

**MANUSCRIPT TITLE:**

Oral bisphosphonate use and age-related macular degeneration: retrospective cohort and nested case-control study

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## **ABSTRACT**

**Background:** Hydroxyapatite (calcium and phosphate) spherules have been implicated in the initiation and establishment of age-related macular degeneration. Bisphosphonates could increase the dissolution of hydroxyapatite crystals and when they are used in elderly patients with osteoporosis they could reduce the risk of developing age-related macular degeneration.

**Objective:** To determine if oral bisphosphonate (BP) use is associated with the incidence of age-related macular degeneration in a large “real-world” population-based cohort of incident hip fracture patients.

**Design:** A cohort of 13,974 hip fracture patients (1999 to 2013) were used to conduct a: (a) propensity score matched cohort analysis and (b) nested case-control analysis.

**Setting:** A population-based study using electronic health records from UK primary care (Clinical Practice Research Datalink).

**Participants:** Hip fracture patients aged  $\geq 50$  years without age-related macular degeneration diagnosis prior to hip fracture date or in the first year of follow-up. Prior BP-users and those who died, transferred out or with last data collected before hip fracture were excluded.

**Exposures:** Incident BP use following hip fracture. BP use was further categorised according to medication possession ratio in quartiles.

**Main outcome measures:** Primary outcome was a diagnosis of age-related macular degeneration after the first year from index date. Propensity scores were used to match 1:1 BP-users to non-BP users. Covariates in the propensity score were index year, age, gender, body mass index, smoking, alcohol drinking, region, drug confounders and comorbidities. Subhazard ratios and their 95% confidence intervals were calculated including death as a competing risk. A nested 1:20 case-control analysis using conditional logistic regression provided risk estimates according to medication possession ratio.

**Results:** Among 6,208 matched patients and during 22,142 person-years of follow-up, 57 (1.8%) and 42 (1.4%) age-related macular degeneration cases occurred in BP-users and non-BP users, respectively. The survival analysis model did not provide significant evidence of a higher risk of AMD in BP-users (subhazard ratio: 1.60; CI: 0.95-2.72;  $P=0.08$ ) although there was a significant increased risk among BP-users with high medication possession ratio (top quartile) relative to non-BP users (odds ratio: 5.08, 3.11-8.30;  $P < 0.001$ , respectively).

**Conclusions:** Overall, oral BP use was not associated with an increased risk of age-related macular degeneration in this cohort of hip fracture patients, although the risk increased significantly with higher medication possession ratio. More data are needed to confirm these findings.

## **KEYWORDS**

Oral bisphosphonates, age-related macular degeneration, hip fracture, propensity score matching, nested case-control study

## INTRODUCTION

Age-related macular degeneration (AMD) is irreversible central vision loss which is involved in 8.7% of all blindness worldwide<sup>1</sup>. It is the leading cause of permanent vision impairment and the most prevalent condition of ocular deterioration in the population aged over 50<sup>2</sup>. In the UK there are around an estimated 71,000 new cases of late AMD per year<sup>3</sup>, contributing to the total £1.6 billion<sup>4</sup> annual cost of AMD. AMD is subdivided into dry (non-neovascular, non-exudative) and wet (neovascular, exudative) forms and is characterized by distortion of central vision, black or grey patches affecting the central field of vision, and difficulty in reading, driving, or seeing fine detail<sup>2, 5</sup>.

Osteoporosis is a musculoskeletal disease defined by low bone mass and degradation of bone microarchitecture, culminating in an escalation in bone frailty and susceptibility to fracture. It is estimated to affect approximately one-tenth of women aged 60 and up to two-thirds of women aged 90<sup>6</sup>, with approximately 200 million women affected worldwide. Several parts of the skeleton are affected with the hip being a common site sustaining a fracture, reported in the region of 65,000 cases each year across England, Wales and Northern Ireland<sup>7</sup>.

The molecular events and their sequence leading to AMD are poorly understood.

