STUDI RETROSPETTIVI: esempi dalla letteratura scientifica

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	N. dosi/conf	N. Confezioni vendute/anno	N. Unità dose/anno	Valore DDD (mg)	N. Unita/DDD	N. DDD cumulative/anno	N. DDD/1000ab/anno	N. DDD/1000ab/die
CIPROFLOXACINA								
CPR RIV 250mg	10	1.320.150	13.201.500	1000	4	3.300.375	57,06	0,16
CPR RIV 500mg	6	2.795.880	16.775.280	1000	2	8.387.640	145,00	0,40
CPR RIV 750mg	12	115.910	1.390.920	1000	1,3	1.043.190	18,03	0,05
Totale		4.231.940	31.367.700			12.731.205	220,10	0,60
LEVOFLOXACINA								
CPR RIV 250mg	5	923.976	4.619.880	250	1	4.619.880	79,87	0,22
CPR RIV 500mg	5	2.866.132	14.330.660	250	0,5	28.661.320	495,49	1,36
Totale		3.790.108	18.950.540			33.281.200	575,36	1,58
MOXIFLOXACINA								
CPR 400mg	5	741.936	3.709.680	400	1	3.709.680	64,13	0,18
NORFLOXACINA								
CPR 400mg	14	1.002.589	14.036.250	800	2	7.018.125	121,33	0,33
CLARITROMICINA								
CPR RIV 250mg	12	802.560	9.630.720	500	2	4.815.360	83,25	0,23
CPR RIV 500mg	14	858.311	12.016.360	500	1	12.016.360	207,74	0,57
CPR RM 500mg	7	308.309	2.158.160	500	1	2.158.160	37,31	0,10
Totale		1.969.180	23.805.240			18.989.880	328,29	0,90
KETOLIDE								
CPR RIV 400mg	10	159.900	1.599.000	800	2	799.500	13,82	0,04

Tabella 1

Esempio di costruzione degli indicatori di intensità di utilizzazione di alcuni antibiotici secondo il sistema DDD utilizzando dati di vendita stimati in Italia nell'anno 03/2001-03/2002 e assumendo una popolazione complessiva di 57.844.000 abitanti.

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Studi caso-controllo prospettici

- "Standard" case-control studies, the most common study design in epidemiologic research, may often be viewed as nested case–control studies **in which a portion of underlying cohort (usually among the non diseased) has not been identified**
- Lo **studio caso-controllo innestato in una coorte** (nested case-control design) è uno studio che origina da una coorte seguita nel tempo
- Un sottoinsieme della coorte (ed eventualmente dei casi) viene estratto con selezione casuale
- Ulteriori informazioni vengono raccolte per i casi e il sottoinsieme della coorte selezionato
- Lo studio nested case-control è impiegato per indagini in cui non è conveniente raccogliere l'informazione per l'intera coorte, ad esempio quando deve essere somministrato un test costoso o quando la coorte è molto numerosa

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Ghirardi *et al. BMC Gastroenterology* 2014, **14**:5
http://www.biomedcentral.com/1471-230X/14/5

BMC Gastroenterology

RESEARCH ARTICLE Open Access

Oral bisphosphonates do not increase the risk of severe upper gastrointestinal complications: a nested case–control study

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https://bmcgastroenterol.biomedcentral.com/articles/10.1186/1471-230X-14-5

clinical evidence of adverse effects than placebo suggesting that these drugs are well tolerated. However, soon after alendronate release, an unexpected higher number of cases of oesophagitis and oesophageal strictures were encountered when the drug was prescribed to the general population, which resulted in changes to the alendronate label [22,23]. From then on nowadays, inconsistent findings on gastrointestinal (GI) safety of BPs have been reported [24-29]. Two meta-analyses on this topic came to conflicting conclusions [30,31], suggesting that evidence on gastrointestinal safety of these agents are still insufficient.

To shed further light on the association between use of BPs and the risk of hospitalization for upper gastrointestinal complications (UGIC), we carried out a large nested case–control study in a cohort of patients hospitalized for osteoporotic fracture.

Methods

Data source

The data used for the present study were retrieved from the health service databases of all the 13 Italian territorial units participating at the AIFA-BEST (Bisphosphonates Effectiveness-Safety Tradeoff) project. The general aim of this project is to provide an assessment of the benefit-risk profile of BPs use. Further details of the study design and procedure can be found elsewhere [32].

Territorial units participant to the AIFA-BEST project were four Regions (Abruzzo, Emilia-Romagna, Marche and Toscana) and nine Local Health Authorities (Caserta, Como, Gorizia, Latina, Lodi, Milano, Monza, Sondrio and Varese). A population of about 17 million of beneficiaries of National Health Service (NHS) residents in these territorial units was covered by the corresponding HCU databases, accounting for nearly 30% of the whole Italian population.

