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Bisphosphonates and cardiovascular risk in elderly patients with previous cardiovascular disease: a population-based nested case-control study in Italy

Ursula Kirchmayer, Chiara Sorge, Janet Sultana, Francesco Lapi, Graziano Onder, Nera Agabiti, Silvia Cascini, Giuseppe Roberto, Giovanni Corrao, Cristiana Vitale, Ersilia Lucenteforte, Alessandro Mugelli, Marina Davoli and the Italian Group for Appropriate Drug Prescription in the Elderly (I-GrADE)

Correspondence to:
Chiara Sorge
Department of Epidemiology, Lazio Regional Health Service, ASL Roma 1, Via Cristoforo Colombo 112, Rome, 00147, Italy
c.sorge@deplazio.it

Ursula Kirchmayer
Nera Agabiti
Silvia Cascini
Marina Davoli
Department of Epidemiology, Lazio Regional Health Service, Rome, Italy

Janet Sultana
Department of Biomedical and Dental Sciences and Morphofunctional Imaging, University of Messina, Messina, Italy

Francesco Lapi
Health Search, Italian College of General Practitioners and Primary Care, Florence, Italy

Graziano Onder
Department of Geriatrics, Catholic University of Rome, Rome, Italy

Giuseppe Roberto
Epidemiology Unit, Regional Agency for Healthcare Services of Tuscany, Florence, Italy

Giovanni Corrao
Laboratory of Healthcare Research & Pharmacoepidemiology, Unit of Biostatistics, Epidemiology and Public Health, Department of Statistics and Quantitative Methods, University of Milano-Bicocca, Milan, Italy

Cristiana Vitale
Department of Medical Sciences, IRCCS San Raffaele Pisana, Rome, Italy

Ersilia Lucenteforte
Department of Neurosciences, Psychology, Drug Research and Children's Health, University of Florence, Florence, Italy

Abstract

Background: In a globally aging population, chronic conditions with a high impact on healthcare costs and quality of life, such as osteoporosis and associated fractures, are a matter of concern. For osteoporosis, several drug treatments are available, but evidence on adverse cardiovascular and cerebrovascular (CCV) events, and in particular the risk of atrial fibrillation (AF), related to anti-osteoporotic drug use is inconclusive. The objective of this study was to evaluate the association between the use of bisphosphonates (BPs), strontium ranelate (SR), and other anti-osteoporosis drugs and the risk of AF and CCV events in a large cohort of patients affected by CCV diseases.

Methods: Based on a cohort of patients aged 65 years and over, discharged from the hospitals of five large Italian areas after a CCV event between 2008 and 2011, two nested case-control studies were conducted. Cases were patients with a subsequent hospital admission for AF or CCV; four controls for each case were randomly selected and matched by age group, sex and follow-up time. A total of three exposure measures were tested: ever use, adherence and recency of use. In the conditional logistic regression models, patients not treated with any anti-osteoporotic medication were considered as the reference category.

Results: The initial cohort accounted for 657,246 patients. Neither BPs nor SR use was associated with an increased risk of AF regardless of the adherence and recency of use. Overall BP and SR use was associated with a slightly increased risk of CCV; however, results reversed when considering higher adherence: odds ratio (OR) 0.81, 95% confidence interval (CI) 0.71–0.92 for BPs and OR 0.71, 95% CI 0.52–0.97 for SR.

Conclusions: BPs do not increase cardiovascular risk and can be prescribed to elderly patients for osteoporosis treatment. However, patients with pre-existing cerebrovascular/cardiovascular conditions should be carefully monitored.

Keywords: adverse events, atrial fibrillation, bisphosphonates, cardiovascular risk, nested case-control study, pharmacoepidemiology

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Background

Osteoporosis and associated fractures are a public health issue of growing importance with a significant impact on healthcare utilization, morbidity and mortality. The incidence of osteoporosis increases with age, and the proportion of

Department of Clinical and Experimental Medicine, University of Pisa, Italy

Alessandro Mugelli
Department of Neurosciences, Psychology, Drug Research and Children's Health, University of Florence, Florence, Italy

old and very old people is steadily rising.[1,2] Consequently, the proportion of patients treated with anti-osteoporotic drugs is rising too.

Several pharmacological therapies are available for osteoporosis prevention and treatment, and, in Italy, bisphosphonates (BPs) are most commonly used, followed by strontium ranelate (SR).

While for both treatments the efficacy in reducing fracture risk is well established in randomized controlled trials,[3–10] there is conflicting evidence about BP use and cardiovascular risk.

