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Prescribers' compliance with summary of product characteristics of dabigatran, rivaroxaban and apixaban—A European comparative drug utilization study

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Abstract

Despite a tremendous increase of direct oral anticoagulants (DOACs) prescriptions in recent years, only few data is available analysing prescribers' adherence to Summary of Product Characteristics (SmPC). We aimed to assess adherence to registered indications, contraindications, special warnings/precautions, and potential drug-drug interactions for three DOAC compounds (dabigatran, rivaroxaban, and apixaban) in six databases of five European countries (The Netherlands, United Kingdom, Spain, Denmark, and Germany). We included adult patients (≥18 years) initiating DOACs between 2008 and 2015. For several SmPC items, broad definitions were used due to ambiguous SmPC terms or lacking data in some databases. Within the study period, a DOAC was initiated in 407 576 patients (rivaroxaban: 240 985 (59.1%), dabigatran: 95 303 (23.4%), and apixaban: 71 288 (17.5%)). In 2015, non-valvular atrial fibrillation was the most common indication (>60% in most databases). For the whole study period, a substantial variation between the databases was found regarding the proportion of patients with at least one contraindication (inter-database range [IDR]: 8.2%-55.7%), with at least one special warning/precaution (IDR: 35.8%-75.2%) and with at least one potential drug-drug interaction (IDR: 22.4%-54.1%). In 2015, the most frequent contraindication was "malignant neoplasm" (IDR: 0.7%-21.3%) whereas the most frequent special warning/precaution was "prescribing to the elderly" (≥75 years; IDR: 25.0%-66.4%). The most common single compound class interaction was "concomitant use of non-steroidal anti-inflammatory drugs" (IDR: 3.0%-25.3%). Contraindications, special warnings/precautions, and potential drug-drug interactions were present in a relevant number of new DOAC users. Due to

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broad definitions used for some SmPC terms, overall proportions for contraindications are prone to overestimation. However, for unambiguous SmPC terms documented in the databases sufficiently, the respective estimates can be considered valid. Differences between databases might be related to "true" differences in prescription behaviour, but could also be partially due to differences in database characteristics.

KEYWORDS
direct oral anticoagulant, drug utilization, pharmacoepidemiology, SmPC adherence

1 | INTRODUCTION

Direct oral anticoagulants (DOACs), including dabigatran, rivaroxaban, apixaban, and edoxaban, have been authorized for various indications within the past years. Regarding the main indication "stroke prevention in patients with non-valvular atrial fibrillation" DOACs exhibited an at least comparable or even better benefit-risk profile in clinical trials compared to warfarin.[1-4] In Europe, the Summary of Product Characteristics (SmPC) is the approved legal document required for marketing authorization. Among other things, this document contains the therapeutic indications (ie drug label), contraindications, and precautions/special warnings all prescribers should adhere to. In addition, potential interactions with other drugs are also stated in this document. Information included in the SmPCs of DOACs is mainly based on randomized clinical trials, but patients included in those trials represent the "real-world" population only to a limited extent.[5,6] Taking into account guidelines favouring DOACs over vitamin K antagonists (VKAs),[7] there is a huge need to describe the populations treated in clinical routine, to examine the extent of SmPC adherence, and to further analyse reasons for SmPC non-adherence. However, prescribing of VKAs is justified for particular patients taking into account the limited external validity of RCTs examining DOACs.[6]

Despite a tremendous increase of DOAC prescriptions in recent years,[8-10] only few studies were published analysing adherence to prescribing advice according to SmPCs or DOAC off-label use. In one of the first drug utilization studies covering the "early" indications of some DOACs (prophylaxis of venous thromboembolism after hip or knee replacement), indications covered by the SmPC's drug label were present in more than 82% of rivaroxaban treatments, but recommended treatment duration was exceeded in the majority of patients.[11] Focussing on stroke prevention in non-valvular atrial fibrillation (NVAF) patients, a retrospective analysis revealed an off-label use (history of valvular disease or lacking atrial fibrillation) in one-fifth of patients receiving dabigatran.[12] Even though ignoring renal dysfunction in terms of a lacking dabigatran dose adjustment was only a minor issue, more than two-thirds of dabigatran patients received a potentially interacting concomitant medication (via p-glycoprotein).[12] In a published US registry study of patients with atrial fibrillation, a SmPC-compliant DOAC dose was found in 87% of patients. Patients receiving off-label dosages were older, were more likely female, were less likely treated by an electrophysiologist, and had higher CHA2DS2-VASc scores and bleeding scores compared to patients receiving a recommended DOAC dose.[13] In a Dutch registry, a slightly higher proportion (91.7%) of dose-adequate DOAC prescriptions was detected in patients with atrial fibrillation.[14]

To sum up, few studies on DOACs reporting selected aspects of non-adherence to SmPCs have been published. However, large cross-country observational studies that comprehensively assess SmPC adherence are lacking. Hence, the objective of this study was to conduct an

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observational study in six European databases representing a population of 43.4 million people in order to assess prescribers' adherence to SmPCs of three DOAC compounds (dabigatran, rivaroxaban, and apixaban) with a special focus on indications, contraindications, special warnings/precautions and potential drug-drug interactions.

2 | METHODS

2.1 | Study design

An observational cohort study among adult patients (≥18 years) initiating a DOAC (dabigatran, rivaroxaban, and apixaban; e-Table 1) was performed. The study cohort consisted of adult users (≥18 years) of DOACs covered by the databases mentioned below. New users were defined as patients initiating DOACs during the study period (2008-2015) without any use of DOACs for at least 12 months (=365 days) prior to the index date (ie date of the first prescription of dabigatran, rivaroxaban or apixaban). Patients registered in the databases for less than 12 months before the index date were excluded. A common protocol was used and is registered and accessible under European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) EU PAS register number 16014 (http://www.encepp.eu/encepp/openAttachment/fullProtocolLatest/24184).