Italian population is entirely covered by the NHS that provides universal and free of charge coverage for many healthcares, such as hospitalizations for any causes and several drug therapies (including medicaments for treatment of osteoporosis). This program is administered by an automated system of databases on the use of health services supplied free of charge from NHS and including: (i) an archive of beneficiaries of NHS (practically the whole resident population), inclusive of demographic and administrative data; (ii) details of hospitalizations in private and public hospitals, inclusive of diagnosis at discharge; and (iii) outpatients medicament prescriptions reimbursable from the NHS [according to Italian rules, outpatients medicaments supplied free of charge from NHS may be dispensed only from pharmacies and only by prescription]. With the aim of obtaining the complete history of healthcare utilization of all the NHS beneficiaries, the different pieces of information recorded into these databases can be linked using a unique personal identification code. In order to preserve privacy, we replaced the original identification code with its digest that is the image of the code through a cryptographic hash function – the Secure Hash Algorithm (SHA-256). Such hash function (i) makes infeasible to obtain the original code from the digest, (ii) is deterministic, i.e. the same digest is always associated to any given individual, and (iii) is collision-resistant, i.e. the probability that two individuals are associated to the same code is insignificant. The specific hash function used (SHA-256) is the industry standard [33] and has been incorporated into the data extraction-transformation-load software produced by the University of Milano-Bicocca.

Data were drawn out from databases by means of standardized queries which were defined and tested according to the study protocol. Additional file 1 provides specific diagnostic and therapeutic codes used for our study.

Cohort selection

We identified patients aged 45 years or older who have been hospitalized for osteoporotic fracture from July 1, 2003 until December 31, 2005 and the date of hospital discharge was designed as that of entry into the cohort. Patients were excluded if, within six months prior the cohort entry date, they had at least one BPs prescription or they have been hospitalized for bone fracture, gastrointestinal adverse events, Paget's disease, coagulation disorders, alcohol abuse, chronic liver disease or cancer. Patients who were registered into the archive of NHS beneficiaries from less than six months prior the entry into the cohort and those who did not reach at least 60 days of follow-up were also excluded. The remaining patients constituted the study cohort.

Each member of the cohort accumulated person-years of follow-up from the date of entry until the earliest date among those of outcome onset (hospital admission for UGIC) or censoring (death, emigration or 31 December 2007).

Selection of cases and controls

We identified patients who during follow-up experienced at least a hospitalization with diagnosis of UGIC including oesophageal/gastrointestinal ulcer, perforation of oesophagus, oesophageal/gastrointestinal haemorrhage (see Additional file 1: Table S1). A patient who experienced at least one of these events was considered as having the outcome. The earliest date of hospital admission recording one of these events was considered as the index date.

Up to twenty controls for each case patient were selected randomly from the cohort to be matched for territorial unit of recruitment, gender, age at cohort entry,

date of entry into the cohort and were at risk for the outcome at the time when the matched case had the event. In these conditions each set established from one case and the corresponding matched controls had the same extension of observational period which began at the date of index prescription and stopped at the event date of the index case.

Exposure assessment

During the study period two drug types (alendronate and risedronate) either on once-daily (10 mg/day and 5 mg/day, respectively) or once-weekly (70 mg/week and 35 mg/week, respectively) regimens were available for free reimbursement by Italian NHS.

Drug-dispensing history of BPs prescribed to cases and controls during the observational period was assessed from the prescription drug database. Exposure was categorized into mutually exclusive groups of current, past, and no use, taking as reference the index date [27]. A patient was defined current user if at least one prescription of BPs was dispensed within 30 days or less prior the index date. Past users were defined as those who at least one prescription of BPs was dispensed later than 31 days prior the index date. No users were patients who during the entire observational period did not experience BPs dispensation.

Covariates

For each case and control the dispensation of some medicaments over the 60-day period prior the index date was investigated. Medicaments included antidepressants, antithrombotic, gastroprotective agents, corticosteroids, statins, calcium channel blockers, other antihypertensive agents and nonsteroidal antiinflammatory agents (NSAIDs) (see Additional file 1: Table S1). In addition, the Charlson comorbidity index score was calculated [34], using the diagnostic information available from inpatient charts in the six months prior the date of entry into the cohort and during the entire period of follow-up. Two categories of the Charlson comorbidity index score were considered, i.e. 0 and 1, respectively denoting absence and presence of at least one comorbidity.