An increased risk of atrial fibrillation (AF) in BP users was reported by several clinical trials[3,11–14] and a meta-analysis,[15] while other authors did not confirm these findings.[5,6,16,17]

Conflicting results are also coming from observational research. While several studies suggest an increased risk of acute myocardial infarction (AMI)[18] and AF among BP users,[13,14,19–22] other studies did not find any association between exposure to BPs and increased cardiovascular risk.[23–26] In one study, the increased risk was limited to AMI and only for longer exposure to BPs.[27]

Some authors even suggest a possible risk reduction of AMI and other cardiovascular diseases.[28–31]

A series of potential mechanisms by which BPs might increase AF risk have been proposed, including an activated inflammatory state, altered electrolytes impacting cardiac conduction, antiangiogenic effects, and long-term atrial structural changes.[28,32,33]

On the basis of the disparate findings reported in trials, observational studies and meta-analyses, some authors recommend that patients with pre-existing risk factors for AF should be monitored when they start BP treatment.[34,35]

The I-GrADE (Italian Group for Appropriate Drug Prescription in the Elderly) project, a recent Italian multicentre programme focussed on inappropriate pharmacological treatments in older adults affected by cardiovascular disease and other chronic comorbidities. A systematic literature review, performed by the group, identified BP use in patients with cardiovascular conditions as being potentially inappropriate.[36] Therefore, in line with the commitment of the I-GrADE consortium, the aim of the present study was to investigate the hypothesis of increased risk of AF and acute cerebrovascular/cardiovascular (CCV) events, in particular acute ischaemic heart disease, heart failure, arrhythmia and acute cerebrovascular events, in a large cohort of older adults with cardiovascular diseases and exposed to BPs in a real-world setting, compared with other anti-osteoporotic treatments and no treatment. Along with the other studies performed in the context of the I-GrADE research programme, our results might contribute to define a reliable list of indicators of inappropriate drug treatment and improve drug prescribing to older adults affected by cardiovascular diseases.

Methods

Setting

The present study was performed in the context of the multicentre I-GrADE project, funded by the Italian Medicines Agency, which has been described in detail elsewhere.[35] Briefly, healthcare data from three Italian regions (Lazio, Lombardy, and Tuscany) and two local health units (Caserta and Treviso), were retrieved for patients aged 65 years or older and discharged from hospital with a diagnosis of acute CCV disease between 2008 and 2012. The database comprises information from administrative claims including demographic data, mortality, hospital discharge records with diagnoses coded using the 9th version of the International Classification of Diseases, with clinical modification (ICD-9 CM), and outpatient drug prescription claims, coded in the Anatomic Therapeutic and Chemical (ATC) classification system. Further details of the cohort inclusion and exclusion criteria have been reported previously.[37,38]

Study population

We performed two nested case-control studies to evaluate the relationship between anti-osteoporotic drug use and the risk of AF (referred to hereafter as 'the AF study') and acute CCV events (referred to hereafter as 'the CCV study'); Figure 1 summarizes the main characteristic of the study design. The study cohort consisted of all patients aged 65 years and over, discharged from hospitals after a CCV event (heart failure, cerebrovascular disease or ischaemic heart disease) between 1 January 2008 and 31 December 2011 (index admission). Exclusion criteria were: less than 12 months of

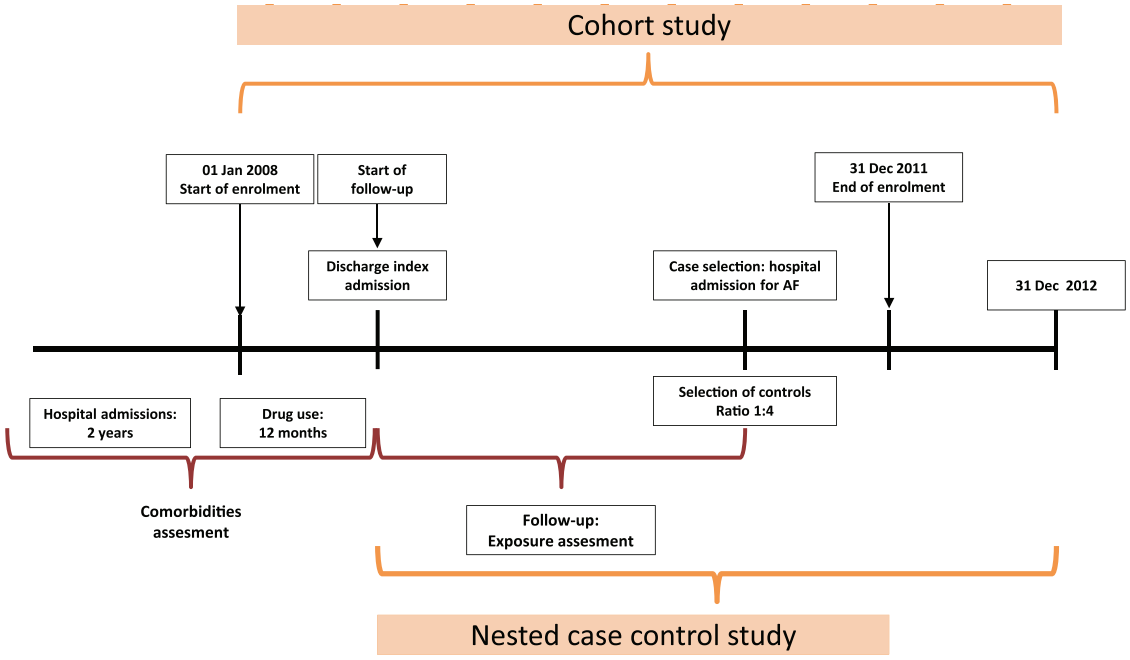

Figure 1. Study design.
AF, atrial fibrillation; CCV, cerebrovascular/cardiovascular.

