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ORIGINAL ARTICLE

Risk of acute myocardial infarction among new users of bisphosphonates: a nested case–control study

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Abstract

Objective To test the hypothesis that bisphosphonates reduce AMI risk among new users and to assess whether the effect depends on the duration of treatment.

Methods Case–control study nested in a primary cohort composed of patients aged 40 to 99 years, with at least 1-year registry in the BIFAP database throughout the study period 2002–2015. Out of this cohort, incident AMI cases were identified and five controls per case were randomly selected, matched by exact age, sex, and index date. The association of AMI with current, recent and past use of bisphosphonates was assessed by computing adjusted odds ratios (AOR) and their corresponding 95% confidence interval (CI) through an unconditional logistic regression. Only initiators of bisphosphonates were considered.

Results A total of 23,590 cases of AMI and 117,612 controls were included. The mean age was 66.8 (SD 13.4) years, and 72.52% was male, in both groups. About 276 (1.17%) cases and 1458 (1.24%) controls were current users of bisphosphonates yielding an AOR of 0.98 (95% CI 0.854–1.14). Recent and past use were not associated with a reduced risk, either, nor was it found a reduction with treatment duration (AOR less than 1 year = 0.92; 95% CI 0.73–1.15; AOR more than 1 year = 1.03; 95% CI 0.86–1.23). Stratified analysis by age, sex and background cardiovascular risk did not show an effect modification by these variables.

Conclusion The results do not support a cardioprotective effect of bisphosphonates regardless of the duration of treatment, age, sex or background cardiovascular risk. However, a small protective effect could have been masked if patients with osteoporosis have had a background higher risk of AMI.

Keywords Acute myocardial infarction · Antiresorptive agents, osteoporosis · Bisphosphonates

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Introduction

Osteoporosis and cardiovascular diseases are epidemiologically associated. Subjects with osteoporosis have a higher vascular calcification load and progressive atherosclerosis when compared with individuals with normal bone mass [1–4]. Each decrease of a standard deviation in bone mineral density (BMD) is associated with an increase between 1.3 and 2.3 times of CV mortality risk [5–8]. In fact, emerging evidence shows that vascular calcification is an actively regulated process that shares some biologic mechanisms with bone mineralization [9–12]. Both in vitro and in vivo studies have shown vascular cells' predisposition to suffer osteoblast differentiation [13, 14]. Similarly, cells similar to osteoclasts have been found in calcified human atherosclerotic lesions [15]. Various bone matrix proteins and other factors have been reported to regulate vascular calcification [9, 12].

Understanding biologic similarities between vascular calcification and bone mineralization has led to the notion that bisphosphonates can have an influence on vascular calcification. Evidence suggests that in addition to inhibiting bone resorption, bisphosphonates can inhibit atherosclerosis and vascular calcification. In several small-scaled clinical trials, etidronate modestly improved some of the atherosclerosis intermediate objectives, such as carotid intima-media thickness, coronary artery calcium score [16] and aortic calcification [17]. Other studies found a lower risk of AMI or stroke among bisphosphonate users in comparison to non-users [18–20]. On the other hand, several observational studies found an increase in AMI risk among patients with fractures treated with bisphosphonates [21]. Furthermore, in recent years, some meta-analyses reported a decrease of calcification in artery wall, while they did not found a decrease of cardiovascular events [22, 23]. Although this epidemiological evidence suggests that bisphosphonates can protect from CV events [24, 25], research conducted to date includes prevalent users, and therefore, a bias overestimating protection cannot be excluded [26]. In order to avoid this bias, a study should be carried out only with new users (initiators) of bisphosphonates [26]. Moreover, a possible increase of atrial fibrillation associated with bisphosphonates [25] can counteract potential benefits.

Currently, there are no randomized clinical trials with bisphosphonates designed to study cardiovascular events. For this reason, analytical observational studies with strategies limiting introduction of bias (new users), but at the same time allowing to reflect real-world evidence, are warranted. This study was carried out to test the hypothesis of whether bisphosphonates can have a protective effect against AMI.