Hydroxyapatite (calcium and phosphate) spherules, has now been identified as a key component in the development of the disease<sup>8</sup>. Bisphosphonates, the first line of treatment for osteoporosis, could increase the dissolution of hydroxyapatite crystals and thus they could reduce the risk of AMD. Our aim in this study was to investigate whether the risk of developing AMD is affected by the oral BP use in a “real-world” population-based cohort of incident hip fracture patients.

## **METHODS**

### **Data source and sample size**

This study was carried out using data from the Clinical Practice Research Datalink (CPRD). CPRD contains primary care data from 674 UK practices and includes 11.3 million patients, covering 7% of the UK population<sup>9</sup>. Many aspects of CPRD have been well validated and it has been applied for a variety of safety studies comprising BPs<sup>10-12</sup>. A cohort of patients with an incident hip fracture was retrieved for the period 1999 to 2013. Mortality data were matched to the Office for National Statistics database.

### **Study design**

Baseline characteristics were collected closest (during the previous 12 months) to the hip fracture event. We used a cohort study design among patients followed forward from hip fracture until the earliest date of either being lost to follow-up, death, or 31 July 2013. A nested case-control study was also conducted to estimate the association between BP dose and risk of AMD.

### **Exposure**

Post index-date prescription records were used to categorise patients as either oral BP-users or non-users. Oral BP use was further classified according to defined daily dose (DDD) and medication possession ratio (MPR). MPR was calculated as DDD between date of first BP

prescription and outcome date (or last prescription). DDDs and MPRs were categorised into quartiles.

Immortal time bias is a common issue in pharmaco-epidemiological studies. In the time from index date until receipt of BP, those in the 'BP-user group' cannot have the outcome by design as otherwise they would have been classified as a non-BP user. To address this issue we used time varying exposures in the survival model, where the time period previous to becoming a BP-user was reclassified as non-use for those in the oral BP-user group.

