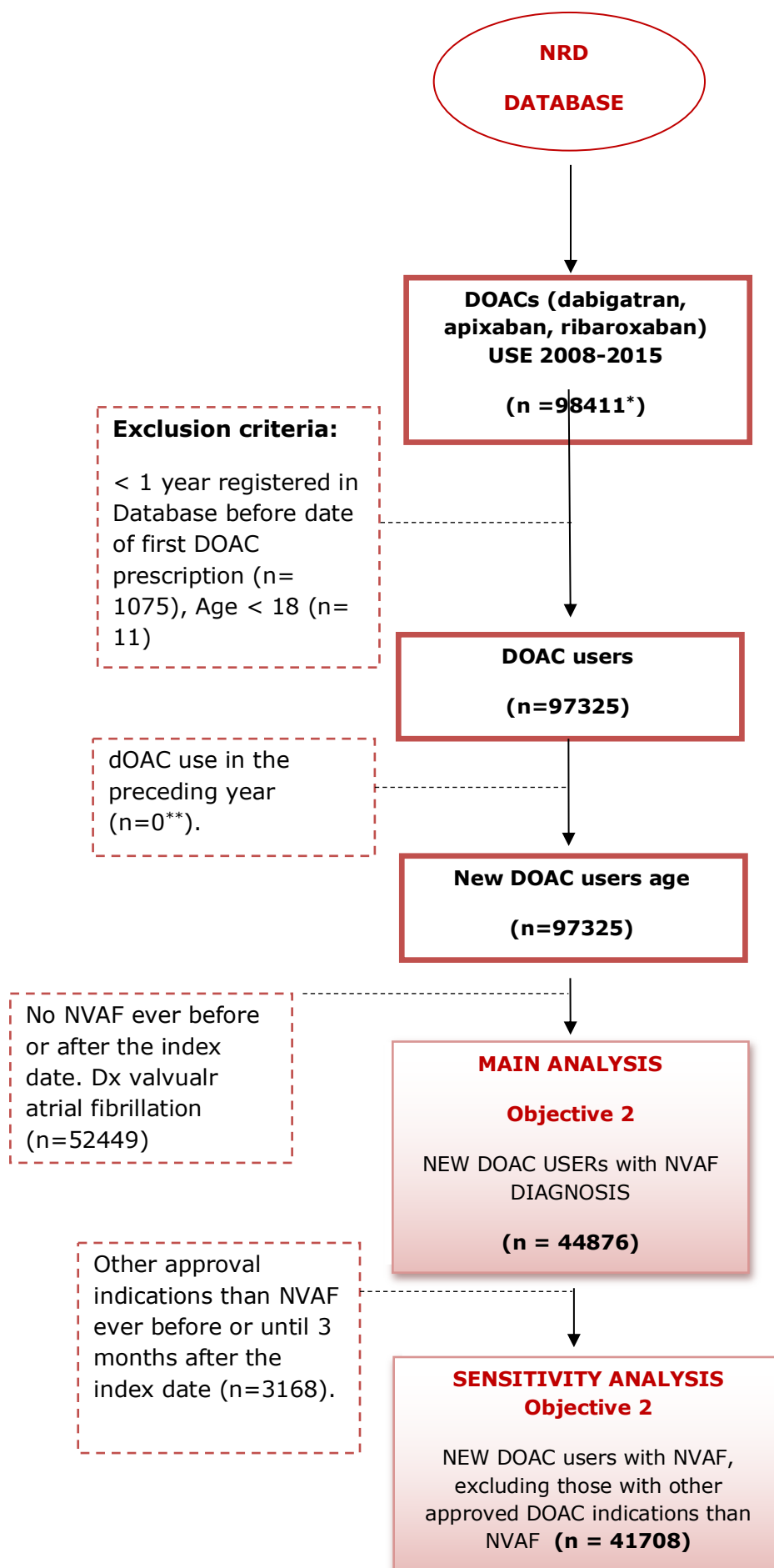
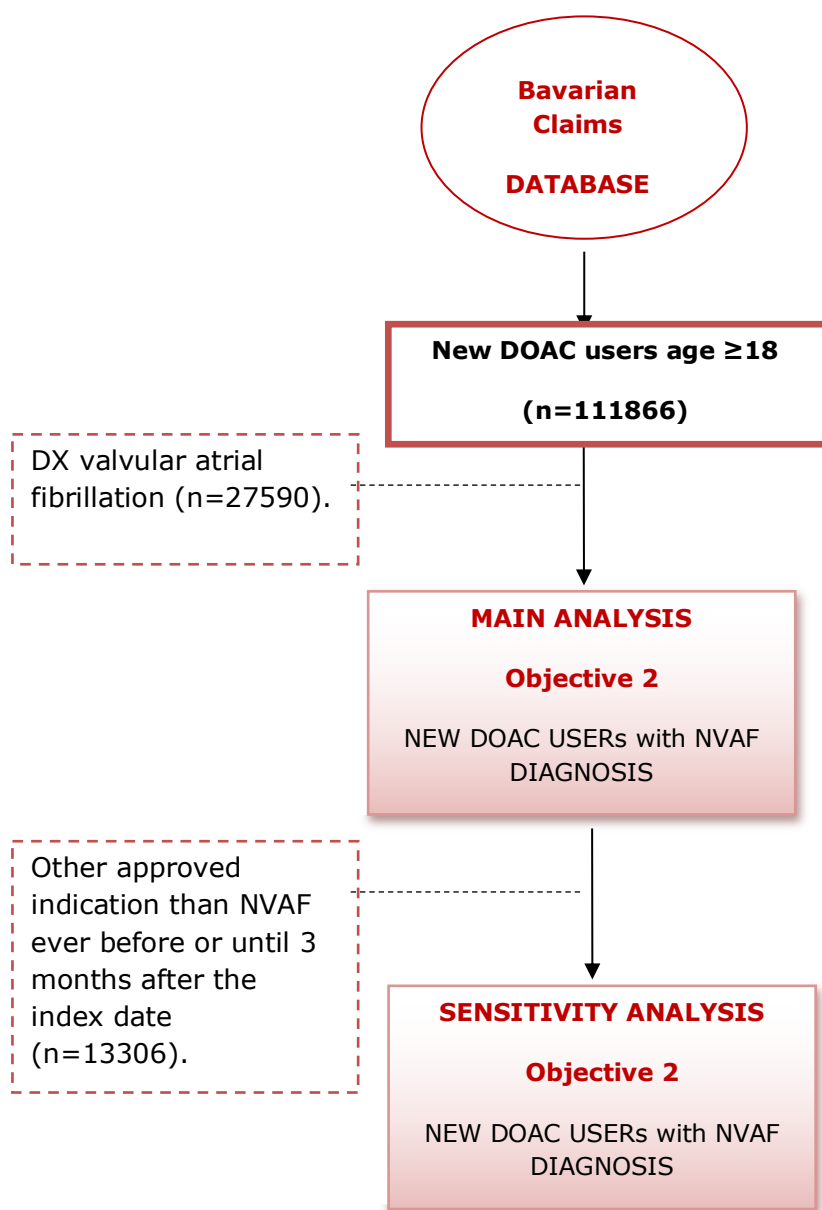


Figure 1. Descriptive study investigating the utilization of DOACs in NVAF patients (Objective 2): Flow-chart of patients selection in EGB database





* Initial 98846 DOAC users of which early users (n=8), users with more than one drug on index date (n=12), non-residents (n=409), and users with error in migration date (n=1) were excluded.. ** All are new users



Annex 5. Answers to questions from EMA and FDA

(See separate document)

Annex 6. Response to EMA reviewers' questions

(See separate document)

Signature

Principal investigator	Dr. Helga Gardarsdottir
Place	Utrecht
Date	
Signature	