2.2 | Data sources

The study was conducted in the following six European databases: the Utrecht General Practitioner Network Database (Julius Huisartsen Netwerk (Mondriaan; The Netherlands)),[15] The United Kingdom Clinical Practice Research Datalink (CPRD; United Kingdom),[16,17] Base de Datos para la Investigación Farmacoepidemiológica en Atencion Primaria (BIFAP; Spain),[18] the Information System for the Development of Research in Primary Care (SIDIAP database; Catalònia, Spain),[19] the Bavarian Association of Statutory Health Insurance Physicians database (Bavarian CD; Germany),[20] and the National Registries Denmark (NR Denmark; Denmark).[21-23] The different databases cover regionally/nationally representative populations between 0.4 and 12.5 million people. The main characteristics of all databases/registries are presented in Table 1.

2.3 | Assessment of indication, comorbidities and concomitant drugs

Indications for prescribing were defined as the following mutually exclusive groups according to the SmPC section 4.1: myocardial infarction/angina (MI-A only), prevention after hip/knee replacement (PHK only), prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation (NVAF only), treatment of deep vein thrombosis (DVT), and pulmonary embolism (PE) including prevention of recurrent DVT and PE in adults (DVT-PE only), the combinations NVAF/MI-A, NVAF/PHK, and NVAF/DVT-PE, MI-A/PHK, MI-A/DVT-PE, PHK/DVT-PE, a combined category for valvular atrial fibrillation (VAF only) and combination of VAF (VAF/MI-A, VAF/PHK, and VAF/DVT-PE), and one combined category for other/other combinations/missing indications (OM). Different coding systems were used searching the databases for identification of the documented indications (see e-Table 2).

Indications related to DOAC prescription were checked or assumed according to the following approaches which were applied in a hierarchical manner. If a direct linkage between indication and the first prescription was available, approach 1 was used. If such a linkage was not available in the database or only available for a part of patients in a database, the subsequent approaches were applied. Approaches: (1) linked indication to the first DOAC prescription (BIFAP, Mondriaan); (2) Medical code for the indication ± 3 months before or after the index date in one of the following databases: (2a) General practitioner record (CPRD, SIDIAP, and BIFAP), (2b) Claims record within the same quarter (Bavarian CD); (3) Medical code for the indication prior to index date + 3 months after the index date in case of hospital record (discharge diagnosis; NR Denmark). In case of a lacking diagnosis, the indication of this prescription was classified as "missing".

Comorbidities listed in the SmPC sections 4.3 and 4.4 (ie contraindications and special warnings/precautions) were assessed during various time periods prior to the index date (ever, 12 months, 6 months, and 6 weeks before the index date), depending on the type of comorbidity. For the Bavarian database, "6 weeks before the index date" was assessed considering the same quarter. Potential comorbidities listed in SmPC sections 4.3 and 4.4 were identified through specific medical codes (e-Tables 3 and 4).

Information on the measurements of weight, body mass index, and renal function was assessed during the 12 months prior to index date. In case of multiple measurements, the one nearest to the index date was selected.

Concomitant use of other (potentially interacting) medications listed in the SmPC sections 4.3, 4.4 and 4.5 was assessed and identified through medical codes (e-Tables 5 and 6), respectively. Use of the potentially interacting drugs was considered concomitant when date of prescribing or filling of prescription was during the DOAC treatment episode as described in study protocol (ENCePP EU PAS register number 16014, available at http://www.encepp.eu/encepp/openAttachment/fullProtocolLatest/24184).

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TABLE 1 Database characteristics

	Mondriaan	National Registries Denmark	Bavarian CD	BIFAP	SIDIAP	CPRD
Country	The Netherlands (National)	Denmark (National)	Germany (Regional)	Spain (National)	Spain (Regional)	United Kingdom (National)
Source population	0.4 m	5.5 m	10.5 m	7.5 m	7.0 m	12.5 m
Type of database	GP prescribing data and pharmacy dispensing data	Dispensing data	Claims database including data for dispensed and reimbursed drugs	General practice prescribing and dispensing data	General practice prescribing data	General practice prescribing data
Data available since	1991	1994	2008	2001	2006	1987
Drug information						
Active international coding	ATC	ATC	ATC	ATC	ATC	BNF
Product coding	HPK	Varenr	PZN	CNF	Yes (is registered but not available for research due to confidentiality reasons)	Product code
Date of prescribing/ dispensing	Yes	Yes	Yes (for each prescription the quarter is documented)	Yes	Yes (for dispensing: MM/ YY)	Yes
Quantity prescribed/ dispensed	Yes	Yes	Yes (package size)	Yes	Yes (Number of reimbursed packages)	Yes
Dosing regimen	No	No	No	Yes	Yes (only in prescribing data)	Yes
Diagnosis information						
Outpatient primary care diagnosis	ICPC	ICD-8, ICD-10 (only outpatient contacts at hospitals)	ICD-10-GM (for each diagnosis the quarter is documented)	ICPC-2, ICD-9	ICD-10	ICD-9, ICD-10
Hospital discharge diagnosis	No	ICD-8, ICD-10	No	Not systematically/as recorded by the GP	No (available for 28% of included population)	ICD-9, ICD-10
Laboratory tests	Yes	No	No	Yes (as requested and recorded by GP)	Yes	Yes

Abbreviations: ATC: anatomical therapeutic chemical; Bavarian CD, Bavarian Association of Statutory Health Insurance Physicians database; BIFAP, Base de Datos para la Investigación Farmacoepidemiológica en Atencion Primaria; BNF, British National Formulary; CNF, Código Nacional Farmacéutico; CPRD, United Kingdom Clinical Practice Research Datalink; GM, German Modification; GP, general practitioner; HPK, Handels Product Code; ICD, International Statistical Classification of Diseases and Related Health Problems; ICPC, International Classification of Primary Care; Mondriaan, Utrecht General Practitioner Network Database; PZN, Pharmazentralnummer (central pharmaceutical number); SIDIAP, Information System for the Development of Research in Primary Care; Varenr, varenummer.