Patients and methods

Data source and study design

A case–control study nested in a cohort selected from BIFAP (Spanish primary care database, see Appendix A for more information) [27] from 1 January 2002 to 31 December 2015. The study cohort consisted of patients 40 to 99 years old, registered by their primary care physician (PCP) for at least 1 year and with no cancer or AMI history. The first day patients that met all criteria mentioned above were considered the "starting date." The study cohort consisted of 3,764,470 subjects. The subjects were then followed-up until one of the following events occurred: AMI incident, 100 years old, cancer diagnosis, death or end of the study period.

Case and control selection

Incident AMI cases were initially searched for by entering codes and text in diagnostic record fields and were validated by manual review of clinical records (see Appendix B for more information). The date of the first record of AMI was considered as the "index date." Five controls matched with cases by exact age, sex and index date were randomly selected from the underlying cohort.

New user design

Analysis was performed for new users of bisphosphonates. To this end, all cases and controls who had bisphosphonates prescribed prior to the starting date were excluded [26] (Fig. 1).

Exposure definition

Bisphosphonates included in this study are those available in Spain for primary care physician prescription (alendronic acid, ibandronic acid and risedronic acid), except for etidronic acid, which is available for prescription but not used practically. Zoledronate is prescribed and administered at hospital level, and then it is not recorded in BIFAP database. Patients were classified as "current users" of bisphosphonates when the last prescription period finished within 30 days before the index date, "recent users" when it finished between 31 and 365 days before the index date, "past users" when it finished over 365 days before the index date, and "non-users" when there was no bisphosphonate prescription recorded before the index date. In a sensitivity analysis current and recent user were pooled together.

Treatment duration was calculated for current users by adding up each prescription duration that was given consecutively (an interval no longer than 90 days between the end of one prescription and the beginning of the following one). Then patients were grouped into two categories: less than

365 days, and 365 days or more. In a sensitivity analysis duration effect was also explored in the pool of current plus recent users.

Potential confounding factors

The following comorbidities (recorded before the index date) were evaluated as possible confounding factors: cerebrovascular disease (ischemic, haemorrhagic or unspecified stroke and transient ischemic attack), heart failure, angina pectoris (recorded as such, and/or use of nitrates), peripheral artery disease (PAD), hypertension, atrial fibrillation, diabetes (recorded as such, and/or use of glucose-lowering medications), dyslipidemia (recorded as such, and/or use of lipid-lowering medications), rheumatoid arthritis, osteoarthritis and chronic kidney disease. In addition, the following factors were considered: number of visits to the PCP in the year prior to the index date (as an indicator of comorbidities), body mass index (BMI), smoking and current use of the following drugs: low dose aspirin, other antiplatelet drugs, oral anticoagulants, non-steroidal anti-inflammatory drugs (NSAIDs), paracetamol, metamizole, calcium and vitamin D supplements, corticosteroids, angiotensin-converting-enzyme inhibitors (ACE inhibitors), angiotensin II receptor blockers (ARBs), calcium channel blockers, beta-blockers, alpha blockers, diuretics and proton-pump inhibitors.

Statistical analysis

The association between incident AMI and exposure to drugs of interest was evaluated by calculating the odds ratio (OR) and its 95% confidence intervals (CI) through an unconditional logistic regression. Firstly, crude ORs only including exposure and matching variables (age, sex and calendar year) were estimated. Secondly, adjusted odds ratios (AORs) were calculated by adding all possible confounding factors mentioned in the above section. In addition, interaction with age (stratified as under 70 years old, and 70 or over), sex and background cardiovascular risk were examined. The latter was defined as follows: high-risk patients with records of peripheral artery disease, angina pectoris, cerebrovascular accident or diabetes; intermediate risk, patients without criteria for high risk and with records of hypertension, dyslipidemia, chronic kidney failure, smoking or BMI > 30 kg/m^2; and low risk, the remainder. We included patients with diabetes mellitus within the high-risk group because it has been reported to have a risk equivalent to ischemic heart disease [28]. For statistical evaluation of interaction, adjusted models were used in different categories of interaction variables, and AOR associated with the current use of bisphosphonates was calculated in comparison with the non-use in each stratum. AORs of different strata were compared using the test of interaction described by Altman and Bland [29]. Results were considered statistically significant when $p < 0.05$.

