

EU PE&PV Research Network

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Principal investigator: Dr. Helga Gardarsdottir, Universiteit Utrecht, h.gardarsdottir@uu.nl

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

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

Methods: A cohort study was conducted among new users (≥ 18 years) of DOACs or OACs with non-valvular atrial fibrillation using electronic health care data from the United Kingdom (UK), Spain, Germany and Denmark. The incidence of major bleeding events (both overall and by type) was compared between periods of current use of DOACs. Cox regression analysis was used to calculate hazard ratios (HR) and 95% confidence intervals (CI) and adjust for confounders.

Results: In total 251,719 patients were included in the four study cohorts (mean age ~ 75 years, % females between 41.3 and 54.3%), with overall hazard ratios of major bleeding risk for DOACs versus OACs 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 type of bleeding event, the risk of gastrointestinal bleeding was statistically significant increased by 48-67% in dabigatran users and 30-50% for rivaroxaban users when compared to OAC users in all data sources except the Danish database. Risk of gastrointestinal bleeding was statistically significant decreased by 20% (Germany, Denmark) or not significantly different (Spain, UK) in apixaban users when compared to OAC. The incidence of intracranial bleeding was low in all four data sources and point estimates were below 1 in all, except for a statistically significant increased risk for rivaroxaban in the UK (adjusted HR 2.37, 95% CI 1.19-4.71).

Conclusion: Compared to OACs, apixaban was not associated with an increased risk of GI bleeding in all data sources and seemed to be associated with the lowest risk of major bleeding events compared to dabigatran and rivaroxaban.

Abstract objective 2

Aim: To estimate the incidence of Direct Oral Anticoagulant Drug (DOACs) use in non-valvular atrial fibrillation (NVAf) and to describe user and treatment characteristics in eight European health databases (DNR, EGB Bavarian CD, AOK Northwest, 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. A incidence percentage change in DOAC use was assessed from 2012-2013 (apixaban 2013-2014) to 2014-2015. Dose adjustment related to change in age and by renal function as well as concomitant use of potential interacting drugs were assessed.

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

Conclusion: The overall incidence of new DOAC users increased 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.

Abstract objective 3

Aim: To analyse prescribers' compliance with recommendations included in sections 4.1 (indications [Ind], 4.3 contraindications [CI], 4.4 (special warnings and precautions [SW/P], and 4.5 (potential drug-drug interactions [pDDIs]) of the Summary of Product Characteristics of each DOAC.

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

Results: 407,576 patients initiated DOACs during the study period (rivaroxaban: 240,985 [59.1%], dabigatran: 95,303 [23.4%], apixaban: 71,288 [17.5%]). In 2015, non-valvular atrial fibrillation was the most common Ind registered, representing more than 60% of incident DOAC users in most databases. A substantial variety was found regarding the proportion of patients with at least one CI (inter-database range: 8.2% to 55.7%) between the databases, with highest values for dabigatran in most databases. The most common CI was malignant neoplasms, which was registered for 1.5% (Spain) to 9.0% (The Netherlands) of the DOAC users and in 20% of the German DOAC users. Patients with a SW/Pc were present in a higher proportion of incident DOAC users (inter-database range: 35.8% – 75.2%) reaching highest values in incident apixaban users. The most common SW/Pc involved prescribing to the elderly (75 years or older), which represented about 30% (The Netherlands) to 60% (Germany, Spain, UK) of the DOAC users. Inter-database range for proportion of patients with potential DDIs was 22.4% to 54.1% reaching highest values in dabigatran initiators. The most common pDDI was use of nonsteroidal anti-inflammatory or acetylsalicylic acid type of drugs, which was co-prescribed for 8-20% of the DOAC users.

Conclusion: CIs, SW/Ps, and potential DDIs were present in a substantial number of new DOAC

users. Differences found between the databases might be related to 'true' differences in prescription behaviour but could partially relate to discrepancies in database characteristics.

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