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

Keywords
DOAC, NVAF, bleeding

Rationale and background

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

Research question and objectives

Objective 1. Assess the risk of major bleeding associated with use of DOACs when compared to other oral anticoagulants (OACs) in patients with non-valvular atrial fibrillation (NVAF) overall and in relevant clinical and demographical subgroups in a real-life setting.
Objective 2. Assess utilization of DOACs in the EU for treatment of NVAF, including the characterization of new DOAC users in NVAF patients.
Objective 3. Prescribers' compliance with recommendations included in sections 4.1, 4.3, 4.4, and 4.5 of the Summary of Product Characteristics of each DOAC.

Abstract objective 1 *updated on 9 September 2020 & reference to publication added*
Aims: The introduction of direct oral anticoagulants (DOACs) has broadened the treatment arsenal for nonvalvular atrial fibrillation, but observational studies on the benefit–risk balance of DOACs compared to vitamin K antagonists (VKAs) are needed. The aim of this study was to characterize the risk of major bleeding in DOAC users using longitudinal data collected from electronic health care databases from 4 different EU-countries analysed with a common study protocol.
Methods: A cohort study was conducted among new users (≥18 years) of DOACs or VKAs with nonvalvular atrial fibrillation using data from the UK, Spain, Germany and Denmark. The incidence of major bleeding events (overall and by bleeding site) was compared between current use of DOACs and VKAs. Cox regression analysis was used to calculate hazard ratios and 95% confidence intervals (CI) and adjust for confounders.
Results/Conclusion: Overall, 251 719 patients were included across the 4 study cohorts (mean age _75 years, % females between 41.3 and 54.3%), with overall hazard ratios of major bleeding risk for DOACs vs VKAs ranging between 0.84 (95% CI: 0.79–0.90) in Denmark and 1.13 (95% CI 1.02–1.25) in the UK. When stratifying according to the bleeding site, risk of gastrointestinal bleeding was increased by 48–

67% in dabigatran users and 30–50% for rivaroxaban users compared to VKA users in all data sources except Denmark. Compared to VKAs, apixaban was not associated with an increased risk of gastrointestinal bleeding in all data sources and seemed to be associated with the lowest risk of major bleeding events compared to dabigatran and rivaroxaban.

Souverein PC, HA van den Ham, Huerta C, et al. Comparing risk of major bleeding between users of different oral anticoagulants in patients with nonvalvular atrial fibrillation. Br J Clin Pharmacol. 2020;1–13. https://doi.org/10.1111/bcp.14450

Abstract objective 2 *(reference to publication added on 9 September 2020)*

Aim: To estimate the incidence of Direct Oral Anticoagulant Drug (DOACs) use in non-valvular atrial fibrillation (NVAF) and to describe user and treatment characteristics in eight European health databases (DNR, EGB Bavarian CD, AOK Nordwest, CPRD, Mondriaan, BIFAP and SIDIAP), and representing six European countries (Denmark, France, Germany, United Kingdom, The Netherlands and Spain).
Methods: Descriptive cohort study of new DOAC users with NVAF from January 2008 to December 2015. A common protocol approach was applied to each database. Annual period incidences and direct standardisation by age and sex were performed. An incidence percentage change in DOAC use was assessed from 2012-2013 (apixaban 2013-2014) to 2014-2015. Dose adjustment related to change in age and by renal function as well as concomitant use of potential interacting drugs were assessed.
Results: A total of 186,405 new DOAC users (≥18 years) were identified. The standardized incidence increased for all DOACs over the study period, with the highest increase for apixaban (554.5%) followed by rivaroxaban (80.7%). The highest incidence for all DOACs was found in Denmark and Germany, with lower values and slight differences among the remaining databases. The incidence of DOAC use increased for both genders in most databases and especially in those older than 75 years. Concomitant use of contraindicated drugs varied between 16.4% (SIDIAP), and 70.5% (EGB) and dose adjustment ranged from 4.6% in the Spanish (BIFAP) to 15.6% in the French (EGB) study population.
Conclusion: The overall incidence of new DOAC users increased during the study period, with the highest increase for apixaban. Cross national drug utilization studies with a standard protocol may help to compare drug use and identify sources of variation enabling health care decisions.