Missing values in some specific covariables such as smoking (49.9%) and BMI (39.3%) were addressed with multiple imputation by chained equations (MICE) models [30] (see Appendix C). All analyses were performed with STATA/SE 15 (StataCorp. College Station, TX, US).

Sensitivity analyses

A sensitivity analysis was performed by also using prevalent users of bisphosphonates. Additionally, we explored the effect of pooling current and recent users.

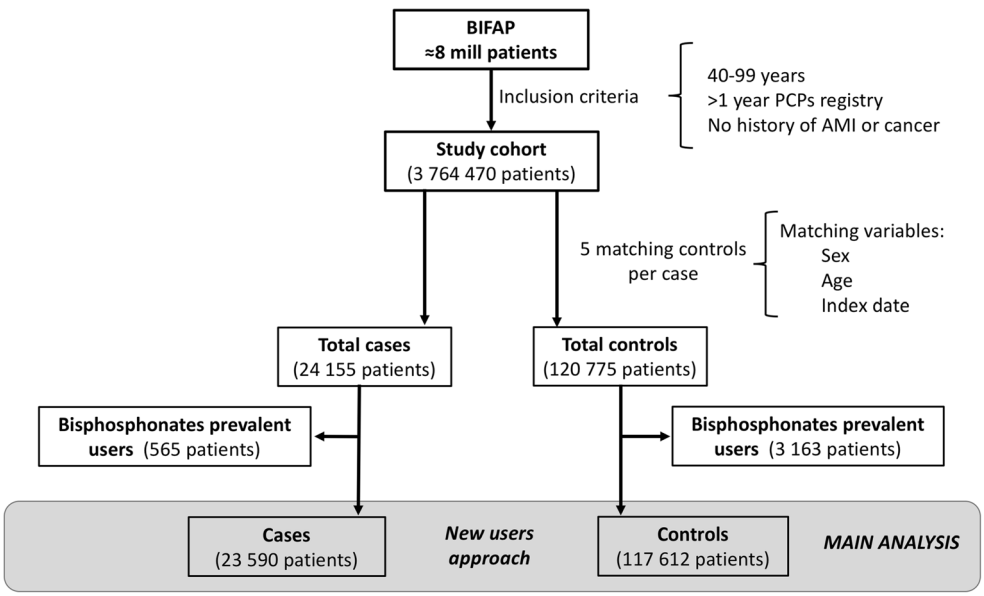

Fig. 1 Flowchart of patient selection

Ethical aspects

The scientific committee of BIFAP granted access to pseudonymized data in the database (#04/2016 project; approval date: 26 May 2016). In accordance with Spanish law, a specific ethical review is not required when the study does not use personal data.

Results

A total of 23,590 incident AMI cases and 117,612 controls were included (Fig. 1). Characteristics are described in Table 1. As expected, prevalence of cardiovascular risk factors and use of cardiovascular drugs were more frequent in cases than in controls.

Bisphosphonates use and AMI risk

Current, recent or past use of bisphosphonates in cases (1.17%/0.46%/0.84%, respectively) was similar to those found among controls (1.24%/0.41%/0.81%, respectively), yielding to an unadjusted OR of 0.93 (95% CI 0.81–1.06), 1.13 (95% CI 0.92–1.40) and 1.04 (95% CI 0.89–1.21), respectively. After full adjustment, results hardly changed: 0.98 (95% CI 0.85–1.14), 1.14 (95% CI 0.91–1.43) and 1.01 (95% CI 0.85–1.20). Table 2 shows results for the whole pharmacological group and for individual drugs.

Bisphosphonates use and AMI risk by treatment duration

Current use according to treatment duration (less than 365 days/365 days or more) was similar in cases (0.41%/0.76%, respectively) and controls (0.48%/0.76%, respectively). This entails an unadjusted OR of 0.85 (95% CI 0.68–1.06) and 0.98 (95% CI 0.83–1.15), respectively. After full adjustment, results were roughly unchanged: 0.92 (95% CI 0.73–1.15) and 1.03 (95% CI 0.86–1.23), respectively. Table 3 shows results by duration for the whole pharmacological group and for individual drugs.

Bisphosphonates use and AMI risk in different subgroups

No evidence of statistical interaction of bisphosphonate current use with sex, age and baseline cardiovascular risk was found (Fig. 2; supplementary table 2).

