EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Procedure under Article 5(3) of Regulation (EC) No 726/2004

INN/active substance: direct oral anticoagulants (DOACs)

Procedure number: EMEA/H/A-5(3)/1487

Note:

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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Table of contents

1. Information on the procedure

On 14 January 2019 the Executive Director triggered a procedure under Article 5(3) of Regulation (EC) No 726/2004, and asked the CHMP to assess the impact of a study on direct oral anti-coagulants (DOACs) that was funded by EMA and conducted be a consortium of research centres led by University of Utrecht. More specifically the CHMP was called to assess the study results and whether those have any clinical implications and to give its scientific opinion if changes to the current conditions of use of these products and/or optimisation of the risk minimisation measures should be recommended.

2. Scientific discussion

2.1. Background

Direct oral anticoagulants (DOACs) have been approved in EU since 2008. DOACs are both rapid and short-acting agents which are considered being at least as effective as warfarin. They are an alternative therapeutic option for blood clot treatment for some patients. Available medications to date in this category include apixaban (Eliquis), dabigatran (Pradaxa), rivaroxaban (Xarelto) and edoxaban (Lixiana, Roteas). These substances carry a risk of bleeding which is inherent to their pharmacodynamic properties in preventing blood from clotting. This known risk is being managed by relevant wording in the product information, adequate pack sizes and additional risk minimisation measures to ensure awareness of prescribers and patients.

In 2015 a workshop was organised by EMA[1] aiming at bringing together experts and stakeholders to discuss the utility of PK and PD measurements in the clinical use of the DOACs. Among the conclusions of this workshop it was requested to conduct further research to support an optimised use of anticoagulants in clinical practice (Salmonson *et al*. 2017).

The EMA initiated a study that was conducted by a consortium of centers led by the University of Utrecht (Netherlands). This non-interventional clinical study had as objectives to assess the risk of major bleeding associated with the use of apixaban, dabigatran and rixaroxaban in patients with non-valvular atrial fibrillation (NVAF) overall and in specific subpopulations when compared to other oral anticoagulants (OACs), to assess their utilisation in the EU for treatment of non-valvular atrial fibrillation (NVAF), and also to assess the compliance with the recommendations of the product information. The data are analysed based on the single databases and together with observational data coming from Canada (same protocol).

This study is detailed in this report and put into the context of the pivotal studies that were supportive of the indication of these products in NVAF at the time of marketing authorisation. In addition, further observational studies and metanalyses addressing efficacy and bleeding risk, in particular, major bleedings, intracranial haemorrhage, intracranial bleeding, of DOACs in patients with NVAF are evaluated in comparison are discussed here:

- One study was based on US data,

- one study based on a German Claims database (database in part overlapping with the EMA initiated study)

- a literature based metanalysis.

[1] https://www.ema.europa.eu/events/role-pharmacokinetic-pharmacodynamic-measurements-use-direct-oral-anticoagulants-doacs

In addition, adherence to information provided in sections 4.3 (contraindications), sections 4.4 (special warnings or precautions) and sections 4.5 on co-medication with potentially interacting drugs in clinical practice of the Summary of product characteristics (SmPC) was investigated for these three DOACs.

Finally, the possible clinical implications of the study for the use of the relevant medicinal products were assessed by the CHMP, as well as the need to changes to the current conditions of use and/or optimisation of the risk minimisation measures should be recommended.

2.2. Introduction

For decades, Vitamin K antagonists (VKA) were the only oral anticoagulants available for the treatment of patients. Although effective for the prevention of thromboembolism, their use required frequent monitoring and dose adjustments. Since 2008 several DOACs have become available for the treatment and prevention of thromboembolic diseases. The direct thrombin inhibitor dabigatran etexilate (Pradaxa) and the direct Factor Xa (FXa) inhibitor rivaroxaban (Xarelto) were approved in the EU in 2008 for the prevention of venous thromboembolic events (VTE) in adult patients who have undergone elective total hip replacement surgery or total knee replacement surgery, followed by the direct FXa inhibitor apixaban in 2011. For all these medicinal products an indication for the prevention of stroke and systemic embolism in adult patients with nonvalvular atrial fibrillation was granted (dabigatran and rivaroxaban 2011, apixaban 2012) with additional indications being approved later. In 2015 the direct FXa inhibitor edoxaban (Lixiana) was approved for prevention in NVAF, for treatment and prevention of deep vein thrombosis and pulmonary empolism, as well as prevention of recurrences in adults. As the study was initiated before the authorisation of Lixiana, edoxaban was not included in this study.

DOACs share similar pharmacokinetic properties with half-life ($T_{1/2}$) around 12 hours and are usually administered without measuring anticoagulant activity. Among the advantages are the rapid onset and offset of the anti-coagulatory effect and the predictability of pharmacokinetics (PK). It has been a matter of discussion, whether monitoring of pharmacodynamic (PD) effects might improve the benefit-risk balance of DOACs in a group of patients or at least in subgroups, but despite of specific situations like in emergency situations it is unclear, whether on a group level dosing by effect provides added value.

Atrial fibrillation (AF) is associated with a 1.5 - 2-fold increased risk of all-cause mortality e.g. due to stroke, heart failure and sudden death (for review see e.g. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS [2]). It is also associated with an increased morbidity of heart failure and stroke. 20–30% of patients with an ischaemic stroke have AF diagnosed at any time. OAC therapy can prevent the majority of ischaemic strokes in AF patients and can prolong life. Clinical risk scores for stroke and embolic events (CHA2DS2-VASc score) and for bleeding risk (HAS-BLED) are important tools to second treatment decisions regarding the benefit-risk balance of anticoagulation either by DOACs or VKAs.

Key information on the benefit-risk balance of DOACs comes from the pivotal randomised prospective trials that were evaluated in the context of the authorisation for the indication in patients with NVAF. Whereas these studies have clear advantages with respect to control of bias, evaluation of endpoints or control of treatment adherence to DOAC and time in therapeutic range for the comparator (VKA) information on their application in clinical practice is limited. Adherence to contraindications, appropriate consideration of possible drug-drug interactions, dose adaption in special patient groups, off-label use or administration in patients not sufficiently represented in the pivotal trials may be

[2] European Heart Journal (2016) 37, 2893–2962

different in clinical practice as compared to the controlled setting of a clinical trial. This may be relevant for the real-life benefit-risk balance.

2.3. Data on efficacy

No new data on efficacy have been raised in the study. Data on stroke not differentiating between ischemic and haemorrhagic of origin were analysed in the observational study discussed below (see section 2.4 Data on safety). In the supportive study based on US data, information in ischemic stroke (efficacy parameter) was analysed. Since these data are only relevant in the context of the safety assessment, they are discussed in that context only.

2.4. Data on safety

i. Study Characteristics

An EMA retrospective study including three sub-studies was performed. The title is:

"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"

Objectives

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 (<50kg or >100kg) 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 utilisation 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.

A tabulated summary of the key data for the study and its different objectives is presented in this section. The summary only contains high level information on the study design, key objectives, the population followed and its inclusion and exclusion criteria, the treatment and the results of this treatment. The detailed information of this study will be found in the pending publications for this data.

Table 1. Overview of key data on safety and drug utilisation

Study ID and design / reference	Key objectives / endpoints	Population	Inclusion/ exclusion criteria	Treatment	Main efficacy results
Therapeutic indication NVAF (objective 1)					
EU PAS register no. 16014 (1) Retrospective cohort study (objective 1)	Retrospective cohort study among incident NVAF patients to assess the risk of major bleeding associated with the use of DOACs and VKAs	Danish Registries, AOK NORDWEST, BIFAP, CPRD.	Patients aged > 18 years with a first-ever recorded diagnosis of NVAF, new users of antithrombotic drugs (D)OACs (2008 – 2015)	DOAC (Apixaban, Dabigatran, Rivaroxaban) or VKA	- HR of major bleeding risk for DOACs versus VKAs ranged between 0.84 and 1.13 - risk of GIT bleeding increased by 48-67% (dabigatran) and 30-50% (rivaroxaban) compared to VKA users (all data sources except for Denmark) - Results for intracranial haemorrhage were heterogeneous (adjusted HRs: 0.46 – 0.63 in 3 databases, and 1.65 in CPRD) - Stroke rate was higher with DOACS than with VKA in three databases (HR HRs 1.06 – 1.76) and lower in AOK NORDWEST (HR 0.88)
Integrated analysis (Metanalysis) with patients		In addition, data from databases from 6 Canadian Provinces			risk of major bleeding (DOAC vs.

from 6 Canadian provinces					VKA): all DOACs:HR 0.94 (95% CI: 0.87-1.02) Rivaroxaban: HR 1.11, 95% CI 1.06-1.16 Apixaban: HR 0.76, 95% (CI 0.69-0.84) Dabigatran: HR 0.85 (95% CI 0.75-0.96) Risk of GIT bleeding: (DOAC vs. VKA): all DOACs: HR HR 1.16, 95% CI 1.05-1.28 Rivaroxaban: 1.28, 95% CI of 1.18-1.38 Apixaban: HR 0.77, 95% CI 0.67-0.87 Dabigatran: HR 1.21, 95% CI 1.07-1.37 ICH: (DOAC vs. VKA): all DOACs: HR 0.60, 95% CI 0.49–0.73 Rivaroxaban: 0.75, 95% CI of 0.61–0.92 Apixaban: HR 0.61, 95% CI 0.51-0.72 Dabigatran: HR

					0.48, 95% CI 0.36–0.65
Therapeutic indication NVAF (objective 2)					
EU PAS register no. 16014 Descriptive drug utilization study Utilization of DOACs in the EU for treatment of NVAF	The utilization of DOACs in the EU for treatment of NVAF, including the characterization of new DOAC users in NVAF patients.	Mondriaan, National Registries Denmark, Bavarian Claims database, AOK NORDWEST, BIFAP, SIDIAP, CPRD, EGB.	Patients aged > 18 years with a first-ever recorded diagnosis of NVAF, new users of antithrombotic drugs (D)OACs 2010–2015	DOAC (Apixaban, Dabigatran, Rivaroxaban) or VKA	Standardized incidences increased for all DOACs between 2008 and 2015 in both genders, in particular in patients > 75 years Highest incidences in DK and DE
All approved indications licenced until 2015 (objective 3)					
EU PAS register no. 16014 Descriptive drug utilization study	Prescribers' compliance with recommendations included in sections 4.1, 4.3, 4.4, and 4.5 of the SmPC of each DOAC	Mondriaan, National Registries Denmark, Bavarian Claims database, BIFAP, SIDIAP, CPRD,	Patients initiating a DOAC (2010 – 2015)	DOAC (Apixaban, Dabigatran, Rivaroxaban)	Large differences between databases regarding treatment in patients with at least one contraindication (8.2% to 55.7%) or Special warnings/precautions (35.8% – 75.2%) And potential drug-drug interactions (22.4% to 54.1%)

Table 2 Overview of key supportive study on safety

Study id and design / reference	**Key objectives / endpoints**	**Population**	**Inclusion/ exclusion criteria**	**Treatment**	**Main efficacy results**
Therapeutic indication NVAF					
DJ Graham et al 2019	retrospective new-user cohort study of patients with NVAF enrolled in US Medicare who	Medicare claims data	Patients aged > 65 years diagnosis of Atrial Fibrillation or Flutter during	DOAC (Apixaban, Dabigatran, Rivaroxaban) or VKA	- Significant reduction in thromboembolic stroke: HR vs. warfarin: Dabigatran: 0.80

	initiated warfarin, Dabigatran, Apixaban or Rivaroxaban		the preceding 6 months, new users of antithrombotic drugs (D)OACs (October 2010 – September 2015)		(0.70 – 0.93) Rivaroxaban: 0.72 (0.63 – 0.83) Apixaban (0.71 (0.60 – 0.83) Significant reduction in intracranial haemorrhage Dabigatran: 0.38 (0.31 – 0.47) Rivaroxaban: 0.65 (0.56 – 0.77) Apixaban (0.54 (0.43 – 0.68) Significant reduction in mortality Dabigatran: 0.73 (0.67 – 0.80) Rivaroxaban: 0.81 (0.75– 0.88) Apixaban (0.66 (0.60 – 0.74) Higher rate of Major GIT bleeding Dabigatran: 1.16 (1.06 – 1.27) Rivaroxaban: 1.48 (1.36 – 1.60) Lower rate of Major GIT bleeding Apixaban (0.52 (0.45 – 0.60)

The authorised indications (up to 2015) are summarised as follows (disregarding minor differences in the wording).