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For several ambiguous SmPC items, broad definitions were used to avoid underestimation. However, estimates for these items (and the respective overall estimates) are prone to overestimation. In addition, in some databases laboratory values are not documented and broad definitions for respective conditions were used. For unambiguous SmPC terms documented in the databases sufficiently, the respective estimates can be considered valid.

2.4 | Statistical analysis

A descriptive statistical analysis was conducted. The frequency and percentage of incident DOAC users related to the total population of new DOAC users were calculated for indications, contraindications, special warnings/precautions, and drug-drug interactions defined by the relevant SmPCs. The analysis was stratified by database, individual DOAC, age group (<75, 75-79 and ≥80 years), sex, and calendar year.

3 | RESULTS

3.1 | New DOAC users

Within the study period, a DOAC was initiated in 407 576 patients (rivaroxaban: 240 985 (59.1%); dabigatran: 95 303 (23.4%); apixaban: 71 288 (17.5%)). Between databases and countries, some discrepancies were found with regard to DOAC preference. The proportion of incident DOAC users receiving dabigatran was between 12.6% (Bavarian CD) and 45.4% (NR Denmark), whereas for rivaroxaban this was 37.5% (SIDIAP) to 70.6% (Bavarian CD), and for apixaban 13.6% (Mondriaan) to 23.2% (BIFAP), respectively (Table 2).

Regarding changes in prescribing/dispensing over time, different patterns were found for the three DOAC compounds (Figure 1A,B). For dabigatran, the number of incident users increased within the study period until 2012 or 2013 and thereafter decreased. For rivaroxaban, a rise was found for the whole study period in most databases, whereas in the Bavarian database the number of incident users peaked in 2013 followed by a decrease. For apixaban, an increase was noticed in all databases during the study period.

Between the databases, some sex- and age-specific differences were found for new DOAC users. The proportion of female patients ranged between 42.9% (Mondriaan) and 55.8% (Bavarian CD), whereas the proportion of patients aged at least 80 years was between 17.3% (Mondriaan) and 38.1% (BIFAP) (e-Table 7).

3.2 | Indications in incident DOAC users

In most databases, "NVAF only" was the most common indication in incident DOAC users. Among incident dabigatran users, the proportion of patients with registered indication "NVAF only" was between 38.9% (Bavarian CD) and 66.6% (BIFAP; e-Table 8). The range for incident rivaroxaban users was 25.3% (Bavarian CD) to 66.4% (Mondriaan), whereas for apixaban the proportion was between 36.6% (Bavarian CD) and 72.7% (Mondriaan; e-Table 8). During the study period, a distinct increase was found for each of the three DOAC compounds regarding the proportion of patients with NVAF (data not shown).

Regarding the proportion of incident users with an indication "prevention of thrombosis after hip/knee replacement (PHK) only," some differences were found between

TABLE 2 Incident DOAC users stratified by database and DOAC compound

	All DOACs		Dabigatran		Rivaroxaban		Apixaban	
	n	%[a]	n	%[b]	n	%[b]	n	%[b]
Mondriaan	757	0.2	186	24.6	468	61.8	103	13.6
NR Denmark	97 325	23.6	44 219	45.4	37 061	38.1	16 045	16.5
Bavarian CD	237 864	58.6	30 047	12.6	167 835	70.6	39 982	16.8
BIFAP	24 977	6.1	7127	28.5	12 048	48.2	5802	23.2
SIDIAP	23 161	5.7	10 048	43.4	8695	37.5	4418	19.1
CPRD	23 492	5.8	3676	15.6	14 878	63.3	4938	21.0
Total	407 576	100.0	95 303	23.4	240 985	59.1	71 288	17.5

Abbreviations: Bavarian CD, Bavarian Association of Statutory Health Insurance Physicians database; BIFAP, Base de Datos para la Investigación Farmacoepidemiológica en Atencion Primaria; CPRD, United Kingdom Clinical Practice Research Datalink; DOAC, direct oral anticoagulants; Mondriaan, Utrecht General Practitioner Network Database; NR Denmark, National Registries Denmark; SIDIAP, Information System for the Development of Research in Primary Care.

[a]Related to the total population of incident DOAC users (all databases).

[b]Related to the total population of incident DOAC users for the respective database.

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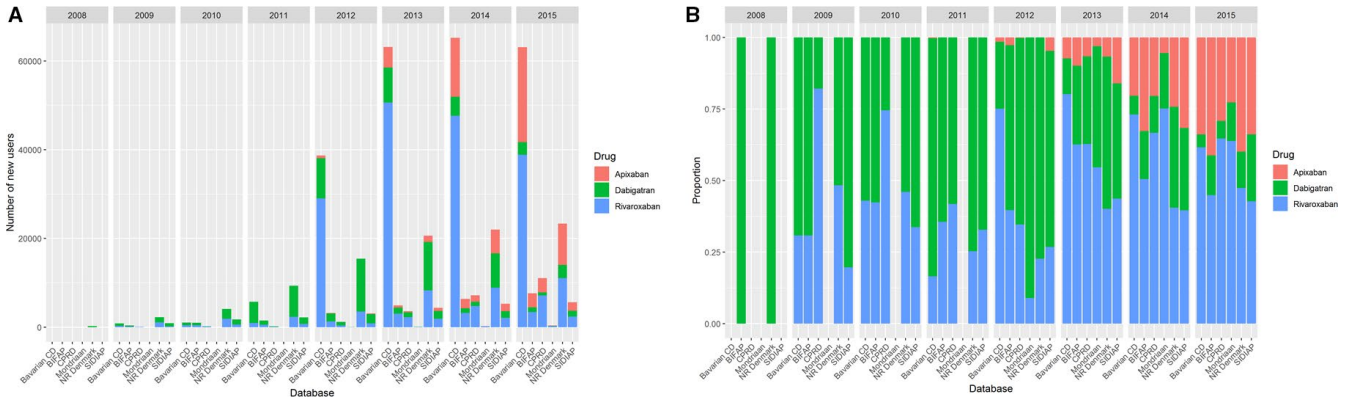

FIGURE 1 Absolute number (A) and proportions (B) of new users stratified for database, DOAC, and calendar year

the databases in 2015 (e-Table 8). Comparing results over the years, a decrease in the proportion of patients with registered PHK was found in BIFAP and CPRD (all DOAC compounds), whereas an increase was found in SIDIAP for dabigatran and rivaroxaban (data not shown).