### **Outcome**

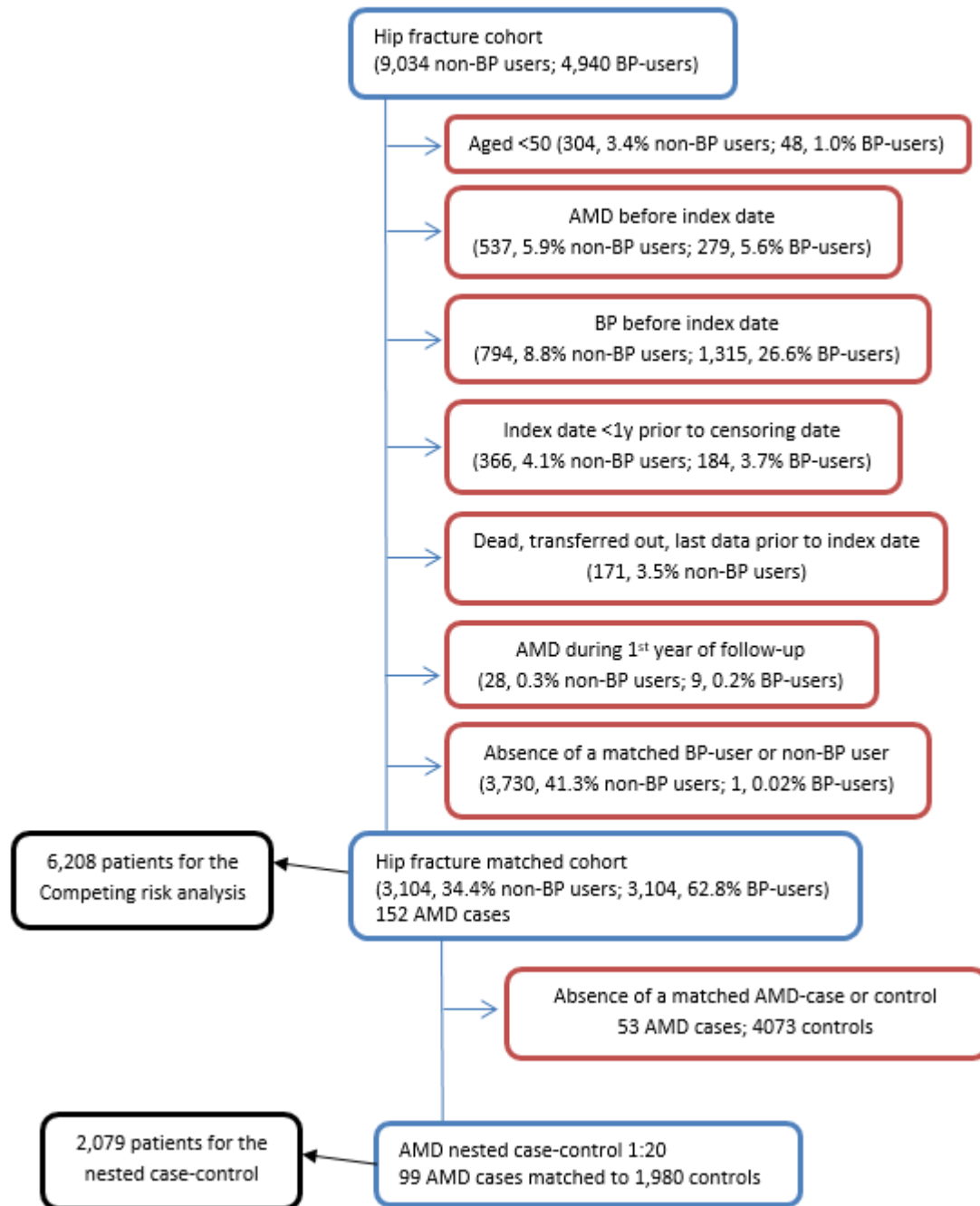
Our defined outcome was AMD recorded at least one year after follow-up initiation. Cases were identified using standard UK clinical terminology "Read" codes: F425100 ("dry senile macular degeneration"), F425200 ("wet senile macular degeneration"), F425z00 ("degeneration of macula or posterior pole, not otherwise specified"), F425.00 ("degeneration of macula and posterior pole"), F425.11 ("senile macular degeneration") and F425000 ("unspecified senile macular degeneration").

### **Exclusion criteria**

Patients younger than 50 years at hip fracture were excluded (Figure 1) given their low risk of AMD<sup>5</sup> and that bisphosphonates are infrequently prescribed in younger individuals. Patients were excluded if they had a diagnosis of AMD either before index date or during the first year of follow-up. Patients with a BP prescription, or who transferred out of CPRD prior to index hip fracture date were also excluded, as were patients with an index hip fracture occurring after 31 July 2012 given that they had insufficient follow-up time (less than one year) to experience the outcome. Finally, patients on non-nitrogen containing BPs

(etidronate), parenteral antiresorptives (zoledronic acid, pamidronate and denosumab) together with those on teriparatide (a bone forming agent) were not included in the study, because the number of those patients was negligible.

**Fig. 1. Flow of included patients.** Proportions of excluded observations at each point of exclusion. BP indicates oral bisphosphonates.



## Confounders

Factors considered potential confounders were calendar year of hip fracture, age, gender, body mass index (BMI), smoking (no, ex-smoker, smoker), alcohol consumption (no, ex-drinker, drinker) and region (North England [North East, North West, Yorkshire & The Humber, East Midlands, West Midlands, East of England], South England [South West, South Central, London, South East Coast], Northern Ireland, Scotland and Wales).