Table 3. Indications and product recommended dose according to SmPCs for dabigatran, rivaroxaban and apixaban up to 2015 (SmPC section 4.1, posology does not reflect dose reduction where applicable)

Indication	Rivaroxaban	Dabigatran	Apixaban
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	Xarelto™ 2.5 mg bid		
Primary prevention of venous thromboembolic events in adult patients who have undergone elective total hip replacement surgery or total knee replacement surgery	Xarelto™ 10 mg qd	Pradaxa™ 110 mg day1 → 220 mg qd	Eliquis™ 2.5 mg bid
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 ≥ 75 years; heart failure (NYHA Class ≥ II); diabetes mellitus; hypertension.	Xarelto™ 20 mg qd	Pradaxa™ 150 mg bid	Eliquis™ 5 mg bid
Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults	Xarelto™ 15 mg bid → 20 mg qd → 10 or 20 mg qd after 6 months	Pradaxa™ 150 mg bid	Eliquis™ 10 mg bid → 5 mg bid → 2.5 mg bid after 6 months

The information as provided above refers to the full doses of the DOACs. Recommendations for dose reduction show some differences between the products. Recommendations for dose reduction for rivaroxaban are based on PK considerations in patients with renal failure. Recommendations for dabigatran include dose reduction in case of concomitant medications and of higher age and a consideration for a dose reduction for patients at increased risk as gastritis, esophagitis or gastroesophageal reflux. For apixaban dose reductions are recommended based on an assessment of age, renal function and body weight.

Recommendations for dose reductions are in place for the following patients:

- For rivaroxaban

In NVAF indication and Treatment and prevention of DVT/PE indication: moderate (creatinine clearance 30 - 49 ml/min) or severe (creatinine clearance 15 - 29 ml/min) renal impairment: dose reduction

In hip or knee replacement: creatinine clearance 15 - 29 ml/min: to be used with caution

In MI/ACS: no dose adjustment

- For dabigatran

In hip or knee replacement: Patients with moderate renal impairment (creatinine clearance (CrCL) 30-50 mL/min): dose reduction recommended

(Treatment in patients with severe renal impairment (CrCL < 30 mL/min) is contraindicated)

Patients who receive concomitant verapamil, amiodarone, quinidine: dose reduction recommended

Patients aged ≥ 75 years: dose reduction recommended

In NVAF indication and treatment and prevention of DVT/PE: Patients aged ≥80 years or patients who receive concomitant verapamil: Dose reduction recommended

Dose reduction for consideration:

Patients between 75-80 years, Patients with moderate renal impairment (CrCL 30-50 mL/min), Patients with gastritis, esophagitis or gastroesophageal reflux, other patients at increased risk of bleeding: Dose reduction for consideration

- For apixaban

In NVAF indication: Dose reduction in case of at least two of the following characteristics: age ≥ 80 years, body weight ≤ 60 kg, or serum creatinine ≥ 1.5 mg/dL (133 micromol/L).

severe renal impairment (creatinine clearance 15-29 mL/min): dose reduction

In treatment and prevention of DVT/PE: severe renal impairment (creatinine clearance 15-29 mL/min) to be used with caution

Methods

Three studies were conducted: Two descriptive drug utilization studies (objectives 2 & 3) and a retrospective cohort study among incident NVAF patients to assess the risk of major bleeding associated with the use of DOACs and VKAs (objective 1). These studies were conducted in the following databases: Mondriaan (objective 2,3), Danish Registries (objective 1,2,3), Bavarian Claims database (objective 2,3), AOK NORDWEST (objective 1,2), BIFAP (objective 1,2,3), SIDIAP (objective 2,3), CPRD (objective 1,2,3), EGB (objective 2). The used data were based either on prescribing/dispensing drugs or on claims/dispending. Two types of databases were used in this study, healthcare utilisation databases (HCU: Bavarian Claims, AOK NORDWEST, and EGB) and medical records based databases (MR: Mondriaan, Danish National Registries, BIFAP, SIDIAP, and CPRD). Hospital records are available by the Danish National Registries and the French EGB (hospital-discharge data).

Study Design

<u>Objective 1 (risk of major bleeding)</u>

A retrospective cohort study among incident NVAF patients to assess the risk of major bleeding associated with the use of DOACs and VKAs.

Study population

Patients aged >18 years with a first-ever recorded diagnosis of NVAF during a patient's period of valid data collection. To make sure that only patients were selected that receive DOACs for the indication of NVAF, there were applied methodologies in a hierarchical manner, but dependent on the availability of data in the data sources.

Within this cohort of NVAF patients, new users of antithrombotic drugs (D)OACs (DOACs and VKAs,) were identified, initiating a (D)OAC on the date of or after NVAF diagnosis during 2008-2015. New users were defined as patients initiating DOACs during the study period (2008-2015) without any use of DOACs for at least 12 months prior to the index date. Patients with a history of valvular atrial fibrillation (mitral stenosis or mechanical heart valves) were to be excluded.

The date of the first prescription of (D)OAC (index date) defined the start of follow-up. Each patient was to be followed until a major bleeding (outcome) occurred or until the end of valid data collection, move or death, whichever came first.

Variables

The primary outcome of interest was any major bleeding which was defined as symptomatic bleeding in a critical area or organ, as agreed by the International Society on Thrombosis and Haemostasis, including

haemorrhagic stroke/intracranial bleeding, gastrointestinal bleeding, or other extracranial or unclassified bleeding. Some of these bleeding events were also assessed individually, such as gastrointestinal bleeding and intracranial haemorrhage.

For the main analysis, all available bleeding events (irrespective of hospital admission) were used. As a sensitivity analysis only major bleeding events leading to a hospital admission were analysed in databases that had such linkage opportunities.

Secondary outcomes included stroke, including ischaemic stroke and haemorrhagic stroke, and all-cause mortality. The analysis was planned to be corrected for patients with a history of any of these events.

Exposure definition

All (D)OAC prescriptions for new users of (D)OACs. Total follow-up time of patients were to be divided into periods of current and past use with patients switching between these periods according to their pattern of use.

Assessment of the length of individual (D)OAC prescriptions

A step-wise uniform approach was used in all databases when assessing exposure duration. The preferred method for calculating the individual prescription duration was by using information on the prescribed number of tablets and the dosage. When information on the prescribed number of tablets and or the dosage was not available the same method for assessing treatment duration to ensure consistency was to be applied. The method used defines duration of use for a single prescription as the median time between prescriptions (individual based and on ATC code). When only 1-2 prescriptions are available for an individual patient, the method of median time between prescriptions cannot be applied. In these cases, the duration was based on the estimated prescription duration for the specific drug in the study population.

Treatment episodes

To assess periods of current use, treatment episodes of (D)OACs were constructed allowing for a 30-day permissible gap between the theoretical end date of a prescription and the subsequent prescription. Treatment episodes were defined as a series of subsequent prescriptions for (D)OAC, independent of dose changes and constructed. In case a subsequent prescription for the same drug was collected before the theoretical end date of a previous prescription, the number of overlapping days is added to the theoretical end date of the subsequent prescription. As estimation of prescription length is difficult in some databases, the number of overlapping days were maximised at 90 days.

If the subsequent prescription was within the same treatment episode included another type of (D)OAC, the patient was considered to have switched therapy and the remaining tablet days from the prior prescription were disregarded. In order to facilitate exposure classification, a new row was created in case a patient switched from one type of (D)OAC to another within a treatment episode. Sensitivity analyses were conducted to assess the impact of the permissible gap length (0 days, 60, days, 90 days) on the association with the outcome.

Past use was defined as the period of time after following end of treatment episode, until a subsequent treatment episode was initiated, death, outcome or end of follow up.

Exposure characteristics

For each current use row in the resultant data matrix, exposure was further classified according to the type of drug (VKAs vs. DOAC, as well by individual product). The last prescribed daily dose (categorized low/medium/high in DDD-equivalent doses) within each exposure row. The cumulative number of DDDs used was treated both continuously, as well as categorical (cumulative DDD of less than 180, ≥180 and <365 and ≥365 DDD).

Potential confounders

Potential confounders considered in this study were based on literature review (i.e., risk factors for major bleeding and ischaemic stroke reported in the literature). No data-driven methods (e.g., change in effect estimate) were applied to select confounders. The presence of a confounding variable was assessed by reviewing the computerised medical records prior to initiation of (D)OAC treatment.

Important risk factors considered for major bleeding were; chronic kidney disease, hepatic impairment, anaemia, thrombocytopenia, (uncontrolled) hypertension, history of cerebrovascular disease, history of major bleeding event, presence of malignancy, concomitant use of medicines that increase bleeding risk (NSAIDs, corticosteroids, SSRI's), excessive fall risk (i.e. benzodiazepine, antidepressant use), history of pulmonary embolism.

Important risk factors considered for ischaemic stroke were: prior stroke/TIA, hypertension, diabetes mellitus, congestive heart failure, vascular disease, proteinuria, and chronic kidney disease. Additionally, where possible, lab-values were used on eGFR for chronic kidney disease and clinical parameters and lab-values that indicate hepatic impairment (Child Pugh Score) if appropriate. Hepatic impairment was also assessed (where possible) using an algorithm which combines liver disease related diagnostic code with a referral and liver test abnormality. Sex, weight (<50, 50-100, >100 kg), body mass index (BMI), smoking status and alcohol status were considered at baseline (i.e., OAC initiation) and considered constant throughout follow-up. Age, comorbidities (ever before), and co-medication (6 months before) use were considered as time dependent confounders and were updated whenever the exposure status changed, or when the exposure state exceeded a period of 6 months.

To assess the impact of missing values for BMI, smoking and alcohol multiple imputations in CPRD and extend the findings in a qualitative manner to the other databases were applied.

Effect modifiers (subgroups)

Subgroups considered for stratified analysis of DOACs and major bleeding included chronic kidney disease, hepatic impairment, age ≥75 years, low/high bodyweight (<50 kg or >100 kg), treatment with contra-indicated or hazardous co-medications as listed in sections 4.3, 4.4 and 4.5 of the SmPC of each product.

Renal function was defined as "normal-mildly reduced" (CrCl 50-80 mL/min), "moderately reduced (CrCl 30-49 mL/min)", "severely reduced (CrCl 15-29 mL/min)", and "very severely reduced (CrCl<15 mL/min)" or haemodialysis. In CPRD, some stages of chronic kidney disease were defined slightly differently from EMA tender technical specification, with CrCl 30-60 ml/min as moderately reduced and CrCl 60-90 ml/min as normal to mildly reduced.

Objective 2 (utilization of DOACs in the EU for treatment of NVAF)

An observational cohort study of new users of DOACs of interest (dabigatran, rivaroxaban, apixaban) with the indication NVAF.

Design

The study cohort consists of new users (≥18 years) of DOACs with non-valvular atrial fibrillation from the respective data sources. To make sure that only patients were selected that receive DOACs for the indication of NVAF. The method selected for each database is dependent on the availability of data in the data sources.

New users were defined as patients initiating DOACs during the study period (2008-2015) without any use of DOACs for at least 12 months prior to the index date. Patients registered in the database less than one year before the index date (date of first DOAC prescription) were excluded.

Variables

Outcomes were to be presented including descriptive analysis of patient characteristics of new DOAC users, the number of patients switching to another antithrombotic agent, and treatment duration.

Description of new DOAC users are presented according to pre-specified parameters including number of patients, patient characteristics (age, gender, low or high body weight (<50kg or >100kg)), co-morbidities (chronic kidney disease, hepatic impairment, previous haemorrhagic episodes, and previous cardiovascular events, concomitant exposures to potential interacting medicine products drug (PIMP) as listed in section 4.5 of the DOAC SmPCs. Concomitant exposures will be defined as prescribing of the aforementioned products during a period of DOAC use, i.e., if the treatment episodes of PIMP and DOAC overlap. Number of DOAC prescriptions prescribed/dispensed per calendar year (dispensing databases: Danish registries; Claims databases: Bavarian, AOK NORDWEST, SNIIRAM/EGB; prescribing database: CPRD; prescribing/dispensing database: BIFAP, Mondriaan, SIDIAP).