3.3 | Contraindications in incident DOAC users

Between the databases, a substantial variation was found regarding the proportion of patients with at least one contraindication with lowest values in SIDIAP and CPRD (8.2%) and with the highest value in the Bavarian CD (55.7%; Table 3). In most databases, the highest proportion of contraindications was found for incident dabigatran users. The respective range for dabigatran was 9.6% (SIDIAP) to 62.7% (Bavarian CD), for rivaroxaban 6.9% (SIDIAP) to 54.5% (Bavarian CD), and for apixaban 7.5% (SIDIAP) to 55.6% (Bavarian CD; Table 3; e-Table 9).

By analysing contraindications in detail, some differences were found between the databases with regard to the three most frequent contraindications (Table 4; e-Tables 10-12). In 2015, the most frequent contraindications were malignant neoplasm (inter-database range (IDR): 0.7%-21.3%), active clinically significant bleeding (IDR: 0.6%-15.6%), and concomitant treatment with "any other [parenteral] anticoagulants" (eg heparins; IDR: 0.0%-11.4%). Renal impairment was of relevance for dabigatran in the Bavarian database and in SIDIAP. Hepatic diseases associated with coagulopathy and clinically relevant bleeding risk were relevant in the Bavarian database only.

3.4 | Most frequent special warnings/precautions in incident DOAC users

Special warnings/precautions were present in 35.8% (Mondriaan) to 75.2% (Bavarian CD) of all incident DOAC patients (Table 3). In all databases, the highest proportion was found for incident apixaban users with a range from 43.7% (Mondriaan) to 81.1% (Bavarian CD). For dabigatran, the range was 33.3% (Mondriaan) to 76.2% (Bavarian CD), whereas for rivaroxaban a range between 35.0% (Mondriaan) and 73.6% (Bavarian CD) was revealed (Table 3; e-Table 13), respectively.

By analysing special warnings/precautions in detail (Table 5; e-Tables 14-16), "age ≥ 75 years" was the most frequent special warning (year 2015; IDR: 25.0%-66.4%). Since the age structure of Mondriaan differs from all other databases, the lowest proportion for special warning/precaution "age ≥ 75 years" was found in this database. "Esophagitis, gastritis or gastroesophageal reflux" was the second most frequent special warning in 2015 (IDR: 0.0%-41.9%).

3.5 | Most frequent potential drug-drug interactions in incident DOAC users

Potential drug-drug interactions (pDDIs) were present in 22.4% (SIDIAP) to 54.1% (BIFAP) of all incident DOAC patients (Table 3). In all databases, the highest proportion was found for incident dabigatran users with a range from 25.8% (SIDIAP) to 61.6% (BIFAP). For rivaroxaban, the respective range was 19.7% (SIDIAP) to 53.4% (BIFAP), whereas for apixaban a range between 9.7% (Mondriaan) and 46.1% (BIFAP) was found (Table 3; e-Table 17).

By analysing pDDIs in detail (Table 6; e-Tables 18-20), some differences were found between the databases regarding the three most frequent pDDIs. In 2015, the most common single compound class pDDI was "concomitant use of non-steroidal anti-inflammatory drugs" (IDR: 3.0%-25.3%).

4 | DISCUSSION

4.1 | New DOAC users

During the period of 2008-2015, we observed an increase in new users of rivaroxaban and apixaban, whereas for

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TABLE 3 Frequency and percentage of new DOAC users with at least one contraindication, special warning/precaution or potential drug-drug interaction stratified for DOAC compound and database

	Total				Contraindications							
	All DOACs	Dabigatran	Rivaroxaban	Apixaban	All DOACs		Dabigatran		Rivaroxaban		Apixaban	
	n	n	n	n	n	%	n	%	n	%	n	%
Mondriaan	757	186	468	103	154	20.3	28	15.1	105	22.4	21	20.4
NR Denmark[a]	97 325	44 219	37 061	16 045	17 591	18.1	9234	20.9	5652	15.3	2705	16.9
Bavarian CD	237 864	30 047	167 835	39 982	132 548	55.7	18 852	62.7	91 448	54.5	22 248	55.6
BIFAP	24 977	7127	12 048	5802	4913	19.7	1702	23.9	2254	18.7	957	16.5
SIDIAP	23 161	10 048	8695	4418	1900	8.2	963	9.6	604	6.9	333	7.5
CPRD	23 492	3676	14 878	4938	1916	8.2	356	9.7	1163	7.8	397	8.0

	Special warning/precaution								Potential drug-drug interaction							
	All DOACs		Dabigatran		Rivaroxaban		Apixaban		All DOACs		Dabigatran		Rivaroxaban		Apixaban	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Mondriaan	271	35.8	62	33.3	164	35.0	45	43.7	176	23.2	51	27.4	115	24.6	10	9.7
NR Denmark[a]	48 069	49.4	20 687	46.8	17 185	46.4	10 197	63.6	47 565	48.9	25 692	58.1	16 671	45.0	5202	32.4
Bavarian CD	178 842	75.2	22 910	76.2	123 515	73.6	32 417	81.1	108 068	45.4	14 559	48.5	76 418	45.5	17 091	42.7
BIFAP	16 046	64.2	4407	61.8	7526	62.5	4113	70.9	13 502	54.1	4387	61.6	6439	53.4	2676	46.1
SIDIAP	11 936	51.5	4712	46.9	4424	50.9	2800	63.4	5189	22.4	2593	25.8	1713	19.7	883	20.0
CPRD	15 734	67.0	2537	69.0	9639	64.8	3558	72.1	5402	23.0	1390	37.8	3264	21.9	748	15.1