Drug confounders were antiarrhythmics, antidepressants, antiepileptics, antiparkinsonians, anxiolytics, proton pump inhibitors (PPI), non-steroidal anti-inflammatory drugs (NSAID), hormone replacement therapy (HRT), selective estrogen receptor modulators (SERMs), strontium ranelate, calcium, non-ocular corticoids, ocular corticoids and insulin. Denosumab and teriparatide were not prescribed to our study population and were not included in the analysis. Comorbidity confounders were Charlson comorbidity index (none, mild (1 to 2), moderate (3 to 4), or severe ( $\geq 5$ )), asthma, inflammatory bowel disease, hypertension, hyperlipidemia, ischemic heart disease, cerebrovascular disease (CVD), chronic obstructive pulmonary disease (COPD), chronic renal failure, cancer, cataract surgery and type 1/type 2 diabetes.

### **Missing data**

Confounders with missing values after applying exclusion criteria and prior to using propensity score matching were BMI (101, 21.1%), smoking (900, 9.1%) and drinking (1,729, 17.4%). They were imputed to avoid the exclusion of a large number of patients from the original sample. We generated a single imputed dataset using a chained equation across 50 iterations to reach a stationary distribution. We included all confounders, BP exposure and the AMD diagnosis in the imputation process.

### **Statistics**



Standard descriptive statistics were used to describe the characteristics and follow-up time of our sample. A propensity score for BP-use was calculated using a logistic regression model<sup>13, 14</sup>, which included all confounders. BP-users were matched to non-BP users on the logit of the propensity score using a caliper width of 0.2 of the standard deviation of the logit of the propensity score<sup>15</sup>. A matching ratio of 1:1 was used<sup>16</sup>. We assessed standardised differences between the two groups, with 10% or more considered as suggestive of imbalance<sup>17</sup>.

Occurrence of AMD between BP-users and non-BP users were evaluated after matching using two-tailed Fisher's exact tests. Kaplan-Meier survival curves were drawn for AMD incidence and differences among BP exposures were compared using the log rank test<sup>18</sup>.

A multivariable competing-risk regression (death as competing event) was fitted to estimate the effect of BPs on AMD occurrence<sup>19, 20</sup>, the output of which was a sub-distributional hazard ratio (sHR) and 95% CI, adjusted for the pairing of patients in the matching process. The confidence interval was informed using robust variance estimators, assuming that observations were independent across groups (pairs of matched patients) but not necessarily within groups<sup>21</sup>. A time-to-exposure variable was calculated splitting follow-up time of BP-users into non-BP users and BP user (when the patient became a user), so as to account for any lag between index date and BP initiation. Effect of BP dose was assessed within a nested case-control study using DDDs and MPR. Each AMD case was matched to 20 controls using the propensity scores obtained previously. A caliper width of 0.2 was again applied. A conditional logistic regression model was fitted to ascertain how the risk of AMD was associated with the degree of exposure to BP in terms of quartiles of prescribed daily dose and MPR. This yielded odds ratios (OR) and 95% CI, adjusted for matched cases and controls.

Analyses were conducted using the Stata version 13.1 statistical software (StataCorp, College Station, Texas). Matching on BP was performed using the R Package “MatchIt”<sup>22</sup>. While matching nested cases with controls used “Matching”<sup>23</sup>.

## RESULTS

### Descriptive statistics

Of the 13,974 hip fracture patients, 4,035 (28.9%) were excluded prior to matching (Figure 1). Of the 9,939 patients meeting the inclusion criteria, 3,105 (31.2%) were BP users. AMD developed in 152 patients. Of them, 57 (37.5%) were on BP. The median time on BP until AMD event was 2.9 years (0.5 to 8.9 years).

For the competing risk analysis 3,104 BP users were matched 1:1 to 3,104 non-BP users, and of these matched patients 99 developed AMD.

For the nested case-control study, all 99 patients that developed AMD were matched 1:20 to 1980 controls that did not develop AMD. Of the 99 AMD cases 57 (57.6%) were BP users compared to 951 (48.0%) in the 1980 matched controls.