follow-back for comorbidities assesment, treatment with anti-osteoporotic drugs (BPs, SR, raloxifene, teriparatide, calcitonin, denosumab, and oestrogens) in the year before the index admission, and fewer than 30 days of individual follow up after the index admission. The length of the wash-out period was driven by data availability.

Follow up

Follow up started on the index date and ended at the occurrence of the study outcome, death, switch to an alternative osteoporosis treatment, or disenrollment from the regional healthcare system, whichever came first.

Nested case-control studies

Overall, two mutually exclusive nested case-control studies were performed within the study cohort. In the AF study, cases were defined as patients with a hospital admission having a primary diagnosis for AF (ICD-9-CM 427.3) occurring after the index hospital admission. In the CCV study, the outcome of interest was a composite endpoint of acute CCV events [acute ischaemic heart disease (ICD-9-CM 410-411), arrhythmia (ICD-9-CM 427.x), acute cerebrovascular events (ICD-9-CM 430-432, 433.x1, 434.x1, 436), and heart failure (ICD-9-CM 428.X)]. For both studies, events occurring within 30 days after the index date were not considered, as they might have been related to the index admission. A total of four controls were matched to each case by sex, 5-year age group and duration of follow up. Controls were chosen among patients with no hospital admission for the specific outcome of interest within the case follow-up time, regardless of hospitalizations for other causes.

Exposure

The exposure of interest was treatment with anti-osteoporotic drugs, considering three different groups: (1) BPs (e.g. clodronic acid, pamidronic acid, alendronic acid, ibandronic acid, risedronic acid, zoledronic acid, neridronic acid), (2) SR and (3) other anti-osteoporotic drugs (e.g. raloxifene, teriparatide, calcitonin, denosumab, oestrogens), using no anti-osteoporotic treatment as a reference group. Exposures were mutually exclusive, and the very few patients switching between treatments during follow up were excluded. Overall, three exposure measures were applied: no use *versus* ever use, defined as at least one prescription during the follow up; the proportion of days covered (PDC), calculated as the number of defined daily doses (DDDs) available to the patient over the days of

patient-level follow up, and divided into three categories (<20%, 20–80%, >80%); time between the date of the last prescription prior to the outcome and the outcome, distinguishing between current users (⩽90 days before the event/end of follow up), recent users (91–180 days before the event/end of follow up), and distant users (>180 days before the event/end of follow up) in line with a previous Italian study.[21]

Covariates

Several potential confounders were taken into account: the CCV condition at enrolment, comorbidities retrieved through hospital admissions during the 2 years before the index admission, both, as primary and secondary diagnoses and drug use in the year before index admission (Table 1) was retrieved from drug claims databases. The choice of different time windows was driven by data availability. Comorbidities and concomitant medications were selected through a stepwise approach. Crude and adjusted association measures were estimated using conditional logistic regression models.

Sensitivity analyses

A total of three sensitivity analyses were performed. In the first analysis, we excluded patients who spent more than 50% of their follow-up time in hospital, accounting for the lack of information on drug treatment in hospital. Secondly, we used the cardiovascular diagnosis at enrolment as a matching variable, rather than as a potential confounder, and thirdly, we considered BP users only and compared different adherence patterns (PDC < 20%, 20–80%, >80%).

All the analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA).

Results

Among over 800,000 patients discharged from hospital with a CCV diagnosis during the study period, 657,246 were enrolled in the study cohort (Figure 2). More than half of the study population were men and the mean age was 78.3 ±7 years. The most frequent conditions at enrolment were heart failure, stroke, AMI and AF. During follow up, 28,090 patients were diagnosed with AF (rate: 1.8/100 person years), and 157,031 patients were hospitalized for the combined CCV outcome (rate: 11.3/100 person years) (Figure S1 and S2). Among the 30,756 patients with anti-osteoporotic treatment, BPs were the most commonly prescribed (70.0%), followed by SR (28.0%). All other agents were much less commonly used.