Abbreviations: Bavarian CD, Bavarian Association of Statutory Health Insurance Physicians database; BIFAP, Base de Datos para la Investigación Farmacoepidemiológica en Atencion Primaria; CPRD, United Kingdom Clinical Practice Research Datalink; DOAC, direct oral anticoagulants; Mondriaan, Utrecht General Practitioner Network Database; NR Denmark, National Registries Denmark; SIDIAP, Information System for the Development of Research in Primary Care.

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

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TABLE 4 Frequency and percentage of new DOAC users with a contraindication[a] (TOP 3) stratified by DOAC compound and database for calendar year 2015

	Dabigatran	Rivaroxaban	Apixaban
Mondriaan	1. Active clinically significant bleeding (n = 6; 11.5%) 2. Malignant neoplasms (n = 6; 11.5%) 3. Haemorrhagic stroke/intracranial bleeding (n = 5; 9.6%)	1. Malignant neoplasms (n = 18; 7.3%) 2. Haemorrhagic stroke/intracranial bleeding (n = 16; 6.5%) 3. Active clinically significant bleeding (n = 14; 5.7%)	1. Active clinically significant bleeding (n = 9; 10.2%) 2. Haemorrhagic stroke/intracranial bleeding (n = 9; 10.2%) 3. Malignant neoplasms (n = 7; 8.0%)
NR Denmark	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 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. 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 = 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 = 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 = 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 = 78; 7.4%) 2. Concomitant treatment with any other anticoagulants (n = 62; 5.8%) 3. Vascular aneurysms or major intraspinal or intracerebral vascular abnormalities (n = 19; 1.8%)	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 = 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. Severe renal impairment (CrCL < 30 mL/min)/chronic and acute kidney disease (n = 47; 3.6%) 2. Concomitant treatment with any other anticoagulants (n = 21; 1.6%) 3. Active clinically significant bleeding (n = 16; 1.2%)	1. Concomitant treatment with any other anticoagulants (n = 35; 1.5%) 2. Malignant neoplasms (n = 35; 1.5%) 3. Vascular aneurysms or major intraspinal or intracerebral vascular abnormalities (n = 27; 1.1%)	1. Concomitant treatment with any other anticoagulants (n = 35; 1.8%) 2. Vascular aneurysms or major intraspinal or intracerebral vascular abnormalities (n = 32; 1.7%) 3. Active clinically significant bleeding (n = 30; 1.6%) 4. Malignant neoplasms (n = 30; 1.6%)
CPRD	1. Malignant neoplasms (n = 16; 2.3%) 2. Prosthetic heart valves requiring anticoagulant treatment (n = 13; 1.9%) 3. Vascular aneurysms or major intraspinal or intracerebral vascular abnormalities (n = 13; 1.9%)	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%) 4. Arteriovenous malformations (n = 83; 1.2%)	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%)

Note: Any oral anticoagulants: vitamin K antagonists, dabigatran, ximelagatran, direct factor Xa inhibitors; Any other anticoagulants: heparin group, other antithrombotic agents, desirudin, lepirudin, argatroban, melagatran, bivalirudin; Antiplatelet therapy: platelet aggregation inhibitors excl. heparin.

Abbreviations: Bavarian CD, Bavarian Association of Statutory Health Insurance Physicians database; BIFAP, Base de Datos para la Investigación Farmacoepidemiológica en Atencion Primaria; CPRD, United Kingdom Clinical Practice Research Datalink; CrCL, creatinine clearance; Mondriaan, Utrecht General Practitioner Network Database; NR Denmark, National Registries Denmark; SIDIAP, Information System for the Development of Research in Primary Care.

[a]Time window for identification of events: malignant neoplasms: within 6 mo prior to index date; active clinically significant bleeding: within 6 wk prior to index date; haemorrhagic stroke/intracranial bleeding: within 6 mo prior to index date; severe renal impairment (CrCL < 30 mL/min)/chronic and acute kidney disease: within 12 mo prior to index date.

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TABLE 5 Frequency and percentage of new DOAC users with a special warning/precaution[a] (TOP 3) stratified by DOAC compound and database for calendar year 2015

	Dabigatran	Rivaroxaban	Apixaban
Mondriaan	1. Age ≥ 75 y (n = 13; 25.0%) 2. Major trauma (n < 5) 3. Hip fracture (n < 5)	1. Age ≥ 75 y (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 y (n = 35; 39.8%) 2. Major trauma, bacterial endocarditis, bronchiectasis or history of pulmonary bleeding, hip fracture, mild or moderate hepatic impairment (Child Pugh A or B), use of thrombolytic agents for the treatment of acute ischaemic stroke (each n < 5)
NR Denmark	1. Age ≥ 75 y (n = 1,375; 46.3%) 2. Esophagitis, gastritis or gastroesophageal reflux (n = 235; 7.9%) 3. Major trauma (n = 75; 2.5%)	1. Age ≥ 75 y (n = 4345; 39.3%) 2. Esophagitis, gastritis or gastroesophageal reflux (n = 952; 8.6%) 3. Major trauma (n = 399; 3.6%)	1. Age ≥ 75 y (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 y (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 y (n = 17 257; 44.4%) 2. Esophagitis, gastritis or gastroesophageal reflux (n = 16 245; 41.8%) 3. Congenital or acquired coagulation disorders (n = 6261; 16.1%)	1. Age ≥ 75 y (n = 13 060; 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 y (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 y (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 y (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 y (n = 624; 47.6%) 2. Moderate renal impairment (CrCL 30-50 mL/min) (n = 139, 10.6%) 3. Low body-weight (eg <50 kg/60 kg) (n = 69; 5.3%)	1. Age ≥ 75 y (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 y (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 y (n = 374; 54.2%) 2. Esophagitis, gastritis or gastroesophageal reflux (n = 184; 26.7%) 3. Moderate renal impairment (CrCL 30-50 mL/min) (n = 130; 18.8%)	1. Age ≥ 75 y (n = 3552; 49.7%) 2. Esophagitis, gastritis or gastroesophageal reflux (n = 1852; 25.9%) 3. Bronchiectasis or history of pulmonary bleeding (n = 409; 5.7%)	1. Age ≥ 75 y (n = 1916; 59.3%) 2. Esophagitis, gastritis or gastroesophageal reflux (n = 849; 26.3%) 3. Bronchiectasis or history of pulmonary bleeding (n = 178; 5.5%)