Sensitivity analysis

The inclusion of prevalent users of bisphosphonates was associated with a slight risk reduction of AMI among current users (AOR = 0.89; 95% CI 0.79–0.99) (supplementary table 1). Pooling current and recent users yielded an AOR of 1.02 (95% CI 0.90–1.17) overall, and 1.01 (95% CI 0.86–1.19) with treatment duration of 365 days or longer.

Discussion

This study does not find evidence that bisphosphonate treatment, by group or by active ingredient (alendronate, ibandronate and risedronate), is associated with a reduction of AMI risk, irrespective of treatment duration, age, sex or baseline cardiovascular risk.

Diverse mechanisms have been postulated to explain a potential reduction of CV events with bisphosphonates use: induction of macrophage apoptosis, prevention of macrophage foam cells from forming, reduction of cholesterol levels by inhibiting the mevalonate pathway and a potential anti-inflammatory effect [10, 11, 24, 25]. Bisphosphonates have proved to prevent atherosclerosis development or to reduce atherosclerosis degree in animal models [31–34]. As for humans, etidronate has been studied in various clinical trials as a vascular calcification inhibitor. In patients with high CV risk, bisphosphonates decreased the carotid intima-media (CIM) thickness in 0.038 mm [35], coronary artery calcium scoring (CACS) in 372 mm^3 [16] and aortic calcification by 14–15% [17]. Values in the mentioned reduction of CIM thickness were comparable to the effects observed with some statins: pitavastatin decreased CIM thickness by 0.024 mm/year in patients with known atherosclerosis [36], while rosuvastatin decreased CIM thickness by 0.0014 mm/year in low-risk subjects [37]. Evidence with other bisphosphonates is mixed. Alendronate reduced CIM thickness by 0.025 mm in patients receiving haemodialysis [38], but not in patients with chronic kidney disease [39]. On another note, an ibandronate treatment of 36 months did not alter aortic calcification progression [40]. Despite the benefits of bisphosphonates on intermediate variables, there is no clear evidence of atherosclerotic cardiovascular event reduction in contrast to statins. Some studies suggest that most of the benefits of statins come from plaque stabilization and are not due to atherosclerosis regression [41]. So far, the effects of bisphosphonates on plaque stabilization continue to be unknown. It is also possible that CV protective effects are different among different molecules. For instance, etidronate is considered as the most potent inhibitor of vascular calcification [25], but this study does not count on enough subjects with this drug to provide a meaningful analysis.

This study's results are contrary to findings from other previous observational studies [18–20, 25, 42] and clinical trials with intermediate variables, i.e. CIM thickness [35, 38], coronary artery calcium score [16] and aortic calcification [17, 43], suggesting possible benefits of bisphosphonates in

Table 1 Cases and controls characteristics. Bisphosphonate prevalent users excluded