Switching to another antithrombotic agent and time on therapy before switching are of particular interest and, hence, was evaluated descriptively. A switcher was defined as:

1) any patient with a subsequent prescription within the same treatment episode that includes another type of (D)OAC (at least one prescription of antithrombotic drug (B01AA [VKA], B01AC [antiplatelets], B01AE [direct thrombin inhibitors], or B01AF [direct factor Xa inhibitors] and

Treatment duration, defined as the time on therapy, was calculated as the number of days on therapy between receiving the initial DOAC and the discontinuation of therapy. The expected duration of each prescription was estimated using the prescribed quantity based on package sizes and the prescribed daily dose. In case of missing data (e.g. daily dose or package size were missing), the database-specific median treatment duration was used as a surrogate. The date of the last dispensing/prescription plus the estimated duration of the dispensing/prescription is considered the date of drug discontinuation. A limit on the number of days allowed between refills or prescriptions was defined to consider permissible gaps considering the pharmacological properties of the considered drugs. The gap length is set to 30 days and a sensitivity analyses was performed taking into account a gap of 60 days.

Patients not receiving any other prescription or filling of DOAC within 180 days after the calculated date of drug discontinuation were considered as DOAC permanent discontinuers.

Dose adjustments

Number of users for the different active principles contained in each DOAC tablet (e.g. Eliquis 2.5 mg vs Eliquis 5 mg) were provided by renal impairment categories (when possible), age and sex categories, and other conditions such as co-morbidities (e.g. gastritis, other increasing risk of bleeding) and co-medications (e.g. verapamil) when applicable. Dose adjustments during follow-up were evaluated as appropriate based on renal function and the recommended dose in the SmPC for the indication "non-valvular atrial fibrillation" and expressed as the corresponding number of users. A dose adjustment was defined as switching from one active principle contained in each tablet to another.

Objective 3 (Prescribers' compliance with recommendations in the SmPC)

This is an observational cohort study of new users of DOACs of interest (dabigatran, rivaroxaban, apixaban).

Setting

The study cohort consisted of new users (≥18 years) of DOACs from the respective data sources. New users were defined as patients initiating DOACs during the study period (2008-2015) without any use of DOACs for at least 12 months prior to the index date. Patients registered in the database less than one year before the index date (date of first DOAC prescription) were to be excluded.

Variables

The following outcomes were reported:

Prescriber compliance with recommendations included in SmPC section 4.1 (Therapeutic indications), section 4.3 (Contraindications), section 4.4 (Special Warnings and precautions for use), and 4.5 (Interaction with other medicinal products and other forms of interaction) of each individual DOAC.

The documented ICD/READ/ICPC-coded diagnosis in the databases was used as a proxy of the indication.
Indications were defined according to the following order of approach:

1. A linked indication to the first prescriptions of the DOAC. If not possible, then:
2. A medical code for the indication ±3 months around the index date in one of the following files;

a. GP-record (CPRD, Bifap, SIDIAP, Mondriaan)
b. Claims-record (Bavarian)

A medical code for the indication prior to index date + 3 months after the index date in case of Hospital-record (DK).

A sensitivity analysis was performed where indications were defined as registered any time prior until 3 months after index date. The number of patients without any approved diagnosis was calculated. Indications were defined in the following mutually exclusive groups as: Myocardial infarction/Angina (MI-A), prevention after Hip/Knee replacement (PHK), prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation (NVAF), treatment of deep vein thrombosis and pulmonary embolism including prevention of recurrent DVT and PE in adults (DVT-PE), and other (off-label) indications (OOL).

Table 4. Indication for use of DOACs

Indication	Description
Myocardial Infarction /Angina (MI-A)	Prevention of atherothrombotic events after an acute coronary syndrome (ACS)
Prevention after Hip/Knee replacement (PHK)	Primary prevention of venous thromboembolic events in adult patients who have undergone elective total hip replacement surgery or total knee replacement surgery
Non-valvular atrial fibrillation (NVAF)	Prevention of stroke and systemic embolism in adult patients with NVAF Atrial Fibrillation, with one or more risk factors, such as prior stroke or transient ischemic attack; age ≥ 75 years; heart failure (NYHA Class ≥ II); diabetes mellitus, hypertension registered only
Treatment of deep vein thrombosis and pulmonary embolism including prevention of recurrent DVT and PE in adults (DVT-PE)	Treatment of deep vein thrombosis and pulmonary embolism including prevention of recurrent DVT and PE in adults (DVT-PE)
Combination groups	Combination of above-mentioned indications: - MI-A + PHK - MI-A + NVAF - MI-A + DVT-PE - PHK + NVAF - PHK + DVT-PE - NVAF + DVT-PE
Other/unknown/missing (OOL)	All indications other than those indicated above or when there is no indication available

Co-morbidities listed in the SmPC section 4.3 and 4.4 were assessed during various time periods available prior to index date depending on the co-morbidity. In addition, also the registered co-morbidities were assessed ±3 months around the index date. Potential comorbidities listed in SmPC sections 4.3 and 4.4 were identified.

Concomitant use of other (potentially interacting) medication listed in the sections 4.3, 4.4 and 4.5 were assessed and were identified through their Anatomical Therapeutic Classification (ATC) code. Use of these medications was considered concomitant when prescribed during the DOAC treatment episode Concomitant use of potential interacting drugs during the DOAC treatment episode was determined for each individual DOAC.

ii. Results

Participants

*Objective 1***:** Overall, 251,719 patients started oral anticoagulants in CPRD, BIFAP and AOK NORDWEST and NRD.

Objective 2: 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 was the one that contributed with the lowest new users number (460).

Objective 3: Prescribing of DOACs was assessed in six databases 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).

Descriptive study population

Objective 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 NORDWEST. 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 e.g. for 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. 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.

Objective 2

The number of DOAC users included here 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. The proportion of male users ranged between 46.4% and 58.9%. The mean age ranged from 69.3 (SD 11.3) years to 75.7 (SD 10.5) years.

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 haemorrhagic episodes, previous cardiovascular events). Most users with a comorbidity where 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 were the most frequent comorbidity. The proportion of patients having previous cardiovascular events ranged from 25.4% in Mondriaan to 82.9% in AOK NORDWEST. 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 haemorrhagic episodes was 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 similar to that of all DOACs, with the exception of apixaban in the Mondriaan database that had a higher proportion of previous major haemorrhagic episodes when compared to all DOAC.

Objective 3

44.2 – 56.8% of users were male sex. 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 was found in BIFAP (38.1%) whereas the lowest proportion was found in Mondriaan (17.2%).

Outcome data

Objective 1

There was some variation between data sources in incidence rates 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. 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 NORDWEST, 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 non significant higher risk estimates of major bleeding, but the number of events was low (n=9, adjusted HR 1.59, 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 0.82, respectively). For rivaroxaban no major differences were found.

When assessing the type of bleeding event, 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 (HR) for apixaban was around 1.10 in both BIFAP and CPRD, and protective in both AOK NORDWEST (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 2.38, 95% CI 1.20-4.72). 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 risks 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.

Summary of the results for all DOACs in the study.

The rate of major bleeding events was higher with DOACs in CPRD and AOK NORDWEST (HRs 1.13 and 1.07) and lower in BIFAP and NDR (0.95 and 0.84).

Overall incidence of gastrointestinal (GI) bleeding was similar in all databases for VKA (12.5 – 16.5/ 1000 person years) and was higher for DOACs in each database, respectively (14.1 – 24.9/1000 person years) with adjusted HRs of 1.04 – 1.40 favouring VKA.

For intracranial haemorrhage the results were heterogeneous in the cohort study, with rates of 0.4 – 3.7/1000 patient years for VKA and 0.5 – 2.1/1000 patient years for DOACs, (adjusted HRs: 0.49 – 1.65), but overall there was a trend towards a lower rate of intracranial haemorrhages (ICHs) with DOACs. Intracranial bleeding was lower with DOACs in three databases (BIFAP, AOK NORDWEST, NDR, adjusted HRs 0.49 – 0.63) and higher in CPRD (adjusted HR 1.65).

Stroke (including ischemic and haemorrhagic stroke) was observed more frequently with DOACs in CPRD (UK), BIFAP (ES) and NDR (DK) (HRs 1.06 – 1.76) and less frequently in AOK NORDWEST (HR 0.88).

Comparison with results from the pivotal trials.

Efficacy and bleeding rates in the pivotal trials of DOACs vs. VKA in patients with NVAF have been compared and analysed in a metaanalysis (Ruff *et al*. 2014) including the following four studies: RE-LY (dabigatran), ROCKET-AF (rivaroxaban), ARISTOTLE (apixaban), ENGAGE AF-TIMI 48 (edoxaban).

a) Major bleeding rates (combined)

In the pivotal trials major bleeding rates (all DOACs combined) were numerically lower with DOACs than with VKA (HR 0.86 (0.73 – 1.00) Figure 1, below). This is not in contrast to the variability seen in the four databases. Categorisation and documentation of bleeding events may influence these results.

Figure 1. Major bleeding (Ruff *et al*. 2014)

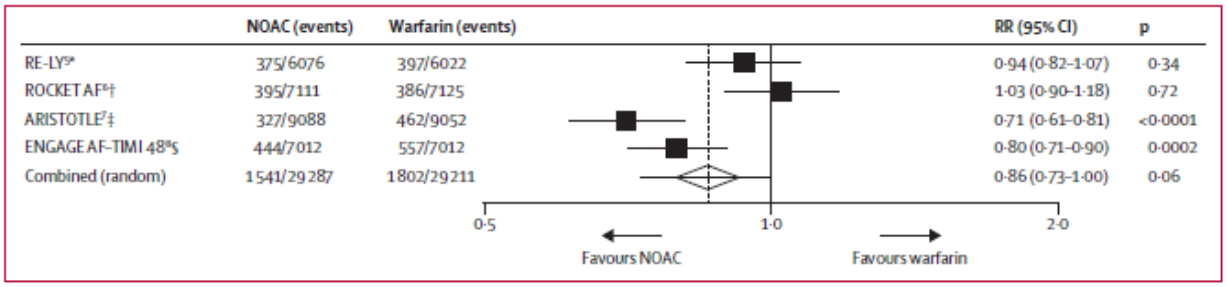

Figure 3: **Major bleeding**
Data are n/N, unless otherwise indicated. Heterogeneity: I^2=83%; p=0·001. NOAC=new oral anticoagulant. RR=risk ratio. *Dabigatran 150 mg twice daily. †Rivaroxaban 20 mg once daily. ‡Apixaban 5 mg twice daily. §Edoxaban 60 mg once daily.

b) GIT bleeding:

Consistent with the results from the databases, the meta-analysis also indicated a higher rate of GI bleeding in the pivotal trials with a HR of 1.25 (1.01 – 1.55) favouring VKA (Figure 2).

Figure 2. Secondary efficacy and safety outcomes (Ruff *et al*. 2014)

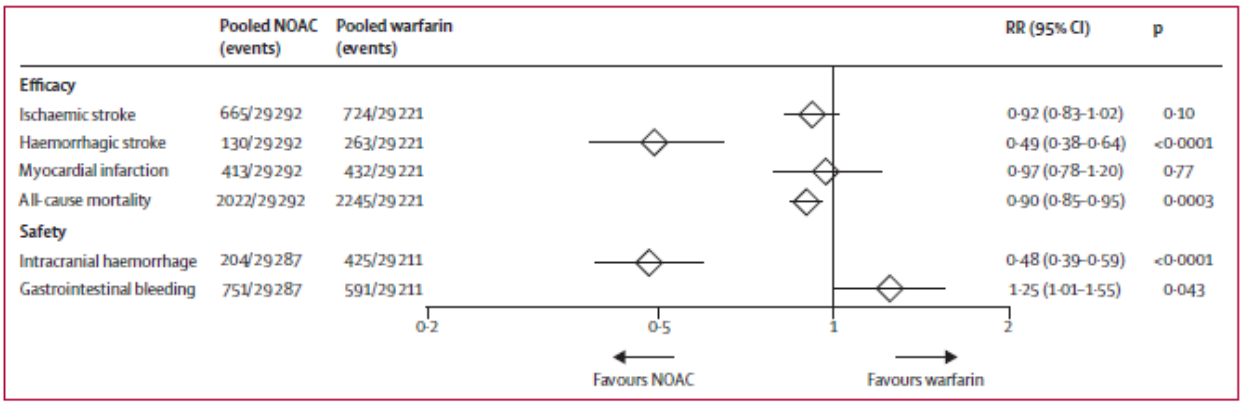

Figure 2: **Secondary efficacy and safety outcomes**
Data are n/N, unless otherwise indicated. Heterogeneity: ischaemic stroke I^2=32%, p=0·22; haemorrhagic stroke I^2=34%, p=0·21; myocardial infarction I^2=48%, p=0·13; all-cause mortality I^2=0%, p=0·81; intracranial haemorrhage I^2=32%, p=0·22; gastrointestinal bleeding I^2=74%, p=0·009. NOAC=new oral anticoagulant. RR=risk ratio.

c) The trend towards lower rates of ICH is consistent with the results from the pivotal trials, where the rate of haemorrhagic strokes and of intracranial bleeding was reduced (haemorrhagic stroke: HR 0.49 (0.38 – 0.64, p<0.0001); intracranial bleeding: Hr 0.48 (0.39 – 0.59, p < 0.0001, Figure 2).