Abbreviations: ACS, acute coronary syndrome; Bavarian CD, Bavarian Association of Statutory Health Insurance Physicians database; BIFAP, Base de Datos para la Investigación Farmacoepidemiológica en Atencion Primaria; CPRD, United Kingdom Clinical Practice Research Datalink; Mondriaan, Utrecht General Practitioner Network Database; NR Denmark, National Registries Denmark; SIDIAP, Information System for the Development of Research in Primary Care; TIA, transient ischaemic attack.

[a]Time window for identification of events: hip fracture: 6 mo prior to index date; major trauma: 6 mo prior to index date; moderate renal impairment (CrCL 30-50 mL/min): 12 mo prior to index date; treatment of ACS in patients with a prior stroke or TIA: 6 mo 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 mo prior to index date; bacterial endocarditis: 6 mo prior to index date; use of thrombolytic agents for the treatment of acute ischaemic stroke: 6 mo prior to index date; severe renal creatinine clearance 15-29 mL/min with caution: 12 mo prior to index date.

dabigatran highest numbers were reached in 2012 or 2013 followed by a decrease. Despite applying different methodologies, our results are in line with the temporal patterns for these three DOAC compounds that have been reported in drug utilization studies conducted in the United States, Canada, and Norway.[8,24,25] The decrease

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TABLE 6 Frequency and percentage of new DOAC users with a potential drug-drug interaction (Top 3) stratified by DOAC compound and database for calendar year 2015

	Dabigatran	Rivaroxaban	Apixaban
Mondriaan	1. NSAID (n = 6; 11.5%) 2. SSRI/SNRI (n < 5) 3. Amiodarone, verapamil, (anticoagulants and antiplatelets, dextran, sulphinpyrazone), ASA (each n < 5)	1. NSAID (n = 21, 8.5%) 2. Anticoagulants and antiplatelets, dextran, sulphinpyrazone (n = 12, 4.9%) 3. Verapamil (n = 10, 4.0%)	1. NSAID, Verapamil, Amiodarone (each n < 5)
NR Denmark	1. Anticoagulants and antiplatelets, dextran, sulphinpyrazone (n = 1237; 41.6%) 2. ASA (n = 320; 10.8%) 3. SSRI/SNRI (n = 269; 9.1%)	1. Anticoagulants and antiplatelets, dextran, sulphinpyrazone (n = 3180, 28.8%) 2. NSAID (n = 1239, 11.2%) 3. ASA (n = 701, 6.3%)	1. Anticoagulants and antiplatelets, dextran, sulphinpyrazone (n = 3469, 37.2%) 2. ASA (n = 757, 8.1%) 3. NSAID (n = 696, 7.5%)
Bavarian CD	1. Anticoagulants and antiplatelets, dextran, sulphinpyrazone (n = 704; 24.3%) 2. NSAID (n = 531; 18.3%) 3. ASA (n = 190; 6.5%)	1. NSAID (n = 9816; 25.3%) 2. Anticoagulants and antiplatelets, dextran, sulphinpyrazone (n = 8339, 21.5%) 3. ASA (n = 1936, 5.0%)	1. Anticoagulants and antiplatelets, dextran, sulphinpyrazone (n = 5276, 24.7%) 2. NSAID (n = 3570; 16.7%) 3. ASA (n = 1728; 8.1%)
BIFAP	1. Anticoagulants and antiplatelets, dextran, sulphinpyrazone (n = 228; 21.5%) 2. NSAID (n = 132; 12.4%) 3. SSRI/SNRI (n = 124; 11.7%)	1. Anticoagulants and antiplatelets, dextran, sulphinpyrazone (n = 716, 20.9%) 2. NSAID (n = 583, 17.0%) 3. ASA (n = 346, 10.1%)	1. Anticoagulants and antiplatelets, dextran, sulphinpyrazone (n = 654, 20.8%) 2. NSAID (n = 455, 14.5%) 3. ASA (n = 306, 9.7%)
SIDIAP	1. SSRI/SNRI (n = 107; 8.2%) 2. Amiodarone (n = 91; 6.9%) 3. Anticoagulants and antiplatelets, dextran, sulphinpyrazone (n = 60; 4.6%)	1. Amiodarone (n = 196, 8.2%) 2. Anticoagulants and antiplatelets, dextran, sulphinpyrazone (n = 120, 5.9%) 3. NSAID (n = 97, 4.0%)	1. Amiodarone (n = 149, 7.8%) 2. Anticoagulants and antiplatelets, dextran, sulphinpyrazone (n = 119, 6.2%) 3. NSAID (n = 94, 4.9%)
CPRD	1. Anticoagulants and antiplatelets, dextran, sulphinpyrazone (n = 88; 12.8%) 2. ASA (n = 71; 10.3%) 3. SSRI/SNRI (n = 65; 9.4%)	1. Anticoagulants and antiplatelets, dextran, sulphinpyrazone (n = 729, 10.2%) 2. ASA (n = 537, 7.5%) 3. NSAID (n = 269, 3.8%)	1. Anticoagulants and antiplatelets, dextran, sulphinpyrazone (n = 340, 10.5%) 2. ASA (n = 250, 7.7%) 3. Amiodarone (n = 147, 4.6%)