	Incident AMI (%) $N = 23,590$	Controls (%) $N = 117,612$	Non-adjusted OR (95% CI)
Age; mean (SD)	66.8 (13.4)	66.8 (13.4)	-
Men	17,107 (72.52)	85,531 (72.72)	-
Visits (last 12 months)			
Up to 5	6823 (28.92)	44,559 (37.89)	1 (Ref.)
6–15	8820 (37.39)	42,547 (36.18)	1.44 (1.39–1.50)
16–24	4363 (18.50)	17,640 (15.00)	1.81 (1.73–1.89)
25+	3584 (15.19)	12,866 (10.94)	2.12 (2.02–2.23)
BMI (kg/m^2)			
Up to 24.9	2617 (11.09)	14,018 (11.92)	1 (Ref.)
25–29	6800 (28.83)	33,043 (28.09)	1.10 (1.05–1.16)
30–34	4069 (17.25)	18,255 (15.52)	1.20 (1.14–1.27)
35–49	1101 (4.67)	4367 (3.71)	1.37 (1.26–1.48)
40+	327 (1.39)	1113 (0.95)	1.57 (1.38–1.80)
Unknown	8676 (36.78)	46,816 (39.81)	0.99 (0.94–1.04)
Smoking			
Never smoking	5255 (22.28)	30,879 (26.25)	1 (Ref.)
Current smoker	6416 (27.20)	19,907 (16.93)	2.04 (1.95–2.13)
Former smoker	1272 (5.39)	6963 (5.92)	1.12 (1.05–1.20)
Unknown	10,647 (45.13)	59,863 (50.90)	1.07 (1.03–1.11)
CVA			
Ischemic	587 (2.49)	2131 (1.81)	1.42 (1.29–1.56)
Hemorrhagic	88 (0.37)	346 (0.29)	1.29 (1.02–1.63)
Unspecified	413 (1.75)	1757 (1.49)	1.20 (1.08–1.34)
TIA	486 (2.06)	1937 (1.65)	1.28 (1.15–1.42)
Heart failure	876 (3.71)	2967 (2.52)	1.51 (1.40–1.64)
Angina pectoris[‡]	2653 (11.25)	5062 (4.30)	2.93 (2.79–3.09)
PAD	1079 (4.57)	2419 (2.06)	2.32 (2.15–2.50)
Atrial Fibrillation	1346 (5.71)	6530 (5.55)	1.03 (0.97-1.10)
Hypertension	12,157 (51.53)	50,503 (42.94)	1.49 (1.45–1.54)
Diabetes[§]	6398 (27.12)	19,460 (16.55)	1.92 (1.86–1.98)
Dyslipidemia[‖]	11,045 (46.82)	41,217 (35.04)	1.68 (1.63–1.73)
Rheumatoid arthritis	203 (0.86)	658 (0.56)	1.53 (1.30–1.79)
Osteoarthritis	2064 (8.75)	9771 (8.31)	1.06 (1.01–1.12)
Chronic kidney failure	900 (3.82)	2817 (2.40)	1.64 (1.52–1.77)
Hyperuricemia			
Asymptomatic	4210 (17.85)	17,030 (14.48)	1.30 (1.25–1.35)
Gout	1161 (4.92)	5102 (4.34)	1.21 (1.13–1.29)
Background CV risk			
Low	3885 (16.47)	33,927 (28.85)	1 (Ref.)
Intermediate	10,522 (44.60)	55,490 (47.18)	1.77 (1.70–1.84)
High	9183 (38.93)	28,195 (23.97)	3.23 (3.09–3.37)
Current use of			
Antiplatelet drugs	4648 (19.70)	14,094 (11.98)	2.07 (1.99–2.15)
Oral anticoagulants	887 (3.76)	4857 (4.13)	0.91 (0.85–0.98)
Calcium (alone)	121 (0.51)	576 (0.49)	1.04 (0.85–1.27)
Calcium + Vitamin D	462 (1.96)	2609 (2.22)	0.86 (0.77–0.95)
Vitamin D (alone)	120 (0.51)	475 (0.40)	1.24 (1.01–1.52)
Paracetamol	2583 (10.95)	11,636 (9.89)	1.20 (1.14–1.26)
Metamizole	909 (3.85)	3283 (2.79)	1.49 (1.38–1.61)
NSAIDs	2345 (9.94)	10,534 (8.96)	1.20 (1.14-1.26)
Corticosteroids	474 (2.01)	1622 (1.38)	1.48 (1.34–1.65)
ACE inhibitors	4099 (17.38)	16,800 (14.28)	1.37 (1.32–1.43)
ARB	3639 (15.43)	14,027 (11.93)	1.43 (1.38–1.49)
CCB	3228 (13.68)	11,062 (9.41)	1.65 (1.58–1.72)

Table 1 (continued)

	Incident AMI (%) $N = 23,590$	Controls (%) $N = 117,612$	Non-adjusted OR (95% CI)
Beta-blockers	2584 (10.95)	7371 (6.27)	1.92 (1.83–2.01)
Alfa-blockers	597 (2.53)	2454 (2.09)	1.23 (1.12–1.35)
Diuretics	2985 (12.65)	12,000 (10.20)	1.38 (1.32–1.45)
PPI	6224 (26.38)	24,163 (20.54)	1.54 (1.49–1.60)