There is a key difference in the rate of bleeding events as reported in the pivotal trials and in the databases analysed in the cohort study. In the pivotal trial the ratio between ICH and GI bleeding events was 0.27 (204 vs. 751) for pooled DOACs and 0.72 (425 vs. 591) for warfarin. In the 4 databases the rate of ICH/ GI bleeding was much lower with relative reporting rates between 0.02 and 0.3: for VKA: CPRD: 1.3/16.5, BIFAP: 1.8/ 15.0, AOK NORDWEST: 0.4/16.2, NDR: 3.7/ 12.5; for DOACs: 2.1/24.4, 0.9/18.9, 0.5/24.9;2.0/14.1.

There are two possible explanations for this difference. Either the relevance of GI bleeding as compared to ICH is much higher in clinical practice than in pivotal trials, or differences in definitions and documentation are the reason for this apparent difference. It is conceivable that events were categorized as ICH in the pivotal trials and as strokes in the databases.

d) The incidence rate /1000 person years for stroke (ischemic + haemorrhagic) was largely similar to the incidence rate of GI bleeding. This is consistent with the pivotal trials, where the number of strokes and GI bleeding events were also in the same order of magnitude (Figure 2).

A trend towards a higher rate of strokes in three databases with DOACs and in particular in GPRD (adjusted HR 1.76 (1.50 – 2.08)) is not exactly in line with the results in the pivotal trial were non-inferiority of DOACs vs. VKA was demonstrated for efficacy. In the metanalysis there was a small beneficial numerical trend of all DOACs vs. VKA together for ischemic strokes (HR 0.92 (0.83 – 1.02)). The rate of haemorrhagic strokes was considerably lower with DOACs in the pivotal trials (haemorrhagic stroke: HR 0.49 (0.38 – 0.64, $p<0.0001$)).

The lack of a differentiation between ischemic and haemorrhagic strokes in the database hampers the analyses. Numerically the results for stroke tend to appear better for DOACs vs. VKA in the pivotal trials and possibly a little worse in the databases.

If this is the case, there are several possible explanations. Bias as described above may have led to treating patients at a higher risk for strokes preferentially with DOACs. Adjustment based on risk factors may not entirely cope with this issue. A similar result was present in the database analysis by Ujeyl and colleagues (2018). Despite of propensity score matching in that analysis patients on DOACs had a higher rate of non-related mortality and a numerically higher rate of ischemic strokes with DOACs indicating bias by treatment for unknown reason. Efficacy of DOACs in preventing ischemic strokes may have been lower in clinical practice, e.g. due to lower compliance. Compliance cannot be assessed on a patient level in the databases. As outlined below, non-adherence based on differences between prescription and drug dispensing was estimated to be up to 15% in selected databases. Non-compliance could in turn result in a lower than expected rate of bleeding events observed with DOACs. Such possibilities are difficult to assess in the absence of data on compliance, on INR control (TTR in the control group) in patients on VKA and considering that the patient populations were not randomised to DOAC vs. VKA.

Summary of the results for individual DOACs

There appeared to be a consistent pattern, when comparing major bleeding for the different DOACs with some specific differences between DOACs. In all databases the HR for major bleeding events was higher with rivaroxaban vs. VKA (adjusted HRs: 1.02 – 1.27) than with dabigatran (0.81 – 1.06), and with apixaban (0.73 – 0.94). There was a trend to a better HR for apixaban vs. VKA than for the other DOACs, being even in favour of apixaban vs. VKA in AOK NORDWEST and NDR.

Consistent differences were seen for the specific bleeding events: The adjusted HR for GIT bleeding events were lower in all 4 databases for apixaban (range 0.4 – 1.08) than for rivaroxaban (1.14 – 1.50) and for dabigatran (1.13 – 1.60).

Regarding intracranial haemorrhages, the HRs were generally in favour of the single DOACs with exception of rivaroxaban in CPRD and NDR and apixaban in NDR. No consistent trend was seen when comparing the different DOACs in the different databases, but the event rate may have been overall too low to draw robust conclusions.

Results for stroke largely depended on the database (HR DOAC vs. VKA: CPRD: 1.76 (1.50 – 2.08), BIFAP: 1.18 (1.00 – 1.39), AOK NORDWEST: 0.88 (0.81 – 0.95), NDR: 1.06 (0.96 – 1.16)) but were overall similar for the 3 DOACs within each database.

Comparison with the results from the pivotal studies

At first glance, the impression of a higher bleeding risk with rivaroxaban than with dabigatran and in particular with apixaban (as assessed in comparison to VKA) appears to be consistent with the results in the pivotal trial as summarised in the metanalysis by Ruff and colleagues (2014) (Figure 1 above). In the pivotal trials the HR (DOAC vs. VKA) for Major bleeding was 1.03 (0.09 – 1.18) for rivaroxaban (ROCKET AF), 0.94 (0.82 – 1.07) for RE-LY (dabigatran) and 0.71 (0.61 – 0.81) for ARISTOTLE (apixaban). However, the authors of the metanalysis did not conclude on drug specific differences.

Re-LY and ARISTOTLE included patients over the whole range of CHADS2-score (including about 1/3rd in CHADS 0 – 1 respectively), whereas in ROCKET-AF all patients had at least a CHDADS2-score of 2. CHADS2 score 0-1 was associated with a lower relative risk (RR) for DOACs (pooled) vs. VKA (pooled) for major bleeding (HR 0.60 (0.45–0.80) vs. 0.88 (0.65–1.20, score 2) and 0.86 (0.71–1.04, score 3 – 6), respectively, p= 0.09).

The number of patients with diabetes included in the pivotal studies was higher in ROCKET-AF (40%) than in Re-LY (23%) and ARISTOTLE (25%). Absence of diabetes was also associated with a lower RR for DOACs (pooled) vs. VKA (pooled) (0.71 (0.54–0.93) than presence of diabetes (0.90 (0.78–1.04), p= 0.12).

More patients in ROCKET-AF (43%) were 75 years or older than in Re-LY (38 – 40%) and ARISTOTLE (31%) which was also associated with a numerically higher RR for DOACs (pooled) vs. VKA (pooled) (0.93 (0.74–1.17) vs. 0.79 (0.67–0.94), p= 0.28). Similar age-related differences have also been observed in the US based observational study for rivaroxaban and dabigatran and in the metanalysis integrating these data from the EU and Canada.

On the other hand, individual median time in therapeutic range for VKA was numerically lower in ROCKET-AF (median: 58 (43–71) than in Re-LY and ARISTOTLE (67 (54–78), 66 (52–77)), which appeared to be associated with a lower RR. Overall, the authors of the metanalysis referred to heterogeneity between studies and did not comment on or speculate about differences in bleeding risk between the DOACs investigated in the trial.

Whereas the results in the pivotal trials seemed to show consistent trends with respect to overall bleeding rates when comparing the different DOACs, in addition to these limitations there is the possibility that use in clinical practice mirrors to some degree the differences between patient populations included in the respective clinical trials thereby reproducing the results.

Taken together, the data indicate a positive benefit-risk balance of either DOAC in the treatment of NVAF when compared to VKAs. Results concerning bleeding risk and efficacy on stroke raise the possibility that there are differences between the DOACs when given at the respective approved doses. For further discussions of the relative bleeding risk in comparison of different DOACs with each other see supportive studies below.

Irrespectively of the robustness of the results, it may be worthwhile assessing whether there are relevant differences in the recommendations for the three DOACs to address dosing in specific patients with NVAF. Such restrictions might have been relevant for B/R in specific patient groups.

Rivaroxaban: Dose reduction is recommended in patients with moderate (creatinine clearance 30 - 49 ml/min) or severe (creatinine clearance 15 - 29 ml/min) renal impairment.

Dabigatran: Dose reduction is recommended in patients aged ≥80 years or in patients who receive concomitant verapamil.

Dose reduction should be considered in patients between 75-80 years, Patients with moderate renal impairment (CrCL 30-50 mL/min), Patients with gastritis, esophagitis or gastroesophageal reflux, other patients at increased risk of bleeding

Apixaban: Dose reduction in case of at least two of the following characteristics: age ≥ 80 years, body weight ≤ 60 kg, or serum creatinine ≥1.5 mg/dL (133 micromol/L).

Dose reduction is also recommended in severe renal impairment (creatinine clearance 15-29 mL/min)

Only for dabigatran there was mentioning that in the presence of risk factors for GIT bleeding like gastroenteritis, esophagitis or gastroesophageal reflux or in patients at increased risk consideration should be given to dose reduction. Referring to particular patients at risk for bleeding events irrespective of PK may have merits. Such a recommendation is neither included in the SmPC of apixaban which numerically showed the lowest relative bleeding risk, nor for rivaroxaban.

However, the data do not indicate that specific reference to consider dose reduction in patients with gastrointestinal disease was relevant for the GIT bleeding rates in case of dabigatran. In all of the databases the adjusted HR for GIT bleeding vs. VKA was higher for dabigatran than for apixaban and in 3 out of 4 databases higher than for rivaroxaban. The data do not support the assumption that a suggestion in the SmPC to reduce the dose in patients at a particular risk is an effective measure for risk reduction.

Both, dabigatran and apixaban refer to age to be considered for dose reduction. Analyses on the importance of age for differences in bleeding risk between DOACs are provided below.

The impact of stratifying by sex, age above or under 75 years of age, weight<50 or >100 kg and renal function was also discussed.

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.

iii. Other Studies

Integrated Analysis with data from Canada (Metanalysis, Risk of Major Bleeding associated with the use of individual direct oral anticoagulants compared to vitamin K antagonists in patients with non-valvular atrial fibrillation: a meta-analysis of results from multiple population-based cohort studies using on a common protocol in Europe and Canada[3])

This was a metanalysis based on integrated data from the EMA initiated study (objective 1) discussed above in detail, and healthcare databases from 6 regions of Canada based on the same protocol. In total 421,523 users of anticoagulants were identified of which 156,636 (37.2%) used a DOAC and 264,887 (62.8%) used a VKA. In the European countries, the use of DOACs was lower than of VKAs,

[3] van den Ham *et al*. (for publication)

ranging from 14.9% in the UK to 38.6% in Germany. In Canada the majority of patients were prescribed a DOAC (56.1%). There was substantial heterogeneity between the studies as present in the European databases which makes a calculation of a common HR to some degree questionable, even if a random effects model is applied. Taken this limitation into consideration the results were overall consistent with the results as discussed for the individual databases.

Risk of major bleeding (DOAC vs. VKA) was not significantly different between DOACs and VKAs: all DOACs HR 0.94 (95% CI 0.87-1.02), rivaroxaban HR 1.11 (95% CI 1.06-1.16), apixaban HR 0.76 (95% CI 0.69-0.84), dabigatran HR 0.85 (95% CI 0.75-0.96)

Apixaban appeared to have the lowest relative bleeding rates but there was considerable variability between the databases. Relative rate of major bleeding was higher but still superior to VKA for dabigatran. Bleeding rates were higher than with VKA for rivaroxaban. There appeared to be a non significant trend towards lower relative risk (DOAC vs. VKA) in younger patients (HR 0.83, 95% CI 0.73-0.95) than in patients ≥75 years (HR 1.01, 95% CI 0.94-1.09).

Risk of GIT bleeding (DOAC vs. VKA) was higher for DOACs when analysed together than with VKAs: HR 1.16, 95% CI 1.05-1.28 When assessing the different DOACs separately, a lower risk compared to VKAs was observed for apixaban (HR 0.77, 95% CI 0.67-0.87). Risk was higher for rivaroxaban (HR 1.28, 95% CI 1.18-1.38) and for dabigatran (HR 1.21, 95% CI 1.07-1.37) compared to VKAs

ICH (DOAC vs. VKA) was lower for all DOACs compared to VKAs (HR 0.60, 95% CI 0.49–0.73). Lower risks were also observed for each of the individual DOACs with the lowest HR for dabigatran and the highest for rivaroxaban; rivaroxaban HR 0.75, 95% CI of 0.61–0.92, apixaban HR 0.61, 95% CI 0.51-0.72, dabigatran HR 0.48, 95% CI 0.36–0.65.