Abbreviations: ASA, acetylsalicylic acid; Bavarian CD, Bavarian Association of Statutory Health Insurance Physicians database; BIFAP, Base de Datos para la Investigación Farmacoepidemiológica en Atencion Primaria; CPRD, United Kingdom Clinical Practice Research Datalink; Mondriaan, Utrecht General Practitioner Network Database; NR Denmark, National Registries Denmark; NSAID, non-steroidal anti-inflammatory drug; SIDIAP, Information System for the Development of Research in Primary Care; SNRI, serotonin and norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor.

of incident dabigatran users might be explained at least to some extent by the results from a meta-analysis of randomized controlled trials which was published in 2015 and reported that the risk of gastrointestinal bleeding was most elevated in dabigatran users.[26] These results have been confirmed in observational studies.[27] The distinct increase in incident apixaban users might be justified by a favourable gastrointestinal safety profile[28] and by taking into account results of a recently published network meta-analysis.[29] In the latter study, apixaban was ranked as being the most effective intervention regarding several outcomes (eg stroke or systemic embolism), the safest compound (lowest incidence of major and gastrointestinal bleedings), and the most cost-effective treatment in comparison to dabigatran, edoxaban, rivaroxaban, and warfarin.

4.2 | Indications in incident DOAC users

During the first years of the study period, prophylaxis of thrombosis after hip or knee replacement was frequently documented for dabigatran and rivaroxaban, whereas at the end of the study period NVAF was the most common indication for all three DOACs. Similar to our study, difficulties in defining the indication of DOAC due to multiple approved indications and overlapping dose recommendations by using secondary data were previously described in a Canadian study.[25] Furthermore, there is limited evidence on how valid post-surgical ICD codes for defining hip and knee replacements ("Z-Codes") are used making it difficult to identify the respective indication ("Primary Prevention of venous thromboembolic events in adult patients who have undergone elective total hip or knee replacement surgery").

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In a single-centre study analysing retrospectively DOAC patients, only 72% of apixaban prescriptions, 52% of dabigatran prescriptions, and 70% of rivaroxaban prescriptions were issued according to anticoagulation service's DOAC protocol.[30] In this study, the most common reasons for anticoagulation service's DOAC protocol deviation for apixaban and rivaroxaban were off-label indications and decreased dosages. For dabigatran users, age ≥ 75 years and off-label indication were the most common reasons for anticoagulation service's DOAC protocol deviations.

4.3 | Contraindications in incident DOAC users

Regarding the proportion of incident DOAC users with at least one contraindication, a wide range was found between the databases (8.2%-55.7%). In particular for the proportion of patients with renal dysfunction assessed as contraindication, a broad range was found between the databases. These differences might be partially explained by the different patients' age distribution of the databases and methodological differences in defining renal dysfunction (laboratory values, coding systems). Furthermore, some databases contain documentation of specialists, where other databases consider general practitioners only. Underlining the importance of contraindications related to severe renal dysfunction (in particular in patients receiving dabigatran), an increased (gastrointestinal) bleeding risk was found in several analyses depending on the severity of renal dysfunction.[31,32]

4.4 | Most frequent special warnings/precautions in incident DOAC users

In our study, precautions and special warnings were also present in a substantial proportion of patients (35.8%-75.2%). Prescribing for elderly patients (≥75 years) was found as most frequent special warning in all databases and for all three compounds in most years. However, from a medical point of view, elderly NVAF patients benefit from DOACs in comparison to warfarin even under real-life conditions.[33] Underlining this issue, the median age for warfarin and DOAC users was 76 years with slight differences between the compounds in the aforementioned Norwegian study.[24] From a medical point of view, age-related changes in pharmacodynamics and pharmacokinetics increase the risk of adverse drug reactions (mainly bleeding events).[28] However, in a nationwide Turkish registry, an undertreatment (mainly for dabigatran) was found in more than 30% of patients aged between 80 and 84 years.[34]

4.5 | Most frequent potential drug-drug interactions in incident DOAC users

Regarding potential interactions, highest prevalence was found for concomitant treatment with anticoagulants/antiplatelets, NSAIDs, SSRI/SNRI, and amiodarone showing large inter-country differences for some compounds. In particular, the observed differences in the proportion of patients receiving NSAIDs or anticoagulants/antiplatelets might be related to inter-country differences with regard to reimbursement strategies for NSAIDs or antiplatelets generally available as over-the-counter products. Similarly, a wide range was reported in the literature. In some studies, more than 50% of DOAC patients received an antiplatelet compound concomitantly,[35] whereas in other studies a proportion of approximately 10% was reported.[28] For other drugs (eg amiodarone), some smaller differences in the proportion of affected patients were found. Apart from potentially differing SmPC adherences of prescribers between the countries, different origins of the databases (GP, national register and claims) may also contribute to the observed differences.

4.6 | Strengths

There are several strengths worth considering. Firstly, our study was conducted using a standardized common protocol for all databases which was registered at ENCePP for transparency reasons. Furthermore, the source population of the databases included in this study sum up to more than 43 million patients covering different European regions in a representative manner.

Different types of databases were used for this study enabling a comprehensive discussion of advantages and disadvantages regarding database size, database type (eg GP database, claims database), representation of medical specialities, comparability of disease coding, and availability of laboratory values. For databases used in this analysis, several studies have shown valid prevalence and incidence estimates for diagnoses, medical procedures, drug intake, and outcomes.[36-42]

In addition, by conducting a retrospective cohort study covering a period from 2008 to 2015, we were able to analyse shifts in indications, contraindications, special warnings/precautions, and potential DDIs over time since market entrance of rivaroxaban and dabigatran.