Abbreviations: *ACE* angiotensin converting enzyme, *ARB* angiotensin II receptor blockers, *BMI* body max index, *CCBs* calcium-channel blockers, *CI* confident interval, *COPD* chronic obstructive pulmonary disease, *CV* Cardiovascular, *CVA* cerebrovascular accident, *NSAIDs* non-steroidal anti-inflammatory drugs, *OR* odds ratio, *PAD* peripheral artery disease, *PPI* proton-pump inhibitors, *SD* standard deviation, *TIA* transient ischemic accident

‡ Recorded as such or when patients were using nitrates

§ Recorded as such or when patients were using glucose-lowering drugs

‖ Recorded as such or when patients were using lipid-lowering drugs

Table 2 AMI risk associated with bisphosphonate Use. Bisphosphonate prevalent users excluded

	Incident AMI (%) $N = 23,590$	Controls (%) $N = 117,612$	Non-adjusted OR (95% CI)	Adjusted OR (95% CI)
Bisphosphonates				
Non-users	23,006 (97.52)	114,720 (97.54)	1 (Ref.)	1 (Ref.)
Current	276 (1.17)	1458 (1.24)	0.93 (0.81–1.06)	0.98 (0.85–1.14)
Recent	109 (0.46)	478 (0.41)	1.13 (0.92–1.40)	1.14 (0.91–1.43)
Past	199 (0.84)	956 (0.81)	1.04 (0.89–1.21)	1.01 (0.85–1.20)
Alendronic acid				
Non-users	23,338 (98.93)	116,421 (98.99)	1 (Ref.)	1 (Ref.)
Current	88 (0.37)	469 (0.40)	0.91 (0.72–1.15)	0.99 (0.78–1.27)
Recent	46 (0.19)	201 (0.17)	1.17 (0.84–1.61)	1.18 (0.84–1.66)
Past	118 (0.50)	521 (0.44)	1.12 (0.91–1.37)	1.14 (0.91–1.41)
Alendronic acid + VitD				
Non-users	23,509 (99.66)	117,155 (99.61)	1 (Ref.)	1 (Ref.)
Current	34 (0.14)	207 (0.18)	0.81 (0.56–1.17)	0.86 (0.59–1.25)
Recent	15 (0.06)	77 (0.07)	0.94 (0.54–1.63)	0.81 (0.45–1.44)
Past	32 (0.14)	173 (0.15)	0.92 (0.63–1.35)	0.85 (0.57–1.27)
Alendronic acid (all)				
Non-users	23,274 (98.66)	116,057 (98.68)	1 (Ref.)	1 (Ref.)
Current	122 (0.52)	671 (0.57)	0.89 (0.73–1.08)	0.96 (0.78–1.18)
Recent	58 (0.25)	261 (0.22)	1.11 (0.83–1.48)	1.06 (0.78–1.44)
Past	136 (0.58)	623 (0.53)	1.08 (0.89–1.31)	1.06 (0.87–1.30)
Ibandronic acid				
Non-users	23,504 (99.64)	117,174 (99.63)	1 (Ref.)	1 (Ref.)
Current	41 (0.17)	216 (0.18)	0.96 (0.68–1.34)	1.02 (0.72–1.45)
Recent	18 (0.08)	69 (0.06)	1.24 (0.74–2.09)	1.42 (0.83–2.43)
Past	27 (0.11)	153 (0.13)	0.87 (0.57–1.31)	0.88 (0.57–1.36)
Risedronic acid				
Non-users	23,355 (99.00)	116,446 (99.01)	1 (Ref.)	1 (Ref.)
Current	102 (0.43)	527 (0.45)	0.95 (0.76–1.18)	1.00 (0.79–1.25)
Recent	47 (0.20)	186 (0.16)	1.27 (0.92–1.75)	1.20 (0.85–1.69)
Past	86 (0.36)	453 (0.39)	0.94 (0.75–1.19)	0.92 (0.72–1.18)

Abbreviation: *OR* odds ratio

Table 3 AMI risk associated with bisphosphonate use according to treatment duration. Bisphosphonate prevalent users excluded