Statistical analyses

Chi-square was used to test differences between cases and controls. A conditional logistic regression model was fitted to estimate the odds ratio (OR), as well as its 95% confidence interval (CI), of UGIC associated with use of BPs (anytime, current or past), taking non-use as reference. Adjustments were made for the above reported covariates. The combined effect of BPs with co-treatments and co-morbidity was estimated by including the corresponding interaction terms in a conditional logistic model. The differential effect of type and regimen of the dispensed BPs was also evaluated by means of stratification analysis.

Sensitivity analyses

The following sets of sensitivity analyses were performed. First, we verified if our estimates were affected by the adopted criteria for defining UGIC. Data were analysed according to alternative diagnostic criteria, i.e. those recently proposed by *Cadarette* et al. while investigating oral BPs safety [28], as well as those used by a collaborative project aimed to exploit European healthcare databases for drug safety signal detection, the so called EU-ADR Project [35]. Second, we verified if our estimates were affected by the adopted criteria for defining exposure. With this aim we used time-window lengths of 7, 15 or 45 days prior the index date for defining current use, alternative to 30 days as in the main analysis.

The SAS statistical package was used for the analyses (SAS, Version 9.1; SAS Institute, Cary, North Carolina, USA). For all hypotheses tested two-tailed p-values less than 0.05 were considered to be significant.

Ethical considerations

The study protocol was notified to the Italian Medicines Agency (AIFA) and to the local ethics committees of all the territorial units involved in the investigation. There was no legal requirement for ethics committee approval since we used only unidentifiable patient data and did not contact the patients.

Results

Sample selection

The distribution of the exclusion criteria is shown in Figure 1. At entry, the 68,970 patients who were included into the cohort had mean age of 76.2 years (SD 12.5 years) and 71% of them were women. During follow-up these patients accumulated 220,135 person-years of observation and generated 804 hospital admissions for UGIC, with an incidence rate of 36.5 cases per 10,000 person-years. The 804 patients who experienced hospitalization for UGIC (case patients) were matched to 12,787 controls.

Patients

At the cohort entry, mean age of cases and controls was 79.9 years (SD: 9.9 years), and nearly 72% of them were women (matching variables). As shown in Table 1, there was not statistical evidence that case patients and controls differed for use to BPs during the entire observational period, as well as during current and past periods. Similarly, there was not evidence that cases and controls differ for BPs type and regimen refilled during the current period. Conversely, with the exception of statins and calcium channel blockers, co-treatments with the other considered drugs, as well as the presence of at least one sign of

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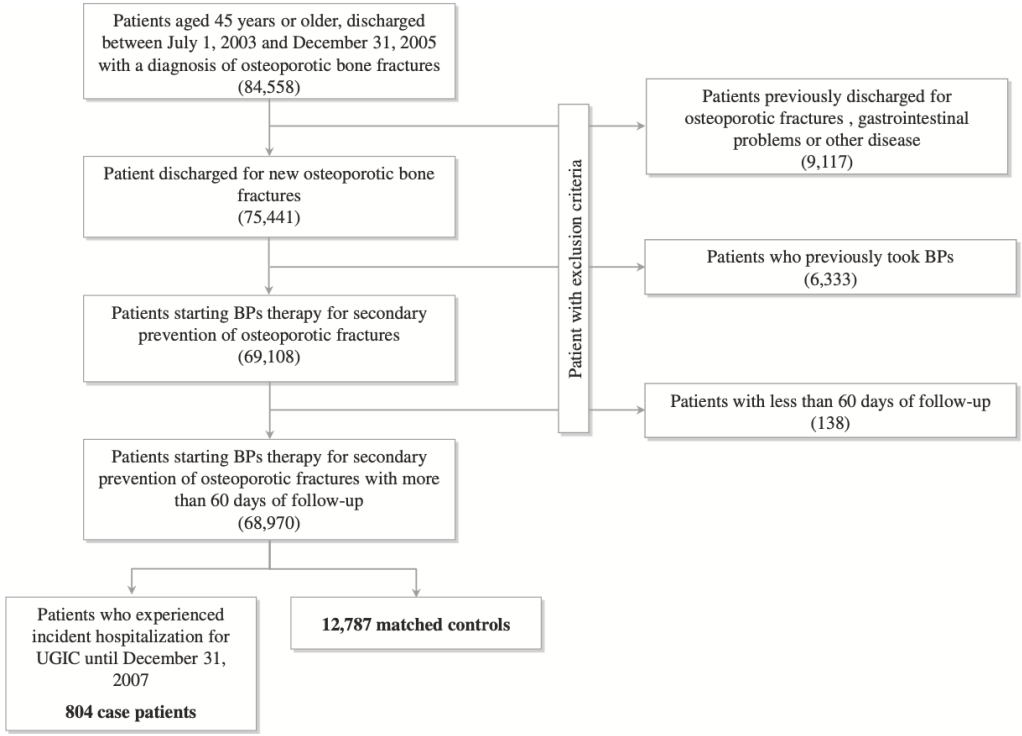

Figure 1 Study flow diagram. AIFA-BEST Project, Italy, 2003–2007. Flow chart of inclusion and exclusion criteria. BPs: Bisphosphonates.