Meta-analyis of the pivotal trials (Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials)

The meta-analyis of the pivotal trials (Ruff *et al*. 2014) included 42,411 participants having received a new oral anticoagulant and 29,272 participants received warfarin included in the pivotal trials for dabigatran, rivaroxaban, apixaban, and edoxaban (RE-LY, ROCKET AF, ARISTOTLE, and ENGAGE AF–TIMI 48).

Allocation to a DOAC overall significantly reduced the composite of stroke or systemic embolic events by 19% compared with warfarin, which was mainly driven by a reduction in haemorrhagic stroke. There was also a small but significant reduction in all-cause mortality. No significant difference was observed for efficacy on myocardial infarction and ischemic stroke. Rate of major bleeding was numerically lower with DOACs. This was related to a lower rate of intracranial haemorrhage (RR 0.48 (0.39 – 0.59)), including haemorrhagic stroke and subdural, epidural, and subarachnoid bleeding. The rate of GIT bleeding was increased with DOACs.

For the individual DOACS the RR (95% CI) vs. VKA for major bleeding was as follows: dabigatran 0.94 (0.82 – 1.07), rivaroxaban 1.03 (0.90 – 1.18), apixaban 0.71 (0.61 – 0.81), edoxaban 0.80 (0.71 – 1.00). Age was not a significant factor for major bleeding but the HR tended to be lower in patients below 75 years (HR vs. VKA 0.79 (0.67 – 0.94) than in those 75 of age or older (HR 0.93 (0.74 – 1.17), p = 0.28)). A cross study comparison between DOACS was not performed in this study. Factors like differences in baseline CHADS2 score and presence of diabetes potentially penalized the HR of rivaroxaban for major bleeding when compared to the other DOACs.

US based study (Comparative stroke, bleeding, and mortality risks in older Medicare patients treated with oral anticoagulants for non-valvular atrial fibrillation)

This was a retrospective new-user cohort study (Graham *et al*. 2019) of patients with nonvalvular atrial fibrillation enrolled in US Medicare who initiated warfarin (n=183,318), or a standard dose of dabigatran (n=86,198), rivaroxaban (n=106,389) or apixaban (n=73,039) between October 2010 and September 2015. A total of 448,944 anticoagulant initiators contributed 159,927 person-years of on-treatment follow-up (mean duration = 130 days). The mean age across cohorts was 75.4 years, of whom 47.4% were female.

The key results are as follows (HR DOAC vs. warfarin, 95% CI): All-cause mortality was significantly lower with all DOACs: dabigatran 0.73 (0.67 – 0.80), rivaroxaban 0.81 (0.75– 0.88), apixaban 0.66 (0.60 – 0.74).

The rate of thromboembolic strokes was significantly lower with all DOACs: dabigatran 0.80 (0.70 – 0.93), rivaroxaban 0.72 (0.63 – 0.83), apixaban (0.71 (0.60 – 0.83)

The rate of intracranial haemorrhages was significantly lower with all DOACs: dabigatran 0.38 (0.31 – 0.47), rivaroxaban 0.65 (0.56 – 0.77), apixaban 0.54 (0.43 – 0.68)

A higher rate of Major GIT bleeding was observed for: dabigatran 1.16 (1.06 – 1.27) and rivaroxaban: 1.48 (1.36 – 1.60), a lower rate of Major GIT bleeding was observed with apixaban 0.52 (0.45 – 0.60)

Rivaroxaban was associated with significantly increased risk of intracranial haemorrhage compared with dabigatran (rivaroxaban vs dabigatran: HR 1.71; 95% CI, 1.35-2.17), and with significantly increased risks of major extracranial bleeding (rivaroxaban vs dabigatran: HR 1.32; 95% CI, 1.21-1.45; rivaroxaban vs apixaban: HR 2.70; 95% CI, 2.38-3.05) and death (rivaroxaban vs dabigatran: HR 1.12; 95% CI, 1.01-1.24; rivaroxaban vs apixaban: HR 1.23; 95% CI, 1.09-1.38), compared with dabigatran or apixaban. Dabigatran was associated with significantly reduced risk of intracranial haemorrhage (HR 0.70; 95% CI, 0.53-0.94) and with significantly increased risk of major extracranial bleeding (HR 2.04; 95% CI, 1.78- 2.32) compared with apixaban.

Subgroup analyses by age indicated an age-related increase in major extracranial bleedings for dabigatran and rivaroxaban, but not for apixaban. The point estimates for the HR (DOAC vs. Warfarin) for patients 65 – 74 years, 75 – 84 years and > 85 years were: dabigatran: 0.77, 1.15, and 1.75, rivaroxaban 1.17, 1.51, and 1.73, apixaban: 0.45, 0.56, and 0.54

Metanalysis of real-world evidence (Meta-analysis of real-world evidence comparing non-vitamin K antagonist oral anticoagulants with vitamin K antagonists for the treatment of patients with non-valvular atrial fibrillation)

This metanalysis (Coleman *et al*. 2019) based on literature search has considerable methodological drawbacks that prevent drawing firm conclusions. The results of the metanalysis are largely consistent with the results of the pivotal trials indicating non-inferiority of efficacy with respect to ischemic and haemorrhagic stroke/systemic thromboembolism and the single components as compared to VKA. Intracranial haemorrhage was lower with all of the DOACs compared to VKA. Gastrointestinal bleedings were higher with rivaroxaban and dabigatran and lower with apixaban.

Cohort study based on AOK NORDWEST (Germany) claims database (Comparative risks of bleeding, ischemic stroke and mortality with direct oral anticoagulants versus phenprocoumon in patients with atrial fibrillation)

The database used in this cohort study (German claims database (AOK)) (Ujeyl *et al*. 2018) is partially overlapping with data analysed in the EMA initiated study. Patients aged ≥ 18 years initiating rivaroxaban, dabigatran, apixaban, or phenprocoumon between 1 January 2012, and 31 December 2013, in a dose licensed for NAVF were matched by propensity matching and analysed. Of the 215,068 users, matched cohorts were obtained with 87,997 phenprocoumon (74.2%) and 87,997 DOAC users (91.3%): 59,449 rivaroxaban (91.8%), 23,654 dabigatran (90.8%), and 4894 apixaban (87.4%). 5742 bleeding events and 2355 ischemic strokes were observed.

With rivaroxaban, the adjusted HR indicated a similar risk of hospitalized bleedings compared to phenprocoumon (HR 1.04 (0.97 – 1.11)), while risk of GIT bleeding was higher (HR 1.28 (1.17 – 1.40)) and risk of ICH was lower (0.57 (0.47 – 1.17)).

With dabigatran the risk of hospitalized bleedings (HR 0.87 (0.77 – 0.98)) and ICH (0.4. (0.27 – 0.58)) was lower than with phenprocoumon, GIT bleedings were higher (1.21 (1.03 – 1.42)).

With apixaban, the risk of hospitalized bleedings (0.65 (0.50 – 0.86)), of ICH (0.79 (0.36 – 1.73)) and of GIT bleedings (0.70 (0.48 – 1.01)) was lower than with phenprocoumon.

Numerically the rate of ischemic stroke was higher with all of the three DOACs compared to phenprocoumon with the highest rate observed for apixaban. Also, all-cause mortality was numerically higher with all of the three DOACs with the highest value for rivaroxaban. The numerically higher mortality rates were unrelated to bleeding or stroke in all cases indicating bias due to differential treatment allocation. The data did not indicate a lower risk of ICH bleedings of apixaban as compared to the other DOACs.

Integrated discussion of the results of all studies

Considering the results of all studies there were some consistent trends.

ICH was lower with all DOACS compared with VKA. Whether there were differences between the DOACs is unclear. The US based study indicates a significantly higher risk with rivaroxaban vs. the other DOACs. The European/Canadian Metanalysis did not find significant differences but numerically ICH was also higher with rivaroxaban. Whereas the Cohort study in AOK NORDWEST Germany did not find such an association.

GIT bleeding was higher with DOACs than with VKA (European/Canadian metanalysis, US based study, Metanalysis of Pivotal trials) but the results were drug specific. Relative GIT bleeding rates (DOAc vs. VKA) were consistently above 1 with dabigatran and rivaroxaban and below 1 with apixaban (European/Canadian study, US bases study, AOK NORDWEST German Cohort study) being the main reason for consistent overall increased rates of major extracranial bleeding events. Such drug specific differences are consistent with the results of the pivotal trials where apixaban did not increase GIT bleeding events compared to VKA (EPAR EMA/641505/2012), whereas GIT bleeding rates were higher for Rivaroxaban (EPAR EMA/42547/2012) and for dabigatran (EPAR EMA/CHMP/203468/2011).

Results for mortality were not consistent. As can be demonstrated by the AOK NORDWEST German Cohort study, all-cause mortality is largely driven by bias due to imbalanced treatment allocation.

Consistency was also observed regarding age as a possible factor influencing relative bleeding rates (DOAC vs. VKA). An age depended increase in HR of major extracranial bleeding (65 – 64, 75 – 84, 85 and higher) was described for dabigatran and to a lesser degree for rivaroxaban in the US based study, but not for apixaban. A similar trend was also seen for age in the metanalysis of the pivotal studies and in the European/Canadian metanalysis for all DOACs together for major bleeding events (below 75 years vs. 75 years and higher). In the individual databases in the European studies the pattern was similar to the one seen in the US based study. For dabigatran HRs were higher in all four databases in

the elderly patients, for rivaroxaban in two databases with similar HRs in the other two, for apixaban there was considerable variability with two databases showing higher and lower HRs (DOAC vs. VKA) respectively.

The data indicate that when used in NVAF the bleeding pattern differs between VKA and DOACs (lower risk of ICH with DOACs, higher risk of GIT bleeding at least with rivaroxaban and dabigatran). The relative bleeding risk was related to age for dabigatran and possibly for rivaroxaban but not for apixaban. It is unclear, whether age related differences in the dose recommendations (present for apixaban, absent for rivaroxaban) are relevant for such differences.

Objective 2

A summary of the results for the objective 2 of the study is presented below.

A total of 186,405 of new DOAC users (≥18 years), in part switching form VKAs/OAC with non-valvular atrial fibrillation (NVAF) were identified in eight databases representing six different European countries in the period 2008-2015. During the study period the overall incidence of new DOAC users increased except in the Bavarian CD and in EGB. Use in patients with NVAF was negligible before the respective dates of issue of the NVAF indications (2011/2012).

There were some differences in the databases. Rivaroxaban was the predominant DOAC in Mondriaan, AOK NORDWEST, and Bavarian Claims database. In EGB database rivaroxaban was prominent up to 2014; in 2015 rivaroxaban and apixaban had the same incidence. In CPRD database rivaroxaban and apixaban reached a higher incidence than Dabigatran over time. The incidence was more balanced for the three DOACs in BIFAP and SIDIAP. Dabigatran was the predominant DOAC in NDR up to 2014, whereas in 2015 rivaroxaban and apixaban showed a higher incidence. Dabigatran incidence peaked around 2012/2013 with no change or a decrease in the years thereafter in all databases.

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.

Male users were slightly more frequent than female with more than 41% of females in all databases, except in the AOK NORDWEST and Bavarian databases, where slightly more females than males were included. The percentage of comorbidities ranged from 31.1% (Mondriaan) to 87.3% (AOK NORDWEST), previous cardiovascular events being the most frequent comorbidity.

Chronic kidney disease by diagnosis was high in the two German databases (20.1 and 24.1% respectively in AOK NORDWEST and BAVARIAN Claims) and low in the other databases (0 – 4.6%). This has to be evaluated in the context of the aim of the databases. Issues related to financing in the statutory insurances are related to diagnoses which may increase the number of diagnoses attributed to a patient by a physician. However, the data from the German databases are consistent with the rate of patients with mild to severely reduced renal function in Mondriaan and SIDIAP (26.9% and 30.4%, respectively), whereas in CPRD most of the patients (77.1%) were reported to have reduced renal function.

There were relevant differences in the reporting rates of potentially interacting medicines between the databases. The highest rate of reporting potentially interacting medicines had EGB (70.5%), the lowest rate SIDIAP (16.4%). Differences between the databases were remarkable for the concomitant use of other anticoagulants (24.3% EGB, 0.4% CPRD). It is unlikely, that such differences reflect real differences in administration of drugs in FR (EGB) and UK (CPRD). From the information provided it is unclear, whether true concomitant administration was documented in the databases or e.g. administration during a given period. E.g. Transition from one anticoagulant to another (VKA, Heparin, DOAC) might be noted as co-medication in one but not in the other database. 24.3 % concomitant administration of other anticoagulants as indicated by EGB would be an unexpectedly high number.