	Incident AMI (%) $N = 23,590$	Controls (%) $N = 117,612$	Non-adjusted OR (95% CI)	Adjusted OR (95% CI)
Bisphosphonates				
Current < 365 days	97 (0.41)	565 (0.48)	0.85 (0.68–1.06)	0.92 (0.73–1.15)
Current 365+ days	179 (0.76)	893 (0.76)	0.98 (0.83–1.15)	1.03 (0.86–1.23)
Alendronic acid				
Current < 365 days	37 (0.16)	188 (0.16)	0.97 (0.68–1.39)	1.05 (0.72–1.52)
Current 365+ days	51 (0.22)	281 (0.24)	0.87 (0.65–1.18)	0.96 (0.70–1.31)
Alendronic acid + VitD				
Current < 365 days	16 (0.07)	88 (0.07)	0.92 (0.54–1.57)	0.97 (0.56–1.68)
Current 365+ days	18 (0.08)	119 (0.10)	0.74 (0.45–1.21)	0.78 (0.47–1.31)
Alendronic acid (all)				
Current < 365 days	52 (0.22)	270 (0.23)	0.95 (0.71–1.29)	1.02 (0.74–1.39)
Current 365+ days	70 (0.30)	401 (0.34)	0.85 (0.65–1.09)	0.92 (0.70–1.20)
Ibandronic acid				
Current < 365 days	13 (0.06)	85 (0.07)	0.75 (0.42–1.35)	0.82 (0.45–1.51)
Current 365+ days	28 (0.12)	131 (0.11)	1.10 (0.73–1.67)	1.15 (0.75–1.78)
Risedronic acid				
Current < 365 days	37 (0.16)	226 (0.19)	0.81 (0.57–1.15)	0.85 (0.59–1.23)
Current 365+ days	65 (0.28)	301 (0.26)	1.05 (0.80–1.38)	1.11 (0.83–1.47)

Abbreviation: *OR* odds ratio

atherosclerotic cardiovascular events. Kang et al [19], using Taiwan's National Health Insurance database, found an AMI risk reduction of 65% in patients receiving at least 1 year of continued treatment with bisphosphonates in comparison with patients with acute osteoporotic fracture who did not received bisphosphonates. In a cohort of patients with rheumatoid arthritis, Wolfe et al. [20] observed a reduction of 28% in AMI rate in subjects treated with bisphosphonates versus those who did not receive bisphosphonates. In another study Sing et al. [41] observed that alendronate was associated with a significantly lower risk of 1-year cardiovascular mortality (HR 0.33; 95% CI 0.17–0.65) and incident myocardial infarction (HR 0.55; 95% CI 0.34–0.89). "Prevalent user bias" is a common potential bias in numerous observational studies when part of the cohort took the drug for some time before the study follow-up began. Prevalent users are "survivors" of the early