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Table 1 Selected tracts of the 804 cases of upper gastrointestinal complications and 12,787 controls

	Case patients	Controls	p-value*
BPs exposure†			
No use	709 (88.2%)	11,345 (88.7%)	0.6029
Current use	38 (4.7%)	643 (5.0%)	
Past use	57 (7.1%)	799 (6.2%)	
Type prescribed during the current period			
Alendronate	30 (79.0%)	412 (64.1%)	0.0620
Risedronate	8 (21.0%)	231 (35.9%)	
Regimen prescribed during the current period			
Weekly	37 (97.4%)	631 (98.1%)	0.7376
Daily	1 (2.6%)	12 (1.9%)	
Use of other medicaments‡			
Antidepressants	139 (17.3%)	1,841 (14.4%)	0.0242
Antithrombotic	240 (29.9%)	3,174 (24.8%)	0.0014
Gastroprotective agents	211 (26.2%)	1,993 (15.6%)	<0.0001
Corticosteroids	65 (8.1%)	533 (4.2%)	<0.0001
Statins	41 (5.1%)	724 (5.7%)	0.5021
Calcium channel blockers	105 (13.1%)	1,548 (12.1%)	0.4223
Other antihypertensive drugs	371 (46.1%)	5,294 (41.4%)	0.0082
Nonsteroidal antiinflammatory drugs	170 (21.1%)	1,529 (12.0%)	<0.0001
Co-morbidity#			
0	629 (78.2%)	11,531 (90.2%)	<0.0001
≥1	175 (21.8%)	1,256 (9.8%)	

BPs: Bisphosphonates.
†A patient was defined current user if at least one prescription of BPs was refilled within 30 days or less prior the index date. A patient was defined past user if at

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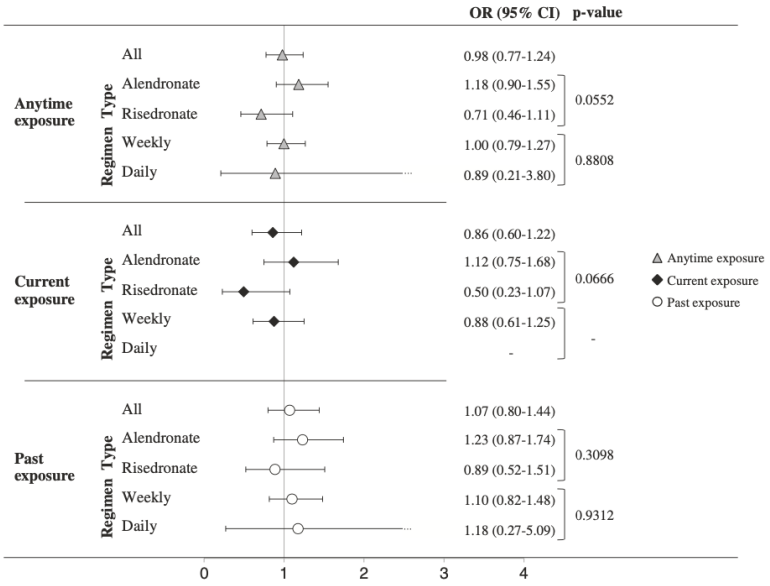

Figure 2 Adjusted odds ratios (and 95% confidence intervals) of upper gastrointestinal complications associated with anytime, current and past exposure to bisphosphonates as a whole (all) as well as to type (alendronate and risedronate) and regimen (daily and weekly) of the latest dispensed bisphosphonates. AIFA-BEST Project, Italy, 2003–2007. Odds ratios estimated with conditional logistic regression model. Estimates concerning main analysis (all) were adjusted for use of other medicaments in the 60-day period and for the Charlson index measured before the index date. Estimates concerning subgroup analysis were obtained by including the interaction terms combining the effect of anytime, current or past exposure to BPs together with type and regimen of the dispensed BPs. P-values concern comparison of BPs effect across patient subgroups. BPs: Bisphosphonates.