4.7 | Limitations

Our study faces some limitations. Despite using a common protocol, we cannot fully discriminate whether the observed

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differences are due to discrepancies in database characteristics or caused by differences in clinical practice of the participating countries. For example, a direct linkage between compound and indication is difficult in some databases (eg CPRD). In addition, indications might have been documented before the study period/time window for defining indication which is probably the main reason for the high proportion of patients in the indication category "other/missing." Furthermore, by analysing data from the primary care sector, hip or knee replacement as indication is underestimated due to lack of coding for these surgical procedures as they are usually performed in hospitals. In addition, a precise medical definition of non-valvular versus valvular atrial fibrillation is lacking and may have impacted the numbers of patients of the respective categories.[43] Whereas some indications listed in section 4.1 of the respective DOAC SmPCs could be covered by the coding systems of the databases quite well (eg deep vein thrombosis and pulmonary embolism), some other indications were 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 SmPC-labelled indication using the databases and coding systems available. In addition, cardiac biomarkers (eg troponin test) are not available in most databases. It is also worth mentioning, that outpatient diagnoses not always reflect diagnoses from hospitals (eg myocardial infarction and surgeries) or chronic conditions, especially within a short time frame as ±3 months. Furthermore, by using only GP data in some databases, diagnoses from specialists might be underreported to some extent whereas for example in the Bavarian CD, data are documented from both, GPs and specialists.

Furthermore, we did not consider dosage strength for analysis of indication due to some overlap in indications treated with a particular strength and potential recommended dose reduction due to, for example 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. A further limitation of our study is that we could not consider the prescribed DOAC dose (unavailable in most databases).

Regarding contraindications and precautions/special warnings, mapping of the respective SmPC terms to the respective coding systems was 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. Naturally, these broad definitions may result in 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 (eg ophthalmic surgery, biopsy, spinal anaesthesia, and invasive procedures) leading to a (probably slight) underestimation of contraindications and special warnings/precautions.

Since no laboratory values were documented in most databases, respective diagnostic codes for renal dysfunction were used. However, similar to the coding issues described above, a broad definition (including somewhat non-specific renal dysfunction codes) was used explaining the high proportion of patients with renal dysfunction found for 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 related to this issue due to the time windows used in our analysis. In addition, switching of DOACs was not taken into account in this analysis. An overestimation of the contraindication "concomitant use of anticoagulants" is possible due to patients switching between these drugs.

Finally, since our study period ended in 2015, we were not able to describe DOAC usage or prescribing adherence to SmPCs (and respective changes) from 2016 onwards.

The number of patients with contraindications, precautions and special warnings or pDDIs within the Bavarian dataset is high compared to other databases. This might be due to a substantial consideration of data from medical specialists in the Bavarian database, whereas many of the other databases in this study consider data from general practitioners only. In addition, resource allocation for German sickness funds is based on the so-called morbidity-oriented risk structure compensation scheme ("Morbiditätsorientierter Risikostrukturausgleich"). This means that the insurants' morbidity burden has a direct impact on the amount of annual health fund allocations. It aims to balance different financial burdens under the statutory health insurance funds and, hence, counteract risk selection effects. For that reason, all diagnoses must be coded sufficently to enable appropriate calculations.[44,45] Furthermore, data in the Bavarian database are coded in a quarterly manner. Hence, exact time windows (eg 6 weeks prior to the index date for defining some comorbidities) could not be exactly applied limiting the comparability of the Bavarian results to some extent.

4.8 | Interpretation of study results

At first glance, results of this study may cause serious concerns regarding DOAC-related prescribing behaviour due to the high proportion of contraindications, special warnings and precautions, and potential DDIs. However, apart from methodological limitations described above, one should carefully interpret our study results and in particular, keep in mind

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patients' needs for an effective anticoagulation. Furthermore, taking into account age-related increases of multimorbidity and polypharmacy[46] as well as age-specific differences of new DOAC users between the databases, one should also carefully interpret our results in terms of country-specific discrepant prescriber's adherence.

In addition, even in patients with comorbidities and co-medication increasing the risk of bleeding, prescribing of a DOAC compound might be justified in some cases after an individual risk-benefit assessment. However, presence of contraindicated comorbidities and co-medication is a major safety issue and might be avoidable to some extent by switching co-medication to less interacting compounds, if possible. In accordance with other recently published studies,[30,47] SmPC adherence may increase by, for example avoiding off-label treatment. However, there is also room for improvement with regard to the SmPCs. More specific information in particular with regard to ambiguous terms and time windows used in the SmPC's section "contraindications" and "special warnings/precautions" is crucial not only for revealing valid and robust estimates in secondary data analyses but also for physicians for assuring an efficacious and safe DOAC treatment in daily practice.

5 | CONCLUSION

Non-valvular atrial fibrillation was the most commonly registered indication in incident DOAC users in six European databases from five European countries. Contraindications, special warnings/precautions, and potential interactions were present in a substantial number of new DOAC users. Due to broad definitions used for some SmPC terms, overall proportions for contraindications are prone to overestimation. However, for unambiguous SmPC terms documented in the databases sufficiently, the respective estimates can be considered valid. Differences found between the databases might be related to "true" differences in prescription behaviour but also due to methodological differences between the databases or discrepancies between patients documented in the databases. An increase in prescriber's adherence to the SmPC may lead to a substantial reduction in the proportion of patients with contraindications, special warnings/precautions and potentially interacting compounds. However, in some patients, DOAC prescriptions will be justified from a medical point of view despite the presence of, for example, comorbidities described as precaution or co-medication listed as potentially interacting in the respective SmPC sections. Future studies are needed to examine off-label use in detail by considering the prescribed DOAC dose.

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CONFLICTS OF INTEREST

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Additional supporting information may be found online in the Supporting Information section.

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APPENDIX 1

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