Concomitant use of antiplatelet drugs ranged from 1% in SIDIAP to 18.1% in EGB respectively. The most frequent concomitant interacting drugs were heparins in AOK NORDWEST, 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 related to potentially interacting medicines 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.

Switchers

In most databases the rate of switchers was lowest for apixaban, highest for dabigatran, and in-between for rivaroxaban. Time effects may be relevant. Coming one year later on the market for the treatment of NVAF might lead to a lower rate of patients switching from apixaban to another DOAC. There were large differences between the databases. The highest percentage of switchers was observed in the AOK NORDWEST database (16%) and the lowest one in the Mondriaan database (2.4%).

Discontinuers

The highest percentage of discontinuers was observed in the Bavarian CD (79.4%) and the lowest one in the CPRD 17.7%. The extremely wide range of discontinuer rates in the different databases raises the question to which degree incomplete documentation may have contributed to the results. It appears not conceivable that patients in Bavaria discontinued treatment in 79.4%, whereas the rate in France was 17.7%. There were gradual differences between the three DOACs regarding switcher rate that do not indicate general user preferences for one or the other DOAC.

Regarding the Kaplan-Meier figures for all DOACs, the CPRD was the database that showed the highest probability of "survival on treatment" at 12 months, in the Mondriaan database "survival on treatment" was lowest. Apixaban had numerically the lowest "survival on treatment" probability in AOK NORDWEST but numerically had the best values in all of the other databases, again only with minor better rates compared to rivaroxaban. The values for rivaroxaban were in between the values for the other drugs in all databases. Overall, the differences were small and it may not be possible to draw firm conclusions on maintenance when comparing the three medicinal products.

Objective 3

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. 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.

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).

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, BIFAP, 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. Interestingly, there were also some inter-country differences regarding the proportion of patients initiating DOAC with 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.

Summarising 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%. 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%.

Summarising all three DOACs, all datatabases 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%.

With regard to the databases, highest proportion of patients with at least 1 special warning / precaution was found in the Bavarian database (75.2%) followed by CPRD (67.0%) whereas lowest values were found in Mondriaan (35.8%).

By analysing special warnings or precautions in detail for calendar years 2012/2013 versus 2015, 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 or precaution some differences were found between the databases regarding the calendar years mentioned above. The proportion of

patients with 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 / distinct lower proportions were found.

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

With regard to potential drug interactions, an overall proportion of 46.8% was revealed for incident DOAC users. For the three DOAC compounds, the 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 the values were somewhat lower for the remaining databases. Such Co medications may not be generally avoidable (e.g. co-medication with amiodarone or quinidine in atrial fibrillation) or may even be in line with current treatment recommendations (e.g. co-medication with antiplatelet drugs in patients with NVAF and PCI). The analyses do not allow concluding on in how many patients switching to other medicinal products (e.g. in case of SSRIs) would have been an option.

The information on an increased bleeding risk when dabigatran is co-administered with SSRIs/SNRIs (section 4.4 warning and section 4.5 interactions) is already implemented in the products product information in 2017. The analysis provided by the authors indicated a relevant degree of co-administration. There was no relevant change before and after the implementation of the changes in the product information. No final conclusions can be drawn about the reasons. E.g. the availability of an adequate alternative to SSRIs/SNRIs in an individual patient cannot be assessed here. Slow or insufficient propagation of the information to the prescribers should be considered.

In conclusion, the analyses show that co-medication with drugs with potential for interaction was frequent. In many instances such co-medication may be unavoidable since similar interactions are relevant for VKA also, or the unavailability of alternative treatments. In other cases, co-medication was in line with current clinical knowledge at the period investigated. The analyses do not allow conclusions possibilities of patient switching to other medicinal products (e.g. in case of SSRIs).

2.5. Discussion

The main concern associated with the administration of DOACs as well as VKAs is bleeding inevitably related to the mechanism of action of these compounds. In particular major gastrointestinal and intracranial bleedings are relevant. Whereas an acceptable benefit-risk balance has been demonstrated and characterised in the setting of controlled clinical trials at the time of the marketing authorisation, it may not fully represent real life data in the clinical practice. Such data were analysed using databases available from several European countries, and in addition from Canada and the US.

The key data regarding bleeding events is coming from a retrospective cohort study among incident NVAF patients aged at least 18 years in the EU to assess the risk of major bleeding associated with the use of DOACs and VKAs (EU PAS register no. 16014) in 4 databases (Danish Registries, AOK NORDWEST, BIFAP, CPRD) for the period 2008 – 2015. The aim of the study was to compare bleeding risk of patients with NVAF treated either with a VKA or with apixaban, dabigatran or rivaroxaban. Overall the study appeared to be appropriately designed.

The data are complemented by databases available from 6 Canadian regions and integrated in a metanalysis including a total of 421,523 patients of which 37.2% used a DOAC and 62.8% used a VKA. Considering the heterogeneity of the data included in this metanalysis, the primary assessment focusses on the analysis of the data within each database separately available for Europe.

Additional information comes from a US based retrospective analysis of Medicare claims data from in total 448,944 Patients aged > 65 years with a diagnosis of atrial fibrillation or flutter during the preceding 6 months, that were new users of antithrombotic drugs (D)OACs (warfarin, apixaban, dabigatran or rivaroxaban) between October 2010 – September 2015. Despite of the difference in the age-related inclusion criteria between the studies the patient characteristics was overall similar in the US based study and in the EU based study.

In addition, the data are discussed in the context of the pivotal trials relevant for authorising the three DOACs in the EU for NVAF based on a metanalysis (Ruff *et al*. 2014). These data are relevant as so far as some limitations of observational studies do not apply to the data from the controlled pivotal trials. An additional metanalysis (Coleman *et al*. 2019) summarizes data on efficacy and safety for the three DOACs in comparison to VKA based on a systematic literature search (December 2016). Due to relevant methodological limitations the conclusions of this analysis are not considered robust. A further Cohort study based on German claims data (AOK NORDWEST) used a database, that is partially overlapping with one of the databases (AOK NORDWEST) included in the key study (Ujeyl *et al*. 2018)

Key results

European Study

A total of 251,719 patients were included in the analysis in the period of 2008-2015 of which 24.4% used a DOAC and 75.6% used a VKA. The patient characteristics were similar in the 4 databases with some peculiarities. Around 40 – 55% of patients were females. 40 – 60% of patients were >75 years old. Risk for atrial fibrillation and VTE increase at higher age. Data for weight and BMI are missing in the German and Danish database, and in more than 50% in the other databases. Where available, the average patient in had a BMI around 30.

The risk of major bleeding for the group of DOACs compared to VKAs showed a pooled HR of 0.94 (95% CI: 0.87-1.02). There were differences in reported incidence of bleeding events between the databases. The highest rate was reported in CPRD (UK) for both VKA (66.8/1000 person years) and DOACs (78.8), the lowest in NDR (DK): VKA: 29.5, DOACs 26.6. Specific differences in the HR of bleeding events (DOAC vs. VKA) were observed between the different databases. Whereas in CPRD (UK) and AOK NORDWEST (DE) bleeding rates were numerically higher with DOACs than with VKA, in BIFAP (ES) and NDR (DK) the overall incidence rate was higher with VKA than with DOACs.

<u>Overall results (all DOACs together)</u>

The overall pattern was as follows:

a) The rate of major bleeding events was higher with DOACs in CPRD and AOK NORDWEST (HRs 1.13 and 1.07) and lower in BIFAP and NDR (0.95 and 0.84, respectively, table 4.)

b) Overall incidence of gastrointestinal (GI) bleeding was similar in all databases for VKA (12.5 – 16.5/ 1000 person years) and was higher for DOACs in each database, respectively (14.1 – 24.9/1000 person years) with adjusted HRs of 1.04 – 1.40 favouring VKA.

c) For intracranial haemorrhage the results were heterogeneous in the cohort study, with rates of 0.4 – 3.7/1000 patient years for VKA and 0.5 – 2.1/1000 patient years for DOACs, (adjusted HRs: 0.49 – 1.65) but overall there was a trend towards a lower rate of ICHs with DOACs. Intracranial bleeding was lower with DOACs in three databases (BIFAP, AOK NORDWEST, NDR, adjusted HRs 0.49 – 0.63) and higher in CPRD (adjusted HR 1.65).

d) Stroke (including ischemic and haemorrhagic stroke) was observed more frequently with DOACs in CPRD (UK), BIFAP (ES) and NDR (DK) (HRs 1.06 – 1.76) and less frequently in AOK NORDWEST (DE) (HR 0.88).

Results for individual DOACs

There appeared to be a consistent pattern, when comparing major bleeding for the different DOACs with some specific differences between DOACs. In all of the databases the HR for major bleeding events was higher with rivaroxaban vs. VKA (adjusted HRs: 1.02 – 1.27) than with dabigatran (0.81 – 1.06), and with apixaban (0.73 – 0.94). There was a trend to a lower HR for apixaban vs. VKA than for the other DOACs, being even in favour of apixaban vs. VKA in AOK NORDWEST and NDR.

Consistent differences were seen for the specific bleeding events: The adjusted HR for GIT bleeding events were lower in all of the four databases for apixaban (range 0.74 – 1.08) than for rivaroxaban (1.14 – 1.50) and for dabigatran (1.13 – 1.60).

Regarding intracranial haemorrhages, the HRs were generally in favour of the single DOACs with the exception of rivaroxaban in CPRD and NDR and apixaban in NDR. No consistent trend was seen when comparing the different DOACs in the different databases, but the event rate may have been overall too low to draw robust conclusions.

Results for stroke largely depended on the database (HR DOAC vs. VKA, CPRD 1.76 (1.50 – 2.08), BIFAP 1.18 (1.00 – 1.39), AOK NORDWEST 0.88 (0.81 – 0.95), NDR 1.06 (0.96 – 1.16) but were overall similar for the three DOACs within each database.

There were no clinically meaningful differences in HRs across subgroups except that the risk of major extracranial bleeding in dabigatran users was reduced in 65- to 74-years old but increased in patients 75 years or older, compared with warfarin (P interaction < .001).

Sensitivity analyses were generally consistent with the primary analysis. The point estimate for thromboembolic stroke for dabigatran compared with apixaban increased slightly and became statistically significant in the 14-day gap analysis (HR 1.23; 95% CI, 1.05-1.45), but the CIs largely overlapped the main analysis.

In the analysis restricted to the period since apixaban's approval, intracranial haemorrhage risk with dabigatran was no longer significantly reduced compared with apixaban (HR 0.92; 95% CI, 0.63-1.32). Post hoc analyses were generally consistent with the primary analysis, except that some comparisons for intracranial haemorrhage changed as to whether differences were statistically significant.

Among the limitations of the study and in addition to the general issues associated with retrospective studies is the relatively short mean duration of anticoagulant use (< 5 months). Conclusions on long term efficacy and safety of a life-long treatment are limited. The study included patients > 65 years. This might have been a factor since the analyses by age indicated a higher relative risk for major bleeding events with rivaroxaban and dabigatran as compared to warfarin in the highest age group > 84 years. However, this represents the key population as the risk for NVAF increases with age.

A part of the study to characterise the use of DOACs in the EU (Objective 2).

A total of 186,405 of new DOAC users (≥18 years), in part switching form VKAs/OAC with non-valvular atrial fibrillation (NVAF) were identified in eight databases representing six different European countries in the period 2008-2015. During the study period the overall incidence of new DOAC users increased except in the Bavarian claims database and in EGB. Use in patients with NVAF was negligible before the respective dates of issue of the NVAF indications (2011/2012).

There were some differences in the databases. Rivaroxaban was the predominant DOAC in Mondriaan, AOK NORDWEST, and BAVARIAN Claims database. In EGB rivaroxaban was prominent up to 2014, in 2015 rivaroxaban and apixaban had the same incidence. In CPRD rivaroxaban and apixaban reached a higher incidence than dabigatran over time. The incidence was more balanced for the three DOACS in BIFAP and SIDIAP. Dabigatran was the predominant DOAC in NDR up to 2014, whereas in 2015 rivaroxaban and apixaban showed a higher incidence. Dabigatran incidence peaked at around 2012/2013 with no change or a decrease in the years thereafter in all databases.

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.