The main characteristics of cases and controls in the two studies are reported in Table 2. In the AF study, cases were more likely to have had a previous episode of AF (12.3% *versus* 4.6%) or arrhythmia (72.4% *versus* 42.0%) and were more frequently treated with cardiac therapy and oral anticoagulant (47.0% *versus* 34.0% and 31.0% *versus* 14.4% respectively). In the CCV study, cases were more commonly treated with diuretics and cardiac therapy in the year before the enrolment in the cohort, compared with controls.

Table 3 reports the results on the association between use of anti-osteoporotic drugs and risk of AF. No significant association was observed for any of the drugs under study. A decreased risk was observed among high adherent patients (PDC > 80%) and current users of BPs and SR, but the results did not reach statistical significance [BP, PDC > 80%: odds ratio (OR) = 0.81, 95% confidence interval (CI): 0.56–1.16; current use: OR = 0.95, 95% CI: 0.81–1.11].

Compared with nonusers, patients with at least one prescription for BPs or SR showed an increased risk of subsequent acute CCV events (OR = 1.07, 95% CI: 1.03–1.12 and OR = 1.24, 95% CI: 1.16–1.32, respectively; Table 4). As in the AF study, higher adherence (PDC > 80%) was associated with a decreased risk of CCV events (OR = 0.81, 95% CI: 0.71–0.92 for BPs and OR = 0.71, 95% CI: 0.52–0.97 for SR). Accordingly, recent and distant users were at an increased risk with respect to current users.

Sensitivity analyses confirmed our findings: matching on the condition at enrolment, led to almost identical estimates for all the three exposures measures and for both outcomes. For example, ever use of BPs corresponded to an OR for AF of 0.94 (95% CI: 0.85–1.04) and an OR of 0.80 (95% CI: 0.57–1.12).

Discussion

Overall, two nested case-control studies were performed to evaluate whether anti-osteoporotic drug use increases the risk of subsequent AF or CCV events in elderly patients with previous

Table 1. Comorbidities and drug use prior to index admission.

Condition	**ICD-9-CM CODE**
	Index and previous hospitalizations
Cancer	140.0–208.9, V10
Diabetes	250.0–250.9
Lipid metabolism disturbances	272
Obesity	278
Blood disorders	280–285, 288, 289
Hypertension	401–405
Previous myocardial infarction	410, 412
Other forms of ischaemic heart disease	411, 413, 414
Heart failure	428
Ill-defined descriptions and complications of heart disease	429
Rheumatic heart disease	391, 393–398
Cardiomyopathy	425
Acute endocarditis and myocarditis	421, 422
Other heart conditions	745, V15.1, V42.2, V43.2, V43.3, V45.0
Conduction disturbances	426
Arrhythmias	427
Cerebrovascular disease	430–438
Vascular disease	440–448, 557
Chronic obstructive pulmonary disease	491–492, 494, 496
Chronic renal disease	582–583, 585–588
Chronic diseases (liver, pancreas, intestine)	571–572, 577.1–577.9, 555, 556
Previous coronary artery bypass graft	36.1, V45.81
Previous coronary angioplasty	00.66, 36.0, V45.82
Cerebral revascularization procedures	00.61, 00.62, 38.01, 38.02, 38.11, 38.12, 38.31, 38.32
Other cardiac operations	35, 37.0, 37.1, 37.3, 37.4, 37.5, 37.6, 37.9
Other vascular operations	38–39.5, excluding: 38.01, 38.02, 38.5, 38.11, 38.12, 38.31, 38.32, 38.93
Thyroid disease	240–246
Drug class	**ATC code**
Cardiac therapy	C01

(Continued)

Table 1. (Continued)

Condition	ICD-9-CM CODE
	Index and previous hospitalizations
Antihypertensives	C02
Diuretics	C03
Beta-adrenergic antagonist	C07
Calcium channel blockers	C08
Acetylcholinesterase inhibitors	C09
Lipid-modifying agents	C10
Oral anticoagulants	B01AA, B01AE, B01AF
Drugs used in diabetes	A10A, A10B
Platelet aggregation inhibitors, excluding heparin	B01AC
Corticosteroids for systemic use	H02
Thyroid therapy	H03

