USE OF BISPHOSPHONATES AND RISK OF CARDIOVASCULAR EVENTS: A POPULATION-BASED RETROSPECTIVE COHORT STUDY

F. Galimberti¹, M. Casula¹, E. Olmastroni¹, E. Tragni¹, G. Corrao², L. Scotti², A.L. Catapano^{1,3}

¹ Epidemiology and Preventive Pharmacology Service (SEFAP), Department of Pharmacological and Biomolecular Sciences, University of Milan, Milan, Italy
² Department of Statistics and Quantitative Methods, Division of Biostatistics, Epidemiology and Public Health, University of Milano-Bicocca, Milan, Italy
³ IRCCS MultiMedica Hospital, Sesto S. Giovanni (Milan), Italy

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BACKGROUND and AIM

Bisphosphonates are widely used in clinical practice to prevent and treat osteoporosis, as they are able to reduce the excessive osteoclast-mediated bone resorption. Emerging evidence indicates that **vascular calcification** is an actively regulated process that shares several biological mechanisms with **bone mineralization**. Therefore it is conceivable that bisphosphonates could interfere in the arterial calcification process and might be able to inhibit atherosclerosis and vascular calcification, which means to be able to reduce the risk of cardiovascular disease.

Aim of the present study was thus to investigate the occurrence of cardio-cerebrovascular (CV) events in patients treated with bisphosphonates in a **population-based real-world retrospective cohort study**.

METHODS

Data were retrieved from the administrative healthcare utilization databases of the Italian **Lombardy region**, and appropriately encrypted: (1) demographic data, (2) outpatient drug prescription data, (3) database on diagnosis at discharge from hospitals.

All beneficiaries of the National Health System, resident in Lombardy of both sex with age >40 years who have received a first prescription (index date) for any bisphosphonates (ATC M05BA) between 2003 and 2006, were selected and followed until the first CV event, death or migration, or the end of observational period (2012/12/31).

Exposure to bisphosphonates was evaluated as “proportion of days covered” (PDC).

$$PDC = \frac{\text{cumulative number of days with medication available (DDD)}}{\text{number of days of follow-up}}$$

The **adherence** was classified as low ($\leq 40\%$), intermediate (from 41% to 80%), and high ($>80\%$) based on PDC values.

The association between **time-varying cumulative exposure to bisphosphonates** and hospitalization for any CV events was assessed using multivariate **Cox proportional hazard model** (adjusted hazard ratios [aHR] and 95% confidence intervals).

The model was adjusted for age, sex, comorbidities (atrial fibrillation, fractures, and Charlson Comorbidity Index), and concomitant CV treatments (antidiabetic, antihypertensive, lipid-lowering, and antithrombotic medications).

RESULTS

A total of **82,704 subjects** (mean age 70.7 years; female 87.0%) were enrolled in the study. Within this cohort, we identified **13,337 (16.1%)** individuals with a hospitalization for ischemic heart disease (N 6508) and/or non-haemorrhagic cerebrovascular disease (N 7298), occurred on average (SD) 3.5 (2.3) years after the index date (**Table 1**).

In the multivariate adjusted analysis, subjects exposed for a period ranged between 41-80%, or $>80\%$, showed **significantly reduced risk** of CV events, compared with individuals with an exposure $\leq 40\%$ (**Table 2**).

Table 1		TOTAL (N= 82,704)
Female sex, N (%)		71,936 (87.0)
Age, mean (SD)		70.7 (10.6)
Age, N (%)	41-60 years	14,483 (17.5)
	61-80 years	53,258 (64.4)
	>80 years	14,963 (18.1)
Bisphosphonates at index date, N (%)	Etidronic acid	217 (0.26)
	Clodronic acid	1114 (1.35)
	Alendronic acid	55,480 (67.08)
	Ibandronic acid	1162 (1.41)
	Risedronic acid	18,250 (22.07)
	Neridronic acid	6481 (7.84)
Charlson score, N (%)	0	72,113 (87.2)
	1	6846 (8.3)
	≥ 2	3749 (4.5)
Previous use of glucocorticoids, N (%)		19,835 (24.0)
Previous use of other anti-osteoporotic drugs, N (%)		216 (0.3)
Use of lipid-lowering drugs, N (%)		29,181 (35.3)
Use of antidiabetic drugs, N (%)		11,331 (13.7)
Use of antihypertensive drugs, N (%)		67,457 (81.6)
Use of antithrombotic drugs, N (%)		55,259 (66.8)
Hospitalization for fractures, N (%)		6676 (8.1)
Hospitalization for atrial fibrillation, N (%)		9318 (11.3)
CV Events, N (%)	Cardiovascular event	6508 (7.9)
	Cerebrovascular event	7298 (8.8)

Table 2		aHR	95% CI
Exposure	PDC $\leq 40\%$	1	Ref
	40%<PDC $\leq 80\%$	0.950	0.905-0.998
	PDC>80%	0.754	0.706-0.805
Sex	Female	1	Ref
	Male	0.645	0.607-0.684
Age		1.080	1.077-1.083
Fractures		1.232	1.146-1.323
Atrial fibrillation		1.639	1.539-1.745
Drugs for diabetes		1.001	1.001-1.002
Drugs for hypertension		1.001	1.000-1.001
Drugs for hypercholesterolemia		1.002	1.001-1.002
Antithrombotic drugs		1.005	1.004-1.005
Use of other drugs (vs. no use)	Glucocorticoids drugs	1.099	1.045-1.156
	Other bone drugs	0.906	0.577-1.421
Charlson comorbidity index	0	1	Ref
	1	1.423	1.330-1.522
	≥ 2	1.833	1.689-1.989

In the analyses performed separately considering cardiovascular and cerebrovascular events as outcomes, a **remarkable reduction** of the incidence for both outcomes was observed in subjects with an exposure higher than 80%. The decrease of the CV risk was also confirmed in all the strata by potential influencing factors, such as sex, age, or follow-up duration (**Figure 1**).

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Finally, as sensitivity analysis, the primary analysis was also performed using different windows of adherence (PDC<25%, from 25% to 49%, from 50% to 74%, and $\geq 75\%$) in order to avoid the arbitrary nature of PDC categorization. Results (**Table 3**) were consistent with the main findings.

Table 3		aHR	95% CI
Exposure	PDC<25%	1	Ref
	25% $\leq$ PDC<50%	0.941	0.885-1.001
	50% $\leq$ PDC<75%	0.927	0.873-0.984
	PDC $\geq 75\%$	0.756	0.709-0.805

CONCLUSIONS

These results suggest a strong reduction of cardiovascular events with increasing number of days covered by bisphosphonate treatment. 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. 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 cardiovascular disease.

Corresponding author:

Federica Galimberti, PharmD
SEFAP - Epidemiology and Preventive Pharmacology Service - Department of Pharmacological and Biomolecular Sciences, University of Milan
federica.galimberti@unimi.it