### Matching on BP

3,104 BP-users were matched 1:1 to a non-BP user (Table 1). Covariate balance was improved after matching compared to before matching, the standardised differences for all the covariates were less than 10%, indicating acceptable balance. E.g., before matching difference between non-BP and BP-users for women was imbalanced (SMD=0.31) and after matching that difference achieved an appropriate balance smaller than 10% (SMD=0.04). After matching, there were 42 (1.4%) vs. 57 (1.8%) AMD cases among non-BP vs. BP-users. The number of AMD cases according to patient characteristics, drug confounders and co-morbidity confounders are shown in Table 2. There were more AMD cases in women, non-

smokers, current drinkers, and individuals using antidepressants, PPIs or NSAIDs. There was also (independent of BP consumption) more AMD cases in those with hypertension. BP-use was associated with more cases among men, former drinkers, antiepileptic-users, PPI-users, those with chronic renal failure and Type 2 diabetes among BP-users. However, the only statistically significant differences found were for drinking ( $P=0.02$ ) and NSAID consumption ( $P=0.04$ ). Person-years of follow-up were 11,793 vs. 10,350 among non-BP vs. BP-users. At year five there were 772 and 926 patients at risk for AMD, and 25 and 32 had developed AMD, respectively.

Table 1. Baseline characteristics among non-BP and BP-users: before and after matching.

	before matching			after matching 1 to 1		
	Non-BP	BP-users	SMD	Non-BP	BP-users	SMD
	(n=6834)	(n=3105)		(n=3104)	(n=3104)	
Age, mean (SD), years	81.04 (10.15)	79.93 (9.34)	0.11	80.28 (10.78)	79.94 (9.34)	0.03
Women	4730 (69.2%)	2552 (82.2%)	0.31	2500 (80.5%)	2551 (82.2%)	0.04
BMI, mean (SD), kg/m <sup>2</sup>	24.30 (4.68)	24.50 (4.64)	0.04	24.59 (4.81)	24.50 (4.64)	0.02
Smoking			0.07			0.02
Never	4184 (61.2%)	1864 (60.0%)		1867 (60.1%)	1864 (60.1%)	
Former	1531 (22.4%)	783 (25.2%)		795 (25.6%)	782 (25.2%)	
Current	1119 (16.4%)	458 (14.8%)		442 (14.2%)	458 (14.8%)	
Drinking			0.06			0.02
Never	2073 (30.3%)	912 (29.4%)		922 (29.7%)	912 (29.4%)	
Former	223 (3.3%)	74 (2.4%)		81 (2.6%)	74 (2.4%)	
Current	4538 (66.4%)	2119 (68.2%)		2101 (67.7%)	2118 (68.2%)	
Index year			0.53			0.06
1999	733 (10.7%)	153 (4.9%)		138 (4.4%)	153 (4.9%)	
2000	684 (10.0%)	135 (4.3%)		121 (3.9%)	135 (4.3%)	
2001	646 (9.5%)	149 (4.8%)		156 (5.0%)	149 (4.8%)	
2002	632 (9.2%)	187 (6.0%)		198 (6.4%)	187 (6.0%)	
2003	626 (9.2%)	205 (6.6%)		218 (7.0%)	205 (6.6%)	
2004	574 (8.4%)	194 (6.2%)		202 (6.5%)	194 (6.2%)	
2005	460 (6.7%)	259 (8.3%)		268 (8.6%)	259 (8.3%)	
2006	460 (6.7%)	289 (9.3%)		309 (10.0%)	289 (9.3%)	
2007	435 (6.4%)	286 (9.2%)		288 (9.3%)	286 (9.2%)	
2008	403 (5.9%)	269 (8.7%)		282 (9.1%)	269 (8.7%)	
2009	347 (5.1%)	287 (9.2%)		272 (8.8%)	287 (9.2%)	
2010	346 (5.1%)	270 (8.7%)		259 (8.3%)	269 (8.7%)	
2011	302 (4.4%)	272 (8.8%)		250 (8.1%)	272 (8.8%)	
2012	186 (2.7%)	150 (4.8%)		143 (4.6%)	150 (4.8%)	

Table 1. Baseline characteristics among non-BP and BP-users: before and after matching  
(continued).