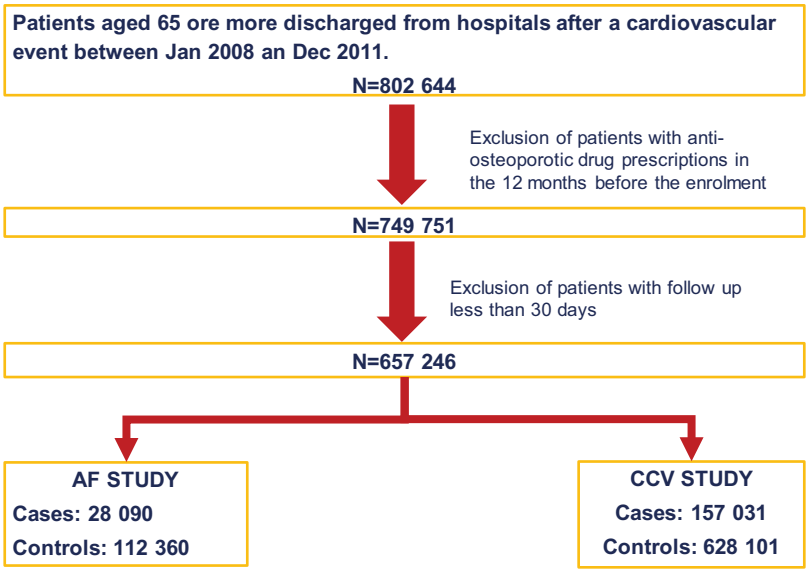

Figure 2. Flow chart cohort enrolment.
AF, atrial fibrillation.

CCV disease and can thus be considered inappropriate for this population.

The present study does not provide evidence for an increased risk of AF or CCV events; moreover, more adherent patients showed a decreased risk of either AF or CCV.

These findings are in line with those from several randomized controlled trials and observational studies, especially with population-based studies from Denmark and the United Kingdom[23–26] and support indications to continue using BPs as a first-line treatment for osteoporosis, keeping patients at high AF and CCV risk closely monitored.[35] On the

Table 2. AF and CCV study: characteristics of cases and controls.

	AF study				CCV study			
	Cases		Controls		Cases		Controls	
	N = 28090		*N* = 112360		*N* = 157026		*N* = 628101	
	N	%	*N*	%	*N*	%	*N*	%
Main diagnosis at index admission								
Acute ischaemic heart disease	1775	6.3	14,013	12.5	6124	3.9	22,674	3.6
Arrhythmia	10,739	38.2	11,861	10.6	4826	3.1	20,471	3.3
Stroke	1043	3.7	10,176	9.1	10,737	6.8	60,003	9.6
Heart failure	3770	13.4	11,046	9.8	30,760	19.6	61,620	9.8
Atrial fibrillation	9663	34.4	8124	7.2	16,173	10.3	42,509	6.8
Comorbidities (any position, 24 months before enrolment)								
Cancer	2032	7.2	9890	8.8	12,833	8.2	54,988	8.8
Diabetes	4180	14.9	21,375	19	35,541	22.6	110,168	17.5
Lipid metabolism disturbances	2317	8.2	11,816	10.5	12,487	8	55,111	8.8
Obesity	696	2.5	2686	2.4	3866	2.5	11,974	1.9
Blood disorders	1903	6.8	8744	7.8	16,145	10.3	55,223	8.8
Hypertension	12,270	43.7	47,282	42.1	67,576	43	261,361	41.6
Previous AMI	2723	9.7	17,315	15.4	27,207	17.3	86,039	13.7
Other forms of ischaemic heart disease (no index)	2056	7.3	7902	7	15,616	9.9	38,502	6.1
Heart failure (no index)	1337	4.8	4007	3.6	12,929	8.2	19,731	3.1
AF (no index)	3447	12.3	5170	4.6	13,166	8.4	27,332	4.4
Ill-defined descriptions and complications of heart disease	1057	3.8	3617	3.2	7471	4.8	18,529	3
Rheumatic heart disease	882	3.1	2224	2	4800	3.1	11,770	1.9
Cardiomyopathy	1444	5.1	4072	3.6	9715	6.2	18,338	2.9
Acute endocarditis and myocarditis	32	0.1	157	0.1	255	0.2	684	0.1
Other heart conditions	1625	5.8	4488	4	9715	6.2	22,528	3.6
Conduction disturbances	956	3.4	3627	3.2	6431	4.1	20,753	3.3
Arrhythmias	20,347	72.4	35,973	32	67,876	43.2	205,166	32.7
Cerebrovascular disease	4317	15.4	37,140	33.1	40,153	25.6	223,523	35.6
Vascular disease	1777	6.3	8668	7.7	13,683	8.7	45,826	7.3
COPD	2723	9.7	12,243	10.9	22,433	14.3	71,442	11.4
Chronic renal disease	2071	7.4	8305	7.4	19,875	12.7	47,877	7.6

(Continued)

Table 2. (Continued)

