

## CUMULATIVE EXPOSURE TO BISPHOSPHONATES AND INCIDENCE OF CARDIOVASCULAR AND CEREBROVASCULAR EVENTS: A POPULATION-BASED COHORT STUDY

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Cardiovascular disease (CVD) and osteoporosis are common age-related conditions; they are both associated with significant morbidity and mortality, and their socioeconomic and health care burden is huge. Recently, an increasing number of biological and epidemiological observations has provided strong support for a link between these two pathological conditions. Although bisphosphonates have been suggested to protect against atherosclerotic cardiovascular (CV) events, due to their ability to reduce calcification in arterial walls, evidence is still conflicting. Thus, we aimed at investigate the occurrence of CV events in patients treated with bisphosphonates.

We carried out a retrospective cohort study selecting from administrative databases of Lombardy (Italy) patients aged >40 years, with a first prescription of bisphosphonates between 2003/01/01 and 2006/12/31. Subjects were followed until the first CV event, death or migration, or end of database coverage (31/12/2012), whichever occurred first. Exposure to bisphosphonates was characterized based on cumulative doses (proportion of days covered, PDC). A Cox proportional hazards model was fitted to estimate the association between time-varying cumulative exposure to bisphosphonates and CV events (hazard ratios [HRs] and 95% confidence intervals). The model was adjusted for both time-dependent and fixed variables, including age, sex, comorbidities (such as atrial fibrillation, fractures, and Charlson Comorbidity Index) at baseline, and cardiovascular concomitant treatments.

Among 82,704 new bisphosphonates users (females 87.0%, mean age  $70.7 \pm 10.6$  years), 16.1% had a CV event during the follow-up. Alendronic acid was the most commonly prescribed bisphosphonate (67.1%), followed by risedronic acid (22.1%). Compared with individuals with an exposure <40% of follow-up, those exposed for 41-80% or more than 80% showed HRs of 0.95[0.91-0.99] and 0.76[0.71-0.81], respectively. A PDC>80% was associated with a remarkable reduction of incidence for both cardiovascular and cerebrovascular events (HRs 0.75[0.68-0.83] and 0.76[0.70-0.83], respectively). In the analysis stratified by sex, we confirmed the reduction of cardiovascular risk associated with a cumulative exposure to bisphosphonates among women (up to 25% risk reduction with PDC>80%), but we highlighted also a significant decrease of about 27% in cardiovascular risk among men with PDC>80%. After stratification by age classes, we found a significant risk reduction with PDC>80% in all age groups, even more pronounced in patients aged 41-60 years (HR 0.51[0.33-0.77]). The sensitivity analysis conducted within the first three years of follow-up from the beginning of the bisphosphonate therapy confirmed the protective effect observed in the main analysis: the risk reduction was significant for all classes of PDC, but even more remarkable for PDC>80% (HR 0.71[0.64-0.78]). Finally, consistent results were found using different cut off of PDC (PDC<25%, from 25% to 49%, from 50% to 74%, and  $\geq 75\%$ ).

Our study demonstrated that cumulative exposure to bisphosphonates results in a significant reduction of cardiovascular events. We believe that it is important to consider bisphosphonates, and a strict adherence to this treatment, as having a potential effect also in the prevention of CV events. Even in light of the robustness of these data, additional studies are needed to confirm the protective CV effect of bisphosphonate therapy and to specifically address the mechanism by which bisphosphonates use could influence CVD.