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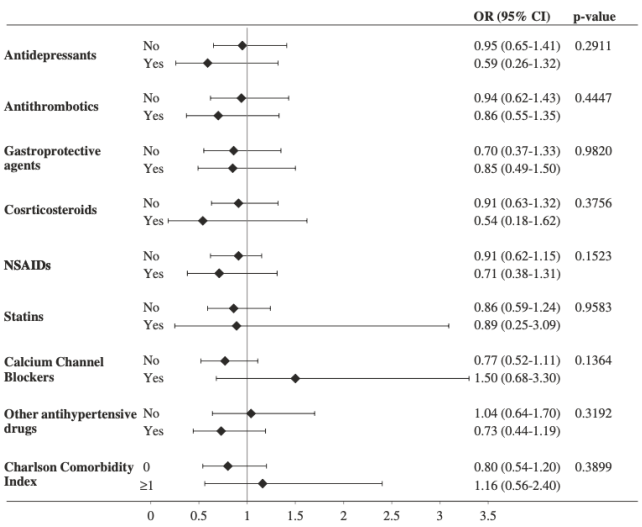

Figure 3 Combined action of current exposure to bisphosphonates, concurrent exposure to other medicaments and categories of Charlson comorbidity index on the risk of upper gastrointestinal complications. AIFA-BEST Project, Italy, 2003–2007. Odds ratios estimated with conditional logistic regression model. Estimates were obtained by including the interaction terms combining the effect of current exposure to BPs together with concurrent use of other medicaments and the categories of the Charlson index. P-values concern comparison of BPs effect across patient subgroups. BPs: Bisphosphonates.

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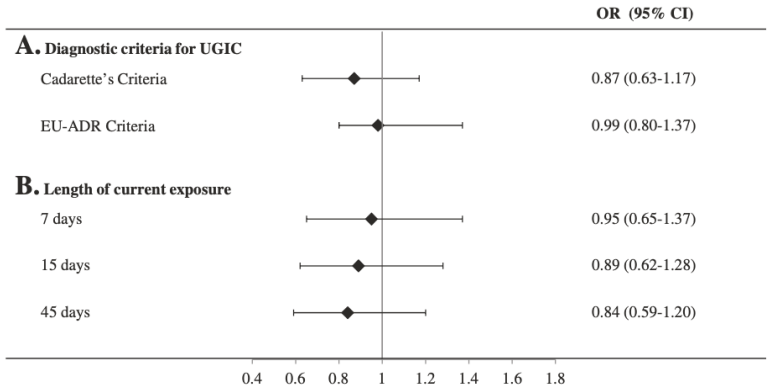

Figure 4 Influences of diagnostic criteria for defining upper gastrointestinal complications (panel A), and of the time-window length for defining current use of BPs (panel B) on the observed odds ratio of upper gastrointestinal complications associated with current exposure to bisphosphonates. AIFA-BEST Project, Italy, 2003–2007. Odds ratios estimated with conditional logistic regression model. Estimates were adjusted for use of medicaments in the 60-day period and for the Charlson index measured before the index date. Details for diagnostic criteria are reported in Additional file 1. BPs: Bisphosphonate.

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Osteoporos Int (2015) 26:1499–1506
DOI 10.1007/s00198-014-3020-y

ORIGINAL ARTICLE

Risk of atrial fibrillation among bisphosphonate users: a multicenter, population-based, Italian study

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Received: 11 February 2014 / Accepted: 23 December 2014 / Published online: 10 March 2015

Abstract
Summary Bisphosphonate treatment is used to prevent bone fractures. A controversial association of bisphosphonate use and risk of atrial fibrillation has been reported. In our study, current alendronate users were associated with a higher risk of atrial fibrillation as compared with those who had stopped bisphosphonate (BP) therapy for more than 1 year.
Introduction Bisphosphonates are widely used to prevent bone fractures. Controversial findings regarding the association between bisphosphonate use and the risk of atrial fibrillation (AF) have been reported. The aim of this study was to evaluate the risk of AF in association with BP exposure.
Methods We performed a nested case-control study using the databases of drug-dispensing and hospital discharge diagnoses from five Italian regions. The data cover a period ranging from July 1, 2003 to December 31, 2006. The study population comprised new users of bisphosphonates aged 55 years and older. Patients were followed from the first BP prescription until an occurrence of an AF diagnosis (index date, i.e., ID), cancer, death, or the end of the study period, whichever came first. For the risk estimation, any AF case was matched by age and sex to up to 10 controls from the same source population. A conditional logistic regression was performed to obtain the odds ratio with 95 % confidence intervals (CI). The BP exposure was classified into current (<90 days prior to ID), recent

Electronic supplementary material The online version of this article (doi:10.1007/s00198-014-3020-y) contains supplementary material, which is available to authorized users.