Male users were slightly more frequent than female with more than 41% of females in all databases, except in the AOK NORDWEST and BAVARIAN Claims databases, where slightly more females than males were included. The percentage of comorbidities ranged from 31.1% (Mondriaan) to 87.3% (AOK NORDWEST)), previous cardiovascular events being the most frequent comorbidity.

Chronic kidney disease by diagnosis was high in the two German databases (20.1 and 24.1%, respectively in AOK NORDWEST and BAVARIAN Claims) and low in the other databases (0 – 4.6%). Issues related to financing in the statutory insurances are related to diagnoses which may increase the number of diagnoses attributed to a patient by a physician. However, the data from the German databases were consistent with the rate of patients with mild to severely reduced renal function in Mondriaan and SIDIAP (26.9% and 30.4%, respectively), whereas in CPRD most of the patients (77.1%) were reported to have reduced renal function.

There were relevant differences in the reporting rates between the databases. The highest rate of reporting potentially interacting medicines had EGB (70.5%), the lowest rate SIDIAP (16.4%). Differences between the databases were remarkable for the concomitant use of other anticoagulants (24.3% EGB, 0.4% CPRD). It is unlikely, that such differences reflect real differences in administration of drugs in France (EGB) and UK (CPRD). From the information provided it is unclear, whether true concomitant administration was documented in the databases or e.g. administration during a given period, e.g. transition from one anticoagulant to another (VKA, Heparin, DOAC) might be noted as co-medication in one but not in the other database. 24.3 % concomitant administration of other anticoagulants as indicated by EGB would be a high number. Concomitant use of antiplatelet drugs ranged from 1% in SIDIAP to 18.1% in EGB respectively. The most frequent concomitant interacting drugs were heparins in AOK NORDWEST, BIFAP, BAVARIAN claims database (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 re-uptake 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.

In most databases the rate of switchers was lowest for apixaban, highest for dabigatran, and in-between for rivaroxaban. Time effects may be relevant. Coming one year later on the market for the treatment of NVAF might lead to a lower rate of patients switching from apixaban to another DOAC. There were large differences between the databases. 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 claims database (79.4%) and the lowest one in the CPRD 17.7%.

The extremely wide range of discontinuer rates in the different databases raised the question to which degree incomplete documentation may have contributed to the results. It raised questions the fact that patients in Bavaria discontinued treatment in 79.4%, whereas the rate in the UK was 17.7%. There were gradual differences between the three DOACs regarding switcher rate that do not indicate general user preferences for one or the other DOAC.

The DOAC use in all patients irrespectively of the indication was addressed in Objective 3.

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. The decrease in dabigatran and rivaroxaban use after 2012/2013 in NRD and BAVARIAN claims database respectively is most likely attributable to an increased prescription of apixaban. A substantial number of patients with 'missing / other indications' found in most databases was probably related to coding issues.

MI (myocardial infraction; acute coronary syndrome) is approved for rivaroxaban only (low dose treatment 2.5 mg bid) but not for other DOACs. However, there was no increase in the percentage of new users for this indication between 2012 and 2015 for Rivaroxaban in 5 out of 6 databases. In addition, the relative rate of patients categorized as new users within this indication was largely similar for all three DOACs with little change over time. Licencing the indication for Rivaroxaban did not change the rate of patients categorized as being treated for MI further indicating a relevant rate of misclassification. It could be concluded that the databases contain incorrect classifications in at least the order of magnitude as seen with MI (about 5 – 6%). In addition, the categorisation of MI and MI other categorisations for all three DOACs is questionable. The approved dose for MI (rivaroxaban only) is not in line with the higher dose in other indications. Similarly, it may be questioned whether all of the patients categorised as treated off-line for valvular atrial fibrillation (VAF) are categorized correctly. However, the relative numbers up to 16.3% in the single databases indicate that there is at least some relevant off-label use in VAF.

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 with a possible documentation related over estimation of diagnoses and contraindicated conditions, somewhat lower proportions of treatment despite of contraindications were found (overall: 15.6%, dabigatran:18.8%, rivaroxaban: 13.4%, and apixaban: 14.1%).

Assessing the actual rate was hampered by several factors. Among these were that the definitions of some of the contraindications as presented in the study report were not exactly in line with the wording of the SmPC in all cases and possibly the range of incidences included in the analysis goes beyond the strict definitions of the respective contraindications. This is also related to the documentation in the databases that is not generally in line with the wording in section 4.3 of the SmPC. When analysing the results in detail, overall the data do not provide robust evidence for the assumption that prescribers ignore contraindications to such an extent that can be considered a general issue of concern.

Due to the nature of the BAVARIAN Claims database (lacking laboratory values) its results are overall not considered valid for this analysis. They are presumably subject to huge over-reporting of diagnoses and contraindicated conditions and overestimation of severity of disease possibly related to reimbursement issues. In the absence of confirmatory lab data this is particularly the case for contraindications like severe hepatic failure und severe renal disease.

For the contraindication on severe hepatic disease that is relevant for survival or associated with coagulopathy and clinically relevant bleeding risk the reported percentages are between 0.0 and 2.5% in the respective years 2009 – 2015/2012 – 2015 for the individual DOACs in the other five databases. These numbers may still represent an overestimation due to the broad definition used that does not necessarily match the clinical judgment of the risk in an individual patient.

Similarly, for the contraindication on the active clinically significant bleeding, the data do not provide robust evidence for a generally inappropriate non-adherence of physicians to the contraindication when initiating DOAC therapy (0.0 – 2.5% in 4 databases, 5.7 – 11.5% in Mondriaan, 5.7 - 18.1% in BAVARIAN Claims database). According to the literature, the positive predictive value of database analyses based on ICD codes for bleeding events on anticoagulants is low. There are inherent difficulties to define the clinically significant bleeding and this allows for interpretation. The data cannot show that DOAC were administered at the time of a bleeding event was considered active. Instead, the time window of up to 6 weeks between a bleeding event and initiation of DOAC therapy makes it likely that many patients received DOACs after cessation of the bleeding when bleeding in the judgment of the treating physician was no longer considered active. Therefore, it can be assumed that, at least to a large degree, the patients counted in the analysis were not considered to have active clinically significant bleeding.

For the contraindication on prosthetic heart valves requiring anticoagulant treatment (for dabigatran only evaluated in the period after labelling in 2013) all ICD-10 codes for prosthetic valves were counted in the analyses including valves that are not subject to the contraindication (e.g. bioprotheses, TAVI procedures with bioprotheses, other non-specified heart-valve-replacement procedures). Therefore, at least a relevant part of the patients counted in this category had no contraindication. There is also the possibility that they were treated with dabigatran for a different indication.

Similarly, the data presented for the contraindication malignancies associated with a high risk of bleeding as a contraindication pose some weaknesses. All patients with any diagnosis of a predefined malignancy (except non-melanoma skin cancer) within 6 months prior to initiation of DOACs were counted. Most of these may not have had an increased bleeding risk. It is not possible to estimate how many of the patients counted in the study were at high risk of bleeding qualifying for the contraindication which may have led to overestimation of cases.

For the contraindication on vascular aneurysms if considered a significant risk factor for major bleeding all intracerebral and intra-spinal aneurysms were counted. However, bleeding risks depend on whether aneurysms are treated (clipped or coiled) or untreated, on size, localisation, morphology and other patient related factors that allow to estimate the risk for rupture on an individual basis. The wording of the contraindication allows for such an individual risk-based assessment and counting all of these aneurysms within the data of the study may lead to an overestimation of the rate of patients treated despite of this contraindication.

Renal failure (CrCL< 30 mL/min) is a contraindication for the administration of dabigatran. There was a huge difference between cases in BAVARIAN claims (severe renal failure/chronic/acute kidney disease increased from 9.1% in 2009 to a plateau in the range of 22.2 – 23.3% (2012 – 2015)) and in the other databases (0.0 – 0.9 with somewhat higher values in SIDIAP (0.4 – 3.6%). In general, the data in BAVARIAN Claims are not considered reliable due to the broad definition used in the absence of Lab values. Among the drawbacks of the analyses for the other databases is the broad time window (lab value within 12 months prior to dabigatran administration), that includes transient declines in renal function and does not allow to draw reliable conclusions on the renal function at the very time of dabigatran administration. Although it is not denied that for some patients administration of dabigatran despite of severe renal failure may have been documented in the databases, the real rate at the time of administration is unclear.

The concomitant treatment with systemic ketoconazole, cyclosporine, itraconazole and dronedarone (or similar wording) is listed as contraindication in section 4.3 or as a warning in section 4.4 of the SmPC. A concomitant administration of dabigitratan with contraindicated product was noted in some cases (< 2 % over all databases and years).

In summary, the analyses indicate to some degree treatment despite of the presence of contraindications. However, for almost all of the contraindications for DOAC use the percentages are considered a possible over-estimation due to too broad definitions of the contraindicated conditions. This is not only relevant to the BAVARIAN Claims database but also for the other databases that contained much lower rates. Based on these data it cannot be concluded with sufficient confidence that disregarding contraindication by prescribers is a general issue of concern at a level that requires regulatory actions.

For special warnings and precautions 4.4, 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%). Whereas for the contraindications the numbers were considerably higher in BAVARIAN Claims database than in the other databases, such differences between the databases are much smaller for warnings and/or precautions (section 4.4). The rate was lower 2008 – 2010 (overall about 34 – 36%) and reached a plateau 2012/2013 – 2015 (overall about 65 – 70%). The sudden increase in the rate of new DOAC users with at least one warning/precaution parallels for each drug the time point of issuing of the NVAF indication with not much of a change thereafter. Patient characteristics and treatment duration of these patients are quite different from those treated after hip or knee replacement for prevention of VTE. The number of patients treated despite of warning and/or precaution conditions is at least in part due to the indication. Prevalence of NVAF increases with age and such patients usually require treatment either with a DOAC or a VKA.

With regard to potential interactions, an overall proportion of 46.8% was revealed for incident DOAC users. For the three DOAC compounds, the 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 the values were somewhat lower for the remaining databases. Such co-medications may not be generally avoidable (e.g. co-medication with amiodarone or quinidine in atrial fibrillation) or may even be in line with current treatment recommendations (e.g. co-medication with antiplatelet drugs in patients with NVAF and PCI). The analyses do not allow concluding on in how many patients switching to other medicinal products (e.g. in case of SSRIs) would have been an option.

In summary, the data on the administration of DOACs in contraindications may represent overestimations. This may have been to some degree unavoidable when considering that clinical judgment is not coded in such databases. In addition, exaggeration of diagnoses and contraindications and both over- and underreporting further hampers the analysis of such databases. To some degree similar considerations also apply to adherence of prescribers to warning/precautions or concomitant prescriptions of potentially interacting drugs. Whereas the data indicate a relevant degree of coadministration of drugs with the potential for interactions, it is not possible to assess, whether alternative treatment options would have been available.

Taking all these into account, it is not possible to conclude on non-compliance of the prescribers to the into contraindication and to the warnings, precautions or concomitant prescriptions of potentially interacting drugs The data were complemented by databases available from six Canadian regions and integrated in a metanalysis including a total of 421,523 patients (37.2% DOAC, 62.8% VKA).

In addition, other data were analysed: A US based retrospective analysis of Medicare claims data from in total 448,944 Patients aged > 65 years with a diagnosis of atrial fibrillation or flutter (Graham *et al*.

2019); A metanalysis (Ruff *et al*. 2014) based on the 4 pivotal trials with DOACs (apixaban, dabigatran, edoxaban, rivaroxaban vs. VKA) in patients with atrial fibrillation; A metanalysis based on a systematic literature search of real world data (Coleman *et al*. 2019), and a cohort study based on German claims data (AOK NORDWEST) (Ujeyl *et al*. 2018), (population partially overlapping with the EU based study) in 96,420 DOAC-treated at a dose licenced for NVAF and 118,648 phenprocoumon-treated patients aged ≥ 18 years initiating rivaroxaban, dabigatran, apixaban, or phenprocoumon between 1 January 2012, and 31 December 2013.

Over all studies there were some consistent trends.

The rate of major bleeding events was higher with DOACs in two databases and higher with VKA in the other two. Gastrointestinal (GI) bleeding rate was higher for DOACs in all databases (14.1 – 24.9/1000 person years) with adjusted HRs of 1.04 – 1.40 favouring VKA. Intracranial bleeding rate was lower with DOACs in three databases (adjusted HRs 0.49 – 0.63) and higher in CPRD (adjusted HR 1.65). All-cause stroke rate was higher with DOACs in 3 databases (HRs 1.06 – 1.76) and lower in one (HR 0.88).