	AF study				CCV study			
	Cases		Controls		Cases		Controls	
	N = 28090		*N* = 112360		*N* = 157026		*N* = 628101	
	N	%	*N*	%	*N*	%	*N*	%
Chronic disease (liver, pancreas, intestine)	623	2.2	2962	2.6	3829	2.4	15,122	2.4
Previous CABG	1055	3.8	4718	4.2	7030	4.5	21,784	3.5
Previous PCI	2228	7.9	14,891	13.3	17,815	11.3	67,486	10.7
Cerebral revascularization procedures	311	1.1	3595	3.2	2443	1.6	17,989	2.9
Other cardiac operations	1668	5.9	4208	3.7	6763	4.3	18,553	3
Other vascular operations	1156	4.1	5961	5.3	8196	5.2	30,760	4.9
Thyroid disease	1597	5.7	4367	3.9	7106	4.5	23,705	3.8
Drug use (12 months before enrolment)								
Cardiac therapy	13,207	47	38,157	34	73,220	46.6	214,825	34.2
Antihypertensives	2618	9.3	9079	8.1	14,501	9.2	47,820	7.6
Diuretics	11,126	39.6	37,808	33.6	77,093	49.1	219,922	35
Beta-adrenergic antagonist	12,134	43.2	39,986	35.6	61,316	39	202,665	32.3
Calcium channel blockers	10,096	35.9	36,049	32.1	55,541	35.4	198,293	31.6
ACE inhibitors	19,571	69.7	72,813	64.8	110,409	70.3	399,383	63.6
Lipid-modifying agents	9363	33.3	40,622	36.2	54,574	34.8	200,799	32
Oral anticoagulants	8721	31	16,169	14.4	32,274	20.6	85,088	13.5
Drugs used in diabetes	5231	18.6	25,889	23	42,501	27.1	131,648	21
Platelet aggregation inhibitors (excluding heparin)	13,694	48.8	58,529	52.1	85,632	54.5	326,715	52
Corticosteroids for systemic use	3794	13.5	15,196	13.5	23,481	15	87,067	13.9
Thyroid therapy	1432	5.1	4216	3.8	6762	4.3	22,623	3.6

ACE, acetylcholinesterase; AF, atrial fibrillation; CABG, Coronary Artery Bypass Graft; CCV, acute cerebrovascular/cardiovascular events; COPD, chronic obstructive pulmonary disease; PCI, Percutaneous Coronary Intervention.

contrary, a previous multicentre study using data from Italy suggested an increased risk of AF among patients using BPs compared with those who had stopped BP therapy for more than 365 days before the event.[21] An increased AF risk was also reported from a recently published observational study from Taiwan, which yet is not strictly comparable with our study, as BPs were compared to vitamin D rather than to other treatments, and the findings were based on small numbers.[22]

On investigating the effect of exposure duration, the lack of association between BPs or SR and AF or CCV persisted. This might be partly due to a healthy adherer effect: patients with higher adherence are likely to have healthier lifestyle habits. Another possible explanation is that clinicians are more likely to continue prescribing drugs with a long-term treatment effect such as anti-osteoporotic drugs in persons with a long life-expectancy and fewer contraindications. Moreover,

Table 3. AF study: use of anti-osteoporotic drugs and risk of atrial fibrillation: analysis of intensity of use (PDC) and role of time.

	Cases		Controls		OR crude	CI 95%	OR adj	CI 95%
	N	%	*N*	%				
Bisphosphonates	**477**	**1.7**	**1955**	**1.7**	**0.98**	**0.88-1.08**	**1.02**	**0.91-1.14**
<20%	260	100.0	984	100.0	1.06	0.92-1.22	1.07	0.92-1.25
20–80%	176	67.7	743	75.5	0.95	0.81-1.12	1.00	0.84-1.2
>80%	41	15.8	228	23.2	0.72	0.52-1.00	0.81	0.56-1.16
Strontium ranelate	**177**	**0.6**	**659**	**0.6**	**1.08**	**0.91-1.27**	**1.09**	**0.91-1.31**
<20%	114	100.0	389	100.0	1.17	0.95-1.44	1.12	0.89-1.42
20–80%	56	49.1	222	57.1	1.01	0.75-1.35	1.11	0.81-1.54
>80%	7	6.1	48	12.3	0.59	0.27-1.30	0.63	0.28-1.46
Others	**128**	**0.5**	**447**	**0.4**	**1.15**	**0.94-1.4**	**1.13**	**0.91-1.42**
<20%	96	100.0	313	100.0	1.24	0.99-1.57	1.21	0.93-1.56
20–80%	25	26.0	97	31.0	1.04	0.67-1.62	1.08	0.66-1.77
>80%	7	7.3	37	11.8	0.76	0.34-1.69	0.88	0.36-2.17
Nonusers (ref)	**27263**	**97.1**	**109144**	**97.1**	**1**	**-**	**1**	**-**
	Cases		**Controls**		**OR crude**	**CI 95%**	**OR adj**	**CI 95%**
	N	%	*N*	%				
Bisphosphonates	**477**	**1.7**	**1955**	**1.7**	**0.98**	**0.88-1.08**	**1.02**	**0.91-1.14**
current users	230	48.2	983	50.3	0.94	0.81-1.08	0.95	0.81-1.11
recent users	61	12.8	258	13.2	0.95	0.72-1.25	0.99	0.73-1.34
distant users	186	39.0	717	36.7	1.04	0.89-1.23	1.13	0.94-1.35
Strontium ranelate	**177**	**0.6**	**659**	**0.6**	**1.08**	**0.91-1.27**	**1.09**	**0.91-1.31**
current users	61	34.5	983	149.2	0.66	0.67-1.17	0.94	0.7-1.28
recent users	23	13.0	258	39.2	0.94	0.59-1.47	1.04	0.64-1.69
distant users	93	52.5	717	108.8	1.3	1.03-1.64	1.27	0.98-1.65
Others	**128**	**0.5**	**447**	**0.4**	**1.15**	**0.94-1.4**	**1.13**	**0.91-1.42**
current users	35	27.3	141	31.5	0.99	0.68-1.43	1.05	0.7-1.59
recent users	18	14.1	59	13.2	1.22	0.72-2.07	1.08	0.6-1.96
distant users	75	58.6	247	55.3	1.24	0.96-1.61	1.18	0.88-1.58
Nonusers (ref)	**27263**	**97.1**	**10,9144**	**97.1**	**1**	**-**	**1**	**-**

