HOW MUCH BENEFITS AND RISKS OF NEW ORAL ANTICOAGULANTS AS OBSERVED IN PIVOTAL RANDOMIZED CLINICAL TRIALS CAN BE GENERALIZED TO A REAL-WORLD SETTING FROM SOUTHERN ITALY?

Ylenia Ingrasciotta[1], Anna Mancuso[1], Andrea Fontana[2], Valentina Ientile[3], Maurizio Pastorello[4], Gianluca Trifirò[1]

[1]Department of Biomedical and Dental Sciences and Morpho-functional Imaging, University of Messina, Messina - Italy, [2]Unit of biostatistics, Fondazione Casa Sollievo della Sofferenza, San Giovanni Rotondo, Foggia - Italy, [3]Unit of Clinical Pharmacology, A.O.U. Policlinico "G. Martino", Messina - Italy, [4]Department of Pharmacy, Palermo Local Health Unit, Palermo - Italy

Introduction: Atrial fibrillation (AF) is the most commonly sustained arrhythmia and it is associated with an increased risk of ischemic stroke. The non-inferiority of new oral anticoagulants (NOACs) compared to warfarin was demonstrated by pivotal randomized controlled trials (RCTs). However, patients enrolled into RCTs may differ substantially from those that are treated in real-world (RW) setting, which may ultimately result in different benefit-risk profile. The study was aimed at comparing benefits and risks of NOACs as observed in patients of pivotal RCTs vs. those being treated in real world setting of Palermo Local Health Unit (LHU).

Material and methods: Fully anonymized data were extracted from the administrative database of Palermo LHU, covering a total population of approximately 1.3million inhabitants from 2012to 2017. From Palermo LHU RW population, all incident NOAC users (no dispensing within one year prior) with atrial fibrillation were identified and grouped based on the dispensed NOAC (low/high dose dabigatran, any dose of apixaban or rivaroxaban), in line with pivotal trials. The enrolment criteria of patients in NOAC pivotal RCTs were extracted from the original publications and applied to the RW population. Individual-level RW patient data were propensity score matched 1:1on simulated RCT patients' data by age, sex and CHADS2score (Parsons' greedy 5to 1digits match algorithm). RCT pseudo-data were generated and matched 1,000 times on the basis of RCTs descriptive statistics. At each iteration, both efficacy (e.g. stroke, myocardial infarction) and safety outcomes (e.g. major bleeding, including intracranial/gastrointestinal bleeding) were assessed within the matched population for RW patients compared to the RCT population.

Results: Among 6,570 incident RW NOAC users during the study years, 794(12.1%) patients started with low dose dabigatran, 635(9.7%) with high dose dabigatran, 3,028(46.1%) with rivaroxaban and 2,113(32.1%) with apixaban. In general, in RW setting, female-male ratio was in favor of females (1.1) and patients were older (mean age: 76± 8years) than RCT population (71± 9years); 37% of these were >80 years old. Of incident RW users, 545(68.6%), 458(72.1%), 1,432(47.3%) and 1,005(47.6%) users of low and high dose of dabigatran, rivaroxaban and apixaban, respectively, had overlapping characteristics (i.e. age, sex and CHADS2score distribution) with pivotal RCTs population. In the matched RW population, patients treated with high dose dabigatran and rivaroxaban were associated to a lower risk of ischemic stroke or myocardial infarction, respectively, as compared to the RCT population (high dose dabigatran: 0.2% vs. 1.8% and 1.0% vs. 1.5%; rivaroxaban: 1.6% vs. 2.1% and 0.9% vs. 1.4%). On the contrary, low dose dabigatran users from RW population were associated with higher risk of myocardial infarction than RCT population (1.8% vs. 1.4%). As found in RCTs, also in the RW population a greater proportion of gastrointestinal bleeding events was observed as compared to intracranial bleeding. However, gastrointestinal events in RW setting were less common than RCT gastrointestinal events.

Conclusions: Patients treated with NOAC in RW setting are substantially different from those included in pivotal trials (e.g. much higher proportion of very old patients and females). Heterogeneity of efficacy and safety outcomes in the RW population was observed. Observational studies using healthcare databases are important tools to rapidly explore the generalizability of findings from pivotal RCTs to real world setting.