Ibáñez L, Sabaté M, Vidal X, et al.Incidence of direct oral anticoagulant use in patients withnonvalvular atrial fibrillation and characteristics of users in 6 European countries (2008–2015): A cross-national drug utiliza-tion study.Br J Clin Pharmacol. 2019;85:2524 2539. https://doi.org/10.1111/bcp.14071

Abstract objective 3 *(revised on 9 November 2020)*

Aim: Despite a tremendous increase of direct oral anticoagulants (DOACs) prescriptions in recent years, only few data is available analysing prescribers' adherence to Summary of Product Characteristics (SmPC). We aimed to assess adherence to registered indications, contraindications, special warnings/precautions, and potential drug-drug interactions for three DOAC compounds (dabigatran, rivaroxaban, and apixaban) in six databases of five European countries (The Netherlands, United Kingdom, Spain, Denmark, and Germany).
Methods: We included adult patients (≥18 years) initiating DOACs between 2008 and 2015. For several SmPC items, broad definitions were used due to ambiguous SmPC terms or lacking data in some databases.
Results: Within the study period, a DOAC was initiated in 407 576 patients (rivaroxaban: 240 985 (59.1%), dabigatran: 95 303 (23.4%), and apixaban: 71 288 (17.5%)). In 2015, non-valvular atrial fibrillation was the most common indication (>60% in most databases). For the whole study period, a

substantial variation between the databases was found regarding the proportion of patients with at least one contraindication (inter-database range [IDR]: 8.2%-55.7%), with at least one special warning/precaution (IDR: 35.8%-75.2%) and with at least one potential drug-drug interaction (IDR: 22.4%-54.1%). In 2015, the most frequent contraindication was "malignant neoplasm" (IDR: 0.7%-21.3%) whereas the most frequent special warning/precaution was "prescribing to the elderly" (≥75 years; IDR: 25.0%-66.4%). The most common single compound class interaction was "concomitant use of non-steroidal anti-inflammatory drugs" (IDR: 3.0%-25.3%).
Conclusion: Contraindications, special warnings/precautions, and potential drug-drug interactions were present in a relevant number of new DOAC users. Due to broad definitions used for some SmPC terms, overall proportions for contraindications are prone to overestimation. However, for unambiguous SmPC terms documented in the databases sufficiently, the respective estimates can be considered valid. Differences between databases might be related to "true" differences in prescription behaviour, but could also be partially due to differences in database characteristics.

Rottenkolber M, Schmiedl S et al. Prescribers' compliance with summary of product characteristics of dabigatran, rivaroxaban and apixaban-A European comparative drug utilization study. Basic Clin Pharmacol Toxicol. 2020 Oct 10. doi: 10.1111/bcpt.13517. Online ahead of print. https://onlinelibrary.wiley.com/doi/10.1111/bcpt.13517

Abstract Joint project *(added on 22 February 2019)*

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 a common protocol in Europe and Canada.

Background: Several observational studies have been carried out before to investigate the real world benefit-risk balance of direct oral anticoagulants (DOACs) compared to vitamin K antagonists (VKAs) in patients with non-valvular atrial fibrillation (NVAF). However, information on the differences in performance within the class of DOACs and for different subgroups of patients is still inconclusive due to the lack of statistical power.
Objective: The aim of this study was to establish the risk of major bleeding in DOAC users (overall and by class) versus VKA users, using healthcare databases from four European countries and six provinces in Canada.
Methods: All research groups used the same protocol to perform a retrospective cohort study. First-users of VKAs or DOACs with a diagnosis of NVAF were included. The main outcome of interest was major bleeding and secondary outcomes included gastrointestinal (GI) bleeding and intracranial haemorrhage (ICH). Incidence rates of events per 1,000 person years were calculated. Hazard ratios (HRs) and 95% confidence intervals (95% CI) were estimated using a Cox proportional hazard regression model. VKA or DOAC exposure and confounders were measured and analysed in a time dependant way. Risk estimates were pooled using meta-analysis techniques with a random effect model.
Results: In total, 421,523 patients were included in the period of 2008-2015 of which 37.2% used a DOAC and 62.8% used a VKA. The risk of major bleeding for the group of DOACs compared to VKAs showed a pooled HR of 0.94 (95% CI: 0.87-1.02). Rivaroxaban showed a modestly increased risk (HR 1.11, 95% CI 1.06-1.16). Apixaban and dabigatran showed a decreased risk of respectively HR 0.76 (95% CI 0.69-0.84) and HR 0.85 (95% CI 0.75-0.96) compared to VKAs. The observed risk on GI bleeding was

elevated around 20% for dabigatran and rivaroxaban and lowered around 30% for apixaban. The observed risk on ICH was for all DOACs lower than for VKAs.

Conclusion: This study confirms that the risk of major bleeding of DOACs compared to VKAs is not increased when combining all DOACs. However, we observed a modest higher risk of major bleeding for rivaroxaban, whereas for apixaban and dabigatran lower risks of major bleeding were observed compared to VKAs.

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