Adjusted for: diagnosis at enrolment, previous AMI, AF, cerebrovascular diseases, cardiomyopathy, rheumatic heart, previous PCI, cerebral revascularization procedures, Cancer, Lipid metabolism disturbances, COPD, hypertension, thyroid disease, cardiac therapy, antihypertensives, beta-adrenergic antagonist, calcium channel blockers, ACE inhibitors, lipid-modifying agents, oral anticoagulants, drugs used in diabetes, thyroid therapy.
ACE, acetylcholinesterase; AF: atrial fibrillation; AMI, acute myocardial infarction; CCV: acute cerebrovascular/cardiovascular events; CI, confidence interval; COPD, chronic obstructive pulmonary disease; OR, odds ratio; PCI, Percutaneous Coronary Intervention; PDC, proportion of days covered.

Table 4. CCV study: use of anti-osteoporotic drugs and risk of CCV outcomes: analysis of intensity of use (PDC) and role of time.

	Cases		Controls		OR crude	CI 95%	OR adj	CI 95%
	N	%	*N*	%				
Bisphosphonates	**2967**	**1.9**	**11350**	**1.8**	**1.05**	**1.01-1.09**	**1.07**	**1.03-1.12**
<20%	1585	53.4	5588	49.2	1.14	1.08-1.21	1.13	1.07-1.20
20–80%	1115	37.6	4312	38.0	1.04	0.98-1.11	1.06	0.99-1.13
>80%	267	9.0	1450	12.8	0.74	0.65-0.85	0.81	0.71-0.92
Strontium ranelate	**1156**	**0.7**	**3939**	**0.6**	**1.18**	**1.10-1.26**	**1.24**	**1.16-1.32**
<20%	762	65.9	2276	57.8	1.35	1.24-1.47	1.37	1.26-1.49
20–80%	347	30.0	1350	34.3	1.03	0.92-1.16	1.10	0.97-1.24
>80%	47	4.1	313	7.9	0.60	0.44-0.82	0.71	0.52-0.97
Others	**578**	**0.4**	**2410**	**0.4**	**0.96**	**0.88-1.06**	**0.99**	**0.90-1.09**
<20%	416	72.0	1689	70.1	0.99	0.89-1.11	1.02	0.92-1.14
20–80%	126	21.8	531	22.0	0.96	0.79-1.16	0.99	0.81-1.20
>80%	36	6.2	190	7.9	0.75	0.53-1.08	0.79	0.55-1.13
Nonusers (ref)	**152032**	**96.8**	**609376**	**97.0**	**1**	**-**	**1**	**-**
	Cases		**Controls**		**OR crude**	**CI 95%**	**OR adj**	**CI 95%**
	N	%	*N*	%				
Bisphosphonates	**2967**	**1.9**	**11350**	**1.8**	**1.05**	**1.01-1.09**	**1.07**	**1.03-1.12**
current users	491	16.5	247	2.2	0.97	0.91-1.03	0.99	0.94-1.06
recent users	302	10.2	673	5.9	1.19	1.06-1.33	1.25	1.11-1.40
distant users	2174	73.3	10430	91.9	1.12	1.05-1.20	1.12	1.05-1.20
Strontium ranelate	**1156**	**0.7**	**3939**	**0.6**	**1.18**	**1.10-1.26**	**1.24**	**1.16-1.32**
current users	183	15.8	101	2.6	0.97	0.87-1.09	1.03	0.92-1.15
recent users	83	7.2	174	4.4	1.10	0.92-1.32	1.18	0.97-1.42
distant users	890	77.0	3664	93.0	1.40	1.28-1.54	1.46	1.32-1.60
Others	**578**	**0.4**	**2410**	**0.4**	**0.96**	**0.88-1.06**	**0.99**	**0.90-1.09**
current users	67	11.6	44	1.8	0.89	0.75-1.05	0.91	0.76-1.08
recent users	50	8.7	67	2.8	1.04	0.82-1.32	1.07	0.83-1.36
distant users	461	79.8	2299	95.4	0.99	0.88-1.12	1.03	0.91-1.16
Nonusers (ref)	**15,2032**	**96.8**	**609376**	**97.0**	**1**	**-**	**1**	**-**

