Drug-utilization of new oral anticoagulants and Vitamin K antagonists in atrial fibrillation: a retrospective study within the REGULUS project.

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Introduction: Atrial Fibrillation (AF) is the most frequent cardiac arrhythmia, with a prevalence in the general population between 0.1 % (patients ≤ 55 years) and 9.0% (patients ≥ 88 years), which could increase the risk of stroke and other thromboembolic events. The only pharmacological treatment able to significantly reduce the risks related to this pathology is the therapy with oral anticoagulants (OACs). In particular, vitamin K antagonists (VKA), such as warfarin and acenocumarol, have been the only oral anticoagulant therapy available for decades. The limitations of VKA, like low therapeutic index or the extreme dose variation for achieving appropriate therapeutic effect, led to the development of a new class of drugs, the new oral anticoagulants (NOAC), which include direct thrombin inhibitors (dabigatran) and direct Xa inhibitors (rivaroxaban, apixaban, edoxaban).

This study, which is part of the REGOLUS project (Observational study on the Risk of intERactions between anticoaGULant drUgS and self-prescribed medications in patients taking oral anticoagulants), aimed to assess the drug-utilization of NOAC and VKA, and to compare the occurrence of bleeding among different drugs.

Methods: This retrospective study was conducted on the administrative databases of the metropolitan area of Florence. All resident patients in the metropolitan area of Florence with at least one prescription of oral anticoagulant between January 1st 2015 and December 31st 2015 were included. We considered all OACs delivered in the years 2015, The bleeding events occurred in the course of TAO were evaluated from emergency department admission (PS) databases and from hospital discharge records (SDO). Current OACs exposition at time of bleeding event was estimated considering the total number of defined daily doses (DDD) of the last drug delivery, on the basis of the AIC code, the number of packs and the DDD provided by the WHO. Patients with a prescription of both VKA and NOACs during 2015 were considered as switchers.

Results: 12.742 patients were treated with OACs. Most part of them were female (6,400; 50.2%) and the most represented age class was > 84 years (27%). Considering OAC treatment, 9,341 were treated only with VKA (VKA group), 2,892 used only NOACs (NOAC group), and 479 switched from a VKA to a NOAC or viceversa during the year (switcher group).

Within the AVK group, 9,215 (98.3%) subjects used warfarin and only 167 (1.8%) used acenocumarol. In NOAC group, 1190 (41.1%) used rivaroxaban, 913 (31.6%) dabigatran, and 842 (29.1%) apixaban. edoxaban was not considered, since it was not available in 2015.

Furthermore, 20.3% in VKA group, 30.4% in group NOAC, and 26.7% in the switcher group showed a concomitant treatment with low molecular weight heparins (EBPM) and/or antiplatelet drugs.

Overall, 599 patients experience hemorrhagic events (4.70% of the examined population). In particular, subjects diagnosed with haemorrhage were 4.92% in the VKA group, 4,29% in the NOAC group, and 2.92% in the switcher group. Comparing the occurrence of haemorrhage among the different active principles, no statistically significant difference emerged between warfarin and rivaroxaban (4.88 vs 4.62%, p>0.05), nor between warfarin vs apixaban (4.88 vs 4.51%, p>0.05); on the other hand, dabigatran was associated with a significantly lower occurrence of haemorrhage compared to warfarin (4.88 vs 3.39%, p=0.04).

Focusing on the different types of haemorrhage, gastrointestinal bleeding was the most frequent (occurring in 0.94% vs 0,93% among VKA and NOAC patients, p>0.05), followed by ocular bleeding (0.97% vs 0.86%, p>0.05). Occurrence of epistaxis was significantly more frequent in the VKA group (0.80% vs 0.28%, p=0.003), whereas no statistically significant difference emerged in the occurrence of cerebral haemorrhage (0.32% vs 024%, p>0.05).

Conclusion: In our study the most commonly used drug classes was VKA, in particular warfarin. In Italy, the prescription of NOAC is limited by strict criteria of eligibility to treatment. Among NOACs, apixaban is the less used, maybe because at that time it was the last drug which entered the Italian market. For dabigatran, the first NOAC introduced, the high number of bleeding events reported in literature could be the reason of his low prescription. On the contrary, rivaroxaban is the most prescribed NOAC; this drug is administered as a single daily dose and it may be preferable in older patients at higher risk of poor treatment adherence. Furthermore, rivaroxaban was the first approved drug for prevention of atherothrombotic events in patients after acute coronary syndrome (ACS). Considering hemorrhage events, no significant variation emerged between AVK and NOACs; however, warfarin was associated with a significant higher occurrence of hemorrhage compared to dabigatran, therefore confirming literature studies on its lower safety.