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Cohort selection

People aged 55 years and over with at least one BP prescription during the study period were recruited, and the date of their first dose was used as their entry into the study. Only new users (with no previous prescription of BP within a 6-month period prior to entry in the study) were included.

Subjects with a history of hospitalization due to malignant neoplasm (ICD-9: 140 to 208) or atrial fibrillation (ICD-9: 427.31) at study entry were excluded (Fig. 1), and each patient was followed from the study entry date until the occurrence of AF, cancer, death, or the end of the study period (December 31, 2006), whichever came first.

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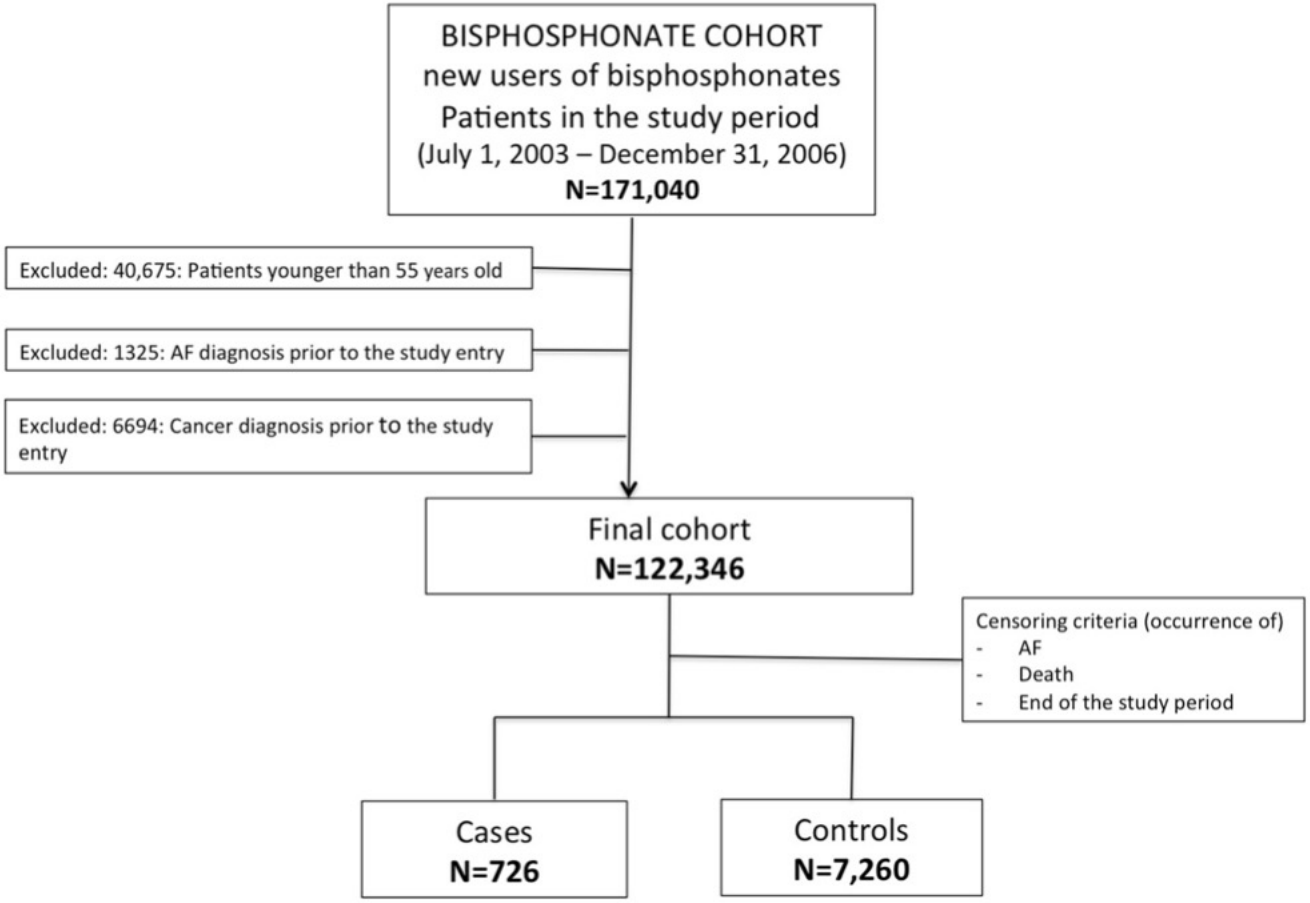
Fig. 1 Flow chart of the bisphosphonate cohort and case-control selection process



Study design

A case-control study nested in a cohort of new users of BP was performed in order to assess the risk of AF with BP use. All analyses were specified a priori in the study protocol.