Adjusted for: diagnosis at enrolment, previous AMI, AF, cerebrovascular diseases, heart failure, blood disorders, vascular diseases, previous PCI, cerebral revascularization procedures, conduction disturbances, thyroid disease, chronic renal disease, cardiac therapy, antihypertensives, beta-adrenergic antagonist, calcium channel blockers, ACE inhibitors, lipid-modifying agents, oral anticoagulants, drugs used in diabetes, thyroid therapy.
ACE, acetylcholinesterase; AF: atrial fibrillation; AMI, acute myocardial infarction; CCV: acute cerebrovascular/cardiovascular events; CI, confidence interval; OR, odds ratio; PCI, Percutaneous Coronary Intervention; PDC, proportion of days covered.

long-term users are typically those patients that tolerate the drug well. Similar findings were reported from a study on the association of BP use and valvulopathy, where a protective effect was indicated with prolonged use.[39] Also, a Danish study reported an increased AF risk after discontinuation of BPs, which is intuitive of selective de-prescribing.[20] A similar study on heart failure in patients treated with BPs found a dose-dependent risk reduction among alendronate users.[40] Similarly, a cohort study comparing alendronate with raloxifene found a lower risk of cardiovascular disease in patients receiving higher doses of alendronate.[41] In another cohort an inverse dose-response relationship between exposure to alendronate and the risk of AMI was detected and the authors concluded that this finding 'precludes that alendronate per se increases the risk of AMI and atherosclerosis'.[42]

When comparing results between studies, one must bear in mind the differences in the study populations. For example, the most recent observational study compared BP treatment *versus* vitamin D and none, rather than different active BP treatments[22] (Yang). Our cases and controls were part of a cohort of patients with pre-existing cardiovascular conditions, and this may lower external validity, that is, results may not be fully comparable with those reported by other researchers. Still, the aim of the present study was to identify potentially inappropriate drug treatment in this population and all enrollees were well characterised for the underlying CCV risk.

Another critical aspect when comparing studies arises from differences in exposure definition, which may have an important impact on the results. In our study, adherence was simulated with DDDs because our data do not provide information on individual dosages or patient's compliance. We used different exposure measures, also accounting for the effect of timing and treatment duration.

Osteoporosis in our administrative claims databases is likely to be under-reported, as this condition does not require hospital admission as a primary cause and is unlikely to be recorded on hospital discharge as a secondary cause. Consequently, osteoporosis diagnosis was not among the inclusion criteria, but we considered the osteoporosis drugs as a sufficient proxy for having the disease. We therefore included SR and other anti-osteoporotic drugs for comparison, also bearing in mind that an association between osteoporosis itself and cardiovascular disease has been suggested.[43] Another limit is the fact, that we could not account for vitamin D treatment, as this is not perfectly retrievable in our databases, and that numbers were too small to analyse single BP active agents separately.

The role of the CCV condition at enrolment of the patient was dealt with through two different approaches, namely including the condition as a covariate in the logistic regression model, and performing sensitivity analysis in which cases and controls were matched on their underlying CCV condition. Both approached produced overlapping results. Residual confounding is an issue in all observational studies, especially when based on administrative healthcare data, which do not comprise detailed clinical data or lifestyle information (e.g. body mass index and smoking). We tried to limit confounders by using a new-user design, matching cases with up to four controls, restricting the study population, and performing sensitivity analysis, which produced robust results. For example, we restricted the study population to BP users, comparing different levels of adherence, to rule out the risk of indication bias. Furthermore, in our study we did not have information regarding the indication of drug use, that is, a diagnosis of osteoporosis. Therefore, we compared the risk of the study outcomes not only between users and nonusers of BPs, but also between different osteoporotic treatments, as a proxy for the condition itself, in order to reduce the role of the underlying condition.

Conclusion

The present multicentre study was based on a large population of elderly patients in five different geographic areas in Italy accounting for about 21 million people, that is, about 35% of the overall Italian population. We found no evidence of an increased risk of AF in patients treated with oral BPs or SR compared with nonusers. BP and SR use was associated with an increased risk of CCV, which disappeared with high adherence, suggesting a healthy adherer effect. According to the results of our study, osteoporosis treatment with BPs cannot be considered inappropriate in elderly patients, but they should be carefully monitored.

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Compliance with ethical standards

The present retrospective study was based on administrative healthcare data, which are accessible to the researchers to the ends of the I-GrADE project. According to Italian legislation there was no need to request ethical approval.

Supplemental material

Supplemental material for this article is available online.

ORCID iD

Chiara Sorge https://orcid.org/0000-0002-7277-5900

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