SAFETY OF NON-VITAMIN K ANTAGONIST ORAL ANTICOAGULANTS AND WARFARIN: ANALYSIS OF EMA PHARMACOVIGILANCE DATABASE REPORTS

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Introduction: Until the introduction of the non-vitamin K antagonist oral anticoagulation agents (NOACs), vitamin K antagonists (VKAs) were the only available oral anticoagulants (OACs). The primary safety concern with OACs is the risk of bleeding; in particular intracranial (IC) bleeding is the most feared adverse drug reaction (ADR) due to irreversible sequelae and high rate of mortality. Gastrointestinal (GI) bleeding is more common but less often fatal. Clinical trials comparing efficacy and safety of NOACs with warfarin reported a lower mortality rate and a reduced incidence of bleeding with NOACs. However, these studies do not allow final conclusions about safety, being designed to evaluate above all efficacy. Several pharmaco-epidemiological methods are widely used for this purpose, but require specific organization, a lot of time and money and the use of databases which are not often built to assess ADRs. Therefore, spontaneous reporting remains the most efficient way to collect safety data despite limitations (under-reporting, selective reporting, lack of denominator). Aim of this study was to expand knowledge about safety profile of OACs and to find any specific safety issues coming from spontaneous reporting of ADRs.

Methods: We obtained all suspected ADRs related to the use of NOACs and warfarin available from EudraVigilance. EudraVigilance database collects suspected ADRs submitted by European national regulatory authorities or directly by marketing-authorization holders (MAHs) for ADRs occurring outside EU. Each individual case safety report (ICSR) is composed of at least one report, which might be integrated by follow-up.

Results: Data updated on march 312019show 235331ICSRs associated with the use of NOACs and warfarin, almost equally distributed between female and male (45.5% and 46.7% respectively), including 101577reports related to rivaroxaban (43.2%), followed by dabigatran (48341, 20.5%), warfarin (41775, 17.8%), apixaban (39741, 16.9%) and edoxaban (3897, 1.7%). Elderly were the most represented patients, in particular in the edoxaban group for which almost 52% of ADRs were reported in patients over 65and almost 20% in patients 85and older. More than 90% of suspected ADRs were serious, in particular for rivaroxaban (95.5%); on the contrary, edoxaban showed the lowest rate of serious ADRs (71%). ADRs with a fatal outcome were overall 35221(8.5%), with the highest percentage reported with dabigatran (12.4%). GI and central nervous system (CNS) disorders were the most represented categories, accounting for 40.8% of fatal ADRs. It is noteworthy that the drug with the highest percentage of fatal GI disorders was dabigatran (10.4%), whereas the one with the highest percentage of fatal SNC disorders was warfarin (26.1%) followed by rivaroxaban (20.4%).

Discussion and conclusions: Data recently published by the European Medicines Agency (EMA) coming from a post-authorization study performed in six EU countries highlighted different safety profiles among OACs in a real-world setting. In particular, the risk of GI bleeding resulted statistically significant increased with dabigatran and rivaroxaban and decreased or not significantly different with apixaban compared to OACs. The incidence of IC bleeding was low, except for a statistically significant increased risk for rivaroxaban. Therefore, compared to OACs, apixaban seemed to be associated with the lowest risk of major bleeding events compared to dabigatran and rivaroxaban. Edoxaban was not included in the analysis. As expected, data collected from Eudravigilance show that GI and CNS disorders were the most represented ADRs. We can assume that the differences in the number of ICSRs and in the percentage of elderly between drugs could be related to their specific characteristics and the peculiar drug use. Further analysis are needed to investigate the higher rate of fatal GI ADRs with dabigatran and fatal SNC disorders with warfarin and rivaroxaban.