Case and control definitions

A case was defined as a person with a primary discharge diagnosis of incidental AF (ICD-9: 427.31) during the study period. The date of a diagnosis of AF was considered as the index date (ID), and every case was matched with up to ten controls from the same cohort by age, sex, and time of cohort entry. Controls were selected using incidence density sampling. In general, this method consists of matching each case to a sample of those who are at risk at the time of case occurrence [28]. The index date of the controls was the same as those for the matched cases.

Exposure assessment

The area of interest included all BP marketed in Italy (ATC: M05BA* and M05BB*). The duration of exposure for each prescription was calculated by dividing the total amount of the drug dispensed by the defined daily drug specific dose (DDD). Three mutually exclusive categories were defined according to the temporal proximity of BP use: current use, if the estimated exposure to BP covered the index date or ended within 90 days prior to ID (i.e., carry-over period) [18]; recent use, if the exposure to BP ended between 91 and 180 days prior to ID; and past use, if the exposure to BP ended 181 and 365 days prior to ID. In addition, distant past use was used as reference category for all the analyses, if the exposure to BP had ended more than 365 days prior to ID.

Covariates

Known risk factors for AF were identified by searching among primary/secondary hospital discharge diagnoses or drug prescriptions. The presence of the following potential risk factors was evaluated for any period prior to ID: myocardial infarction, angina pectoris (defined by diagnosis or use of nitrates), heart failure, diabetes mellitus (defined by diagnosis or use of hypoglycemic drugs), hyperthyroidism, and prior use of antihypertensive drugs (including beta-blockers), lipid lowering drugs, antithyroid drugs, oral corticosteroids, and estrogens/hormone replacement therapy (HRT). In addition, a history of specific types of fractures was also considered: pelvic, hip, femur, tibia, fibula, and vertebral fractures.

Data analysis

Chi-square tests for categorical variables and Student *t* tests for continuous variables were used to assess the differences between cases and controls. The incidence rate of diagnosis of AF in the cohort of new users of BP was calculated as the number of events occurring during follow-up divided by the cumulative person-years of exposure in the study period. A conditional logistic regression was performed to obtain the odds ratio (OR) as an estimate of the relative risk of AF for different BP exposure categories. ORs and 95 % CI were calculated for current, recent, and past use of bisphosphonates,

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Table 1 Incidence rates of atrial fibrillation per 1,000 person-years by sex and age in the Italian cohort of new users of bisphosphonates (n=122,346)

Age groups (years)	All Cases/py	Incidence rate (95 % CI)	Men Cases/py	Incidence rate (95 % CI)	Women Cases/py	Incidence rate (95 % CI)
55–59 years	11/11,118	0.99 (0.53–1.71)	2/1455	1.37 (0.27–4.41)	9/9663	0.93 (0.46–1.7)
60–64 years	37/20,855	1.77 (1.27–2.42)	7/2606	2.69 (1.20–5.27)	30/18,249	1.64 (1.13–2.31)
65–69 years	72/31,766	2.27 (1.79–2.84)	17/3850	4.42 (2.67–6.91)	55/27,916	1.97 (1.5–2.54)
70–74 years	122/37,805	3.23 (2.7–3.84)	16/4597	3.48 (2.07–5.52)	106/33,208	3.19 (2.63–3.84)
75–79 years	215/41,326	5.20 (4.55–5.93)	42/5275	7.96 (5.82–10.65)	173/36,051	4.80 (4.12–5.55)
80–84 years	157/34,882	4.50 (3.84–5.25)	17/4731	3.59 (2.17–5.62)	140/30,151	4.64 (3.92–5.46)
85 years	112/21,119	5.30 (4.39–6.36)	16/2969	5.39 (3.21–8.54)	96/18,150	5.29 (4.31–6.43)
Total	726/198,871	3.65 (3.40–3.92)	117/25,483	4.59 (3.81–5.48)	609/173,388	3.51 (3.24–3.80)
Standardized[a]		2.44(1.91-3.12)				

py person-years, *CI* confidence interval

[a] Age—standardized incidence rate using World Health Organization reference population

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Table 2 Characteristics of cases of atrial fibrillation and controls

