Risk of bone fractures among users of oral anticoagulants: an administrative database cohort study

1)Lucenteforte E. 2)Bettiol A. 3)Lombardi N. 4)Mugelli A. 5)Vannacci A.

University of Florence

Background Although several studies have reported the possible association between warfarin and an increased risk of osteoporotic fracture, only one population-based cohort study was conducted to compare the risk of dabigatran and warfarin, showing a lower risk for dabigatran compared with warfarin, and no study was conducted on direct Xa inhibitors. Thus, the aim of the present study was to investigate the occurrence of osteoporotic fracture with warfarin, dabigatran and direct Xa inhibitors.

Methods A cohort study was performed within the frame of REGULUS (Observational study on the Risk of intERactions between anticoaGUlant drUgS and self-prescribed medications in patients taking oral anticoagulants) on administrative databases of the Florence Metropolitan Area. All patients treated with oral anticoagulants (OACs) in the year 2015 were included. The first date of OACs prescription in the year was considered as the index date. Since the index date, all patients were followed until the occurrence of fracture, death, change of OACs treatment, or end of data availability (December 31st, 2015). Occurrence of fracture during follow-up was evaluated both from hospital discharge records and emergency departments admissions, considering all records with a diagnosis of hip or vertebral fracture in primary or secondary diagnosis fields (ICD9-CM code 820.x or 805.x). For each treatment, the rate of fracture/100 person years was estimated. Moreover, the Hazard Ratios (HRs) and corresponding 95% Confidence Intervals (CIs) of fracture was calculated for patients exposed to direct OACs (DOACs; dabigatran or direct Xa inhibitors) compared to warfarin users, using a multivariate cox models adjusted for gender, age and pattern of OACs use (incident or non-incident).

Findings Among 16,850 patients treated with OACs, 77.7% used warfarin, 14.5% used direct Xa inhibitos, and 7.6% used dabigatran. Overall, the majority of subjects were men (51.09%), aged 75 or more (67.22), and non-incident users (76.71%). Distribution of gender, age and pattern of use significantly differed among OACs. For OAC users overall, rate of fractures per 100 person years was 1.58, 95% CI: 1.37 – 1.81. Comparing DOACs with warfarin, no significant difference emerged in their association with fractures (HR of 1.04 [0.68 – 1.59] for direct Xa inhibitors; 0.96 [0.56 – 1.63] for dabigatran). Among warfarin users, the occurrence of fractures was significantly higher among female subjects and patients aged ≥75 years; on the other hand, among users of DOACs, occurrence of fractures did not significantly differ among genders or age classes. In all OACs groups, occurrence of fractures was comparable among different strata of pattern of use.

Interpretation OACs is an inevitable treatment, and the choice of whether using warfarin or one of DOACs is still debated. Recently, it has been proposed that osteoporotic fractures could be a crucial factor in the choice between dabigatran or warfarin, since an increased risk in the latter compared to the former was reported. Data from our study do not confirm differences in risk, and

provided further evidence on the lack of such effect for other OACs (i.e., direct Xa inhibitors). According to these results, drug choice should not be based on the aim of avoiding this adverse event; nevertheless, female and elderly subjects appear to have a higher rate of fractures, particularly when treated with warfarin.