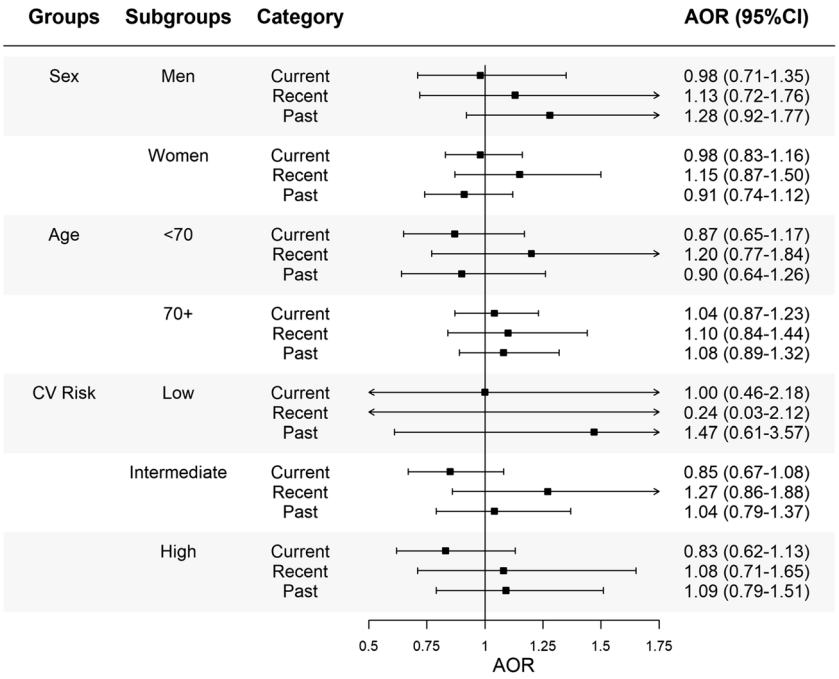

Fig. 2 AMI risk associated with bisphosphonate use by sex, age and background cardiovascular risk. Bisphosphonate prevalent users excluded (see supplementary table 2 for details). OR odds ratio. Definitions of different categories of CV risk: high risk: patients with records of peripheral artery disease, angina pectoris, cerebrovascular accident or diabetes; intermediate risk: patients without criteria for high risk and with records of hypertension, dyslipidemia, chronic kidney failure, smoking or BMI > 30 kg/m^2; low risk: the remainder

period of pharmacotherapy, and therefore, there is a trend to spuriously overestimate the protective effect of drugs. To avoid this potential bias, it has been suggested to restrict the study cohort to new users [26], this way mimicking clinical trials that recruit "new users" by definition. This design is employed in our study, which may explain the discrepancies mentioned above regarding previous observational studies. In fact, a slight protective effect of 11% was found in our study when prevalent users were included in the analysis, supporting the notion of a potential "prevalent user bias." Results obtained in this study are similar to those from two meta-analyses of randomized clinical trials (RCTs) [22, 23], where no such cardioprotective effect from bisphosphonates was found either. Kim et al. [22] analysed a total of 58 RCTs without finding any association between treatment with commonly prescribed bisphosphonates (alendronate, ibandronate, risedronate and zoledronic acid) with significant clinical effects in CV events. Moreover, they found a slight increase of risk for atrial fibrillation with intravenous zoledronic acid, although evidence was not conclusive [22]. Kranenburg et al. analysed a total of 61 RCTs including patients with osteoporosis and patients with cancer. Bisphosphonates had beneficial effects regarding arterial calcification, but not regarding arterial stiffness. Any effects due to bisphosphonate treatment were not found in cardiovascular events (RR 1.03; 95% CI 0.91–1.17), while a non-statistically significant decrease of cardiovascular mortality risk (RR 0.81; 95% CI 0.64–1.02) and a decrease of all-cause mortality (RR 0.90; 95% CI 0.84–0.98) were observed [23]. Other recent clinical trials not included in the above-mentioned meta-analyses, such as the study by Reid et al. [44] and a post-hoc analysis [45], observed a trend (not statistically significant) towards a possible cardioprotective effect of zoledronate in women with osteopenia.

Strengths of this study are as follows: (1) researchers who validated the cases were blind to drug exposure, which prevented from a differential misclassification of AMI cases conditioned by exposure; (2) controls were randomly extracted from the underlying cohort, ensuring the representation of the exposure in the source population and avoiding a bias in control selection; and (3) only new users of bisphosphonates were taken into consideration in order to avoid the "prevalent user" bias [26].

Main limitations of this study are as follows: first, it is an observational study, and therefore, there is a possibility for residual confounding due to unknown or unmeasured factors; second, since there is evidence that low bone mass is a risk factor for AMI (4), and bisphosphonates are mostly prescribed for osteoporosis, we cannot rule out the possibility of a confounding by indication, which might have masked a possible protective effect of bisphosphonates as a result; however, we would like to note that in our study we did adjust for use of calcium and vitamin D supplements which can be considered as a marker of an underlying osteoporosis, thereby minimizing this potential bias; third, misclassification of the exposure due to a deficient recording of drugs prescribed is quite unlikely because clinicians write the prescriptions using the computerized system, but adherence to treatments by patients cannot be guaranteed; and fourth, exposure to bisphosphonates other than the ones included was too low to perform a meaningful analysis (zoledronate and etidronate).

Conclusions

Bisphosphonates that are most commonly prescribed (alendronate, risedronate and ibandronate) do not show beneficial or harmful effects for AMI, irrespective of treatment duration, age, sex or baseline cardiovascular risk. However, a small protective effect could have been masked if patients with osteoporosis have had a background higher risk of AMI.

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Compliance with ethical standards

Conflicts of interest None

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Outcomes, discussion, and conclusions have been issued by the authors of this study and do not necessarily reflect the position of AEMPS.

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