Characteristics	Cases n=726	Percent	Controls n=7260	Percent	p value
Gender, female	609	83.88	6090	83.88	–
Age[a]	76.9±7.64		76.9±7.65		–
Age categories					
55–65 years	59	8.10	602	8.30	
66–75 years	219	30.20	2155	29.70	
76–85 years	361	49.70	3637	50.10	
>85 years	87	12.00	866	11.90	
Cardiovascular diseases					
Angina pectoris	203	27.96	1215	19.95	<0.001*
Myocardial infarction	20	2.75	92	1.51	0.001*
Heart failure	80	11.02	199	3.27	<0.001*
Antihypertensive drugs	627	86.36	5186	85.16	<0.001*
Diabetes mellitus	84	11.57	780	12.81	0.494
Estrogen/hormone replace therapy	35	4.82	334	5.48	0.787
Any type of fractures	78	10.74	669	10.99	0.177
Prior use of drugs					
Use of lipid lowering	181	24.93	1497	20.62	0.007*
Oral corticosteroids	271	37.33	2184	30.08	<0.001*
Antithyroid	18	2.48	87	1.20	0.004*

*p<0.05 (significant)

[a] The data is mean±standard deviation

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Table 3 Association between exposure to oral bisphosphonates and atrial fibrillation

	Cases *n*=726 (%)	Controls *n*=7260 (%)	Crude OR (95 % CI)	Adjusted OR (95 % CI)
Current	373 (51)	3129 (43)	1.71 (1.41–2.08)	1.78 (1.46–2.16)
Recent	78 (11)	667 (09)	1.68 (1.26–2.23)	1.70 (1.27–2.28)
Past	96 (13)	1006 (14)	1.38 (1.06–1.80)	1.41 (1.07–1.85)
Distant past	179 (25)	2458 (34)	Reference	Reference

Adjusted for angina pectoris, heart failure, antihypertensive drugs, myocardial infarction, use of lipid lowering drugs, oral corticosteroids, and antithyroid drugs. Categories of users: current (0–90 days prior to index date), recent (91–180 days), past (181–365 days), and distant past (365+days)

CI confidence interval, *OR* odds ratio

Table 4 Associations between atrial fibrillation and oral bisphosphonates by single compound

	Cases n=726 (%)	Controls n=7260 (%)	Crude OR (95 % CI)	Adjusted OR* (95 % CI)
Current users (0–90 days)				
Etidronate	0 (0.00)	7 (0.10)	(NA)	NA
Clodronate	4 (0.55)	34 (0.47)	1.66 (0.58–4.76)	1.68 (0.58–4.88)
Alendronate	255 (35.12)	1930 (26.58)	1.88 (1.53–2.31)	1.97 (1.59–2.43)
Risedronate	82 (11.29)	868 (11.96)	1.36 (1.03–1.79)	1.35 (1.01–1.79)
Neridronic acid	12 (1.65)	119 (1.64)	1.43 (0.77–2.66)	1.46 (0.78–2.75)
Alendronate plus colecalciferol	15 (2.07)	132 (1.82)	1.67 (0.94–2.96)	1.79 (1.00–3.21)
More than one BP within the same period of time.	5 (0.69)	39 (0.54)	1.83 (0.71–4.7)	2.07 (0.79–5.46)
Recent users (91–180 days)				
Etidronate	0 (0.00)	6 (0.08)	(NA)	NA
Clodronate	3 (0.41)	12 (0.17)	3.42 (0.95–12.23)	4.12 (1.1–15.36)
Alendronate	44 (6.06)	420 (5.79)	1.50 (1.06–2.13)	1.49 (1.04–2.14)
Risedronate	20 (2.75)	165 (2.27)	1.76 (1.07–2.88)	1.87 (1.13–3.08)
Neridronic acid	1 (0.14)	43 (0.59)	(NA)	NA
Alendronate plus colecalciferol	7 (0.96)	16 (0.22)	6.72 (2.63–17.17)	6.63 (2.48–17.70)
More than one BP within the same period of time.	3 (0.41)	3 (0.04)	13.64 (2.73–68.12)	11.38 (2.24–57.73)
Past users (181–365 days)				
Etidronate	0 (0.00)	6 (0.08)	(NA)	NA
Clodronate	1 (0.14)	16 (0.22)	(NA)	NA
Alendronate	63 (8.68)	635 (8.75)	1.44 (1.06–1.95)	1.46 (1.06–1.99)
Risedronate	28 (3.86)	251 (3.46)	1.62 (1.06–2.48)	1.63 (1.05–2.51)
Neridronic acid	2 (0.28)	76 (1.05)	(NA)	NA
Alendronate plus colecalciferol	0 (0.00)	13 (0.18)	(NA)	NA
More than one BP within the same period of time.	2 (0.28)	11 (0.15)	(NA)	NA
Distant past user of any BP>365 days	179 (24.66)	2458 (33.90)	Reference	Reference

Adjusted for angina pectoris, myocardial infarction, heart failure, antihypertensive drugs, use of lipid lowering drugs, oral corticosteroids, and antithyroid therapy