Results for mortality were not consistent. As can be demonstrated by the AOK Germany Cohort study, all-cause mortality is largely driven by Bias due to imbalanced treatment allocation.

There was a consistent observation of high age as a factor influencing relative bleeding rates (DOACs overall vs. VKA) with numerically/significantly higher HR of bleeding for DOACs vs. VKA in the pivotal studies and the European/Canadian metanalysis, and for dabigatran > rivaroxaban in the US based study and similar in the European study. The HR was not increased for apixaban vs. VKA in these studies.

The data indicate that when used in NVAF, the bleeding pattern differs between VKA and DOACs with a lower risk of intracranial bleeding with DOACs, higher risk of GI bleeding with rivaroxaban and dabigatran. The relative bleeding risk was possibly related to age for dabigatran and to some degree for rivaroxaban but not for apixaban. It is unclear, whether differences in the dose recommendations for elderly patients (present for apixaban, and dabigatran, absent for rivaroxaban), daily dose levels, posology (b.i.d. vs. qd) or product specific differences are relevant for such differences.

Overall, study results confirm the data from the pivotal trials, in that DOAC users are less likely to suffer intracranial bleedings as compared to VKA users, whereas the risk of gastrointestinal bleeding is not reduced or even increased, at least for rivaroxaban and dabigatran.

The generally higher risk of bleeding among DOAC users aged >75 years is in line with the results from the pivotal studies; however, it should be noted that these patients also usually have a higher risk of thrombotic events and it should be considered whether a dose reduction based on age should be discussed as a way forward to bring down the bleeding rates in patients of a higher age.

These data were not sufficient to recommend dosage changes in this population. The marketing authorisation holders for these medicines should carry out further analysis to determine whether any modification of the dosing recommendations would be beneficial in elderly patients, taking into account several factors related to this population.

2.6. Conclusions

The benefit-risk balance of all DOACs investigated in the EMA study (Eliquis, Pradaxa, Xarelto) in the treatment of patients with NVAF and in the other respectively approved indications remains positive. Irrespectively of possible differences in bleeding risk between the DOACs non-inferiority in efficacy

paralleled by a sufficiently established bleeding risk vs. VKA has been demonstrated in the pivotal trials for all DOACs assessed here.

The study's strength is that it includes real-world data from a large number of DOAC treated patients. This may pose some relevant limitations which need to be considered when interpreting the study results. For instance, real life data are not randomised, bias due to confounders and changing of confounders over time cannot be entirely controlled, treatment assignment to DOAC vs. VKA may be risk based, there are documentation issues, both over-reporting of disease states and contraindications, as well as, under-reporting.

The data may be used for a discussion, whether the safety profile of DOACs may be improved for specific patient groups. The consistent finding of a higher relative risk in all cause bleeding events at increasing age for dabigatran and, to some degree, also for rivaroxaban raises the question whether the benefit- risk balance could be improved in these patients, for example by modifying recommendations for dose adaptations in elderly patients. Whether optimisation of the dosing recommendations could improve the benefit-risk balance in the treatment of NVAF in the elderly population should be further analysed by the MAHs, preferentially by generating additional data in the future.

3. Expert consultations and Stakeholders input

3.1. PRAC advice

The CHMP requested input from PRAC regarding whether any additional risk minimisation measures regarding the bleeding pattern to improve the safe use of DOACs in patients with NVAF, are warranted.

The PRAC agreed that, overall, the data assessed regarding bleeding risk and pattern do not bring substantial new knowledge in comparison with the currently described safety profile of these products, as reflected in their respective product information. It is noted that bleedings and anaemia are included as undesirable effects in section 4.8 of the SmPC, with a frequency of 'common' for all DOACs. Furthermore, there are appropriate contraindications and warning statements in the product information addressing the risk for bleeding. There are also educational materials focusing on the risk of bleeding in place for all DOACs.

Regarding the results concerning objective 3 of the study it is suggested that a high percentage of patients received DOACs despite the presence of a contraindication. The PRAC was asked whether any further measures would be necessary to increase compliance of physicians with the SmPC. The PRAC considered that there appears to be an overestimation regarding the use in patients with contraindications, due to a possibly wider definition of contraindications (for example regarding the definition of renal insufficiency or use of artificial heart valves) in the study than those reflected as strict contraindications in the product information.

Overall, the PRAC considered it useful to get further clarity from the authors on key points in relation to definition of contraindications in the different study databases, before a final conclusion on the need for additional measures, and on the type of measures, can be reached.

3.2. Study authors input

The CHMP asked the study Authors for clarifications on the data on objective 3 and especially regarding the overall results are largely driven by a very high number of patients in the Bavarian

Claims database. In that respect clarifications on the definition of contraindications as applied in the study and their relation with the definitions in the SmPC were given.

The Authors explained also that there is no clear definition of hepatic diseases with coagulopathy and clinically relevant bleeding risk, and for assigning patients to Child Pugh B or C, not only lab values but also a clinical assessment of ascites and encephalopathy is needed. In addition, lab values are not documented in some databases as well (e.g. Bavarian Claims Database). Taking into account these limitations not allowing an unequivocal definition of codes for the respective medical conditions, to the authors used a broad definition of e.g. ICD codes.

A further clarification was given on whether the association between clinically significant bleeding and DOAC use (in Bavarian Claims: 12.6 – 16.0%) reflects DOAC administration despite of bleeding or whether e.g. concomitant reporting and prescription may reflect bleeding as an AE of DOAC use irrespectively of whether administration of the DOAC was continued or not. It was clarified that there is also no clear definition of a clinically significant bleeding. Since hospital admission data are not documented in the Bavarian CD, a sensitivity analysis could not be conducted regarding bleedings leading to hospital admission. Different surrogates for bleeding were considered (e.g. anaemia) but this could be attributed from other systemic diseases. The Authors made clear that where the database data was allowing for specific differentiations these were taken into account. However due to limitations of ICD codes, lab data available in the databases, and also related to one DOAC rather than the others, these codes may have led to an overestimation of patients with a contraindication.

Also the Authors clarified that in most databases, only drugs and diagnoses are coded but there is no clear assignment of a particular drug to a particular diagnosis in terms of an indication. Hence, due to lacking documentations of indications, a misclassification cannot be excluded since only diagnoses (and not indications) are available in most databases used for this analysis.

All codes used for the analyses have been agreed by the study participants in a consensus approach including scientists from the Netherland, Denmark, and Germany. Scientists from other countries/ databases reviewed the codes and appropriate codes for other coding systems were defined by the respective database representative. The Authors also clarified questions on biostatistical methodology and concomitant administrations of other anticoagulants, and interactions with of interactions with SSFIs/SNRIs.

Overall, the Authors clarified that the results were presented for those databases that showed a proportion of concomitant ACO drugs >10% (EGB, BIFAP, AOK NORDWEST, Bavarian databases). In the EGB database the median number of potential interacting anticoagulant drug dispensing per patient was 1.0 for VKA, heparin group and, other antithrombotic drugs. In the BIFAP database almost all concomitant anticoagulant drugs belong to the heparin group (99.8%) with a median number of dispensings per patient of 1.7. In the AOK NORDWEST database the median number of VKA dispensing per patient was higher, 2.0 (p25%-75%:1.0-4.0). Results for the Bavarian database were not available due to the quarterly structure of diagnoses and prescriptions.

These results showed that most patients had very few dispensing/prescriptions of concomitant anticoagulant drugs and suggest that they had been probably prescribed / dispensed for consecutive use in a transition period of change between anticoagulants. However, the results in the AOK NORDWEST database show a slightly higher dispensing per patient (Ibanez *et al*. 2019).

In conclusion, the Authors clarified that the analyses show that co-medication with drugs with the potential for interactions is frequent. In many instances such co-medication may not be avoidable since similar interactions are relevant for VKA also. In other cases co-medication is in line with current clinical knowledge at the period investigated. The analyses do not allow concluding on how many patients switching to other medicinal products (e.g. in case of SSRIs) would have been an option.

4. Overall Conclusions

Direct oral anticoagulants (DOACs) have been approved in EU since 2008. They are an alternative option from warfarin for blood clot treatment in appropriately selected patients. Available medications in this category include apixaban (Eliquis), dabigatran (Pradaxa), rivaroxaban (Xarelto) and edoxaban (Lixiana, Roteas). These substances carry a risk of bleeding which is contributable to their pharmacodynamic properties in preventing blood from clotting.

Key information on the benefit-risk balance of DOACs comes from the pivotal randomised prospective trials that were evaluated in the context of the authorisation for the indication in patients with NVAF. Adherence to contraindications, appropriate consideration of possible drug-drug interactions, dose adaption in special patient groups, off-label use or administration in patients may be different in clinical practice as compared to the controlled setting of a clinical trial. In order to get more insight into the use of DOACs in daily clinical practice, EMA has initiated a study in order to generate such information based on data representing a broad range of patients.

The study assessed the risk of bleeding in patients treated in NVAF of DOACs (apixaban, dabigatran, rivaroxaban) as compared to VKA, characterised the utilisation of the use of DOACs in the EU in the treatment of patients with NVAF, and finally assessed the compliance with recommendations in contraindications, warning and precautions and interactions with other medicinal products of each DOAC. Edoxaban (Lixiana, Roteas) was not included in this study as the study started before the marketing authorization of edoxaban was approved.

The EMA study had three sub-studies. A retrospective cohort study among incident NVAF patients to assess the risk of major bleeding associated with the use of DOACs and VKAs (objective 1) and two descriptive drug utilization studies (objectives 2 & 3). These studies were conducted in the following databases: Mondriaan, Danish Registries, Bavarian Claims database, AOK NORDWEST, BIFAP, SIDIAP, CPRD, EGB.

Overall, the new data obtained from registries, insurance and claim databases confirm the bleeding patterns of DOACs vs. VKA already observed in clinical trials. The data indicate the possibility of differences in the bleeding risk between DOACs in the treatment of NVAF and some of the results, e.g. the higher rate of gastrointestinal bleeding for dabigatran and rivaroxaban but not for apixaban compared to VKAs and the numerically lower rate of intracranial bleeding events with DOACs are consistent with what has been described in the pivotal studies. Irrespectively of possible differences in bleeding risk between the DOACs, non-inferiority in efficacy paralleled by a sufficiently established bleeding risk vs. VKA has been demonstrated in the pivotal trials for all DOACs assessed.

Due to the limitations of the study data and analyses it is difficult to draw final conclusions when comparing the three DOACs investigated and these data cannot support a change in the product information. There was consistency between the US based study and the European/Canadian data indicating an age dependent increase in HR of major extracranial bleeding / major bleeding events for dabigatran and rivaroxaban. However, currently available data are not sufficient to support changes in the recommended dosages for older patients. The MAHs of the DOACs are recommended to explore the generation of appropriate data and analyses in order to assess whether the benefit-risk balance in the elderly population could be improved by potentially refining the dosing recommendations taking into account factors like age, renal function, weight or additional risk factors for bleeding.

In terms of use of DOACs in the six countries, this study shows an increased incidence of use of DOACs related to NVAF in the study period. The differences among the countries could be explained by different national guidelines or prescription patterns. Further studies on several databases across

different countries using a standard protocol may help comparisons of use to support healthcare choices.

The data on the administration of DOACs in the presence of contraindications are not robust evidence indicating that contraindications are disregarded at a high rate. There are limitations such as broad definitions of contraindications, wide time window between events or lab values and the administration of DOACs and in some instances wrong allocations may have led to overestimations. This may have been to some degree unavoidable due to the nature of the data as the clinical judgment cannot be coded in such databases. Therefore, the results do not allow with sufficient confidence to conclude on a high rate of prescribers not taking contraindications into account. Similar considerations may also apply to adherence of prescribers to warning and precautions or concomitant prescriptions of potentially interacting drugs. Whereas the data indicate a relevant degree of co-administration of drugs with the potential for interactions, it was not possible to assess whether alternative treatment options would have been a viable option.

Having reviewed the information included already in the respective SmPC of the DOACs in light of the results of this study, the CHMP considered that no need of additional risk minimisation measures is necessary at this stage. The current wording in the SmPC of these products is considered adequate.

The CHMP took also into account the consultation with PRAC and the clarifications given by the Authors of the study.

Thus, the benefit-risk balance of all DOACs investigated in the EMA study (Eliquis, Pradaxa, Xarelto) in the treatment of patients with NVAF and in the other respectively approved indications remains positive.

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