	<b>before matching</b>			<b>after matching 1 to 1</b>		
	<b>Non-BP</b>	<b>BP-users</b>	<b>SMD</b>	<b>Non-BP</b>	<b>BP-users</b>	<b>SMD</b>
<b>Region</b>			0.09			0.02
North England	3310 (48.4%)	1469 (47.3%)		1477 (47.6%)	1468 (47.3%)	
South England	2413 (35.3%)	1053 (33.9%)		1055 (34.0%)	1053 (33.9%)	
Northern Ireland	303 (4.4%)	199 (6.4%)		190 (6.1%)	199 (6.4%)	
Scotland	334 (4.9%)	157 (5.1%)		148 (4.8%)	157 (5.1%)	
Wales	474 (6.9%)	227 (7.3%)		234 (7.5%)	227 (7.3%)	
<b>Drug confounders</b>						
Antiarrhythmics	483 (7.1%)	209 (6.7%)	0.01	206 (6.6%)	209 (6.7%)	<0.01
Antidepressants	2446 (35.8%)	1139 (36.7%)	0.02	1169 (37.7%)	1139 (36.7%)	0.02
Antiepileptics	429 (6.3%)	212 (6.8%)	0.02	220 (7.1%)	212 (6.8%)	0.01
Antiparkinson	366 (5.4%)	118 (3.8%)	0.07	124 (4.0%)	118 (3.8%)	0.01
Anxiolytics	1325 (19.4%)	601 (19.4%)	<0.01	610 (19.7%)	601 (19.4%)	0.01
PPI	2207 (32.3%)	1166 (37.6%)	0.11	1176 (37.9%)	1165 (37.5%)	0.01
NSAIDS	5585 (81.7%)	2671 (86.0%)	0.12	2652 (85.4%)	2671 (86.1%)	0.02
Systemic HRT	374 (5.5%)	344 (11.1%)	0.21	285 (9.2%)	344 (11.1%)	0.06
SERMS	2 (0.0%)	4 (0.1%)	0.04	1 (0.0%)	3 (0.1%)	0.03
Strontium	10 (0.1%)	2 (0.1%)	0.03	3 (0.1%)	2 (0.1%)	0.01
Calcium	718 (10.5%)	438 (14.1%)	0.11	443 (14.3%)	437 (14.1%)	0.01
Non-ocular corticoids	440 (6.4%)	265 (8.5%)	0.08	245 (7.9%)	265 (8.5%)	0.02
Ocular corticoids	160 (2.3%)	85 (2.7%)	0.03	90 (2.9%)	85 (2.7%)	0.01
Insulin	100 (1.5%)	28 (0.9%)	0.05	33 (1.1%)	28 (0.9%)	0.02

Table 1. Baseline characteristics among non-BP and BP-users: before and after matching

(continued).

	before matching Non-BP	BP-users	SMD	after matching 1 to 1 Non-BP	BP-users	SMD
<b>Co-morbidity confounders</b>						
Charlson Comorbidity in previous 5-years			0.11			0.03
None	3614 (52.9%)	1808 (58.2%)		1774 (57.2%)	1807 (58.2%)	
Mild (1 to 2)	2160 (31.6%)	884 (28.5%)		899 (29.0%)	884 (28.5%)	
Moderate (3 to 4)	707 (10.3%)	272 (8.8%)		275 (8.9%)	272 (8.8%)	
Severe (5+)	353 (5.2%)	141 (4.5%)		156 (5.0%)	141 (4.5%)	
Asthma	825 (12.1%)	456 (14.7%)	0.08	440 (14.2%)	456 (14.7%)	0.02
Inflammatory bowel disease	81 (1.2%)	41 (1.3%)	0.01	39 (1.3%)	41 (1.3%)	0.01
Hypertension	3075 (45.0%)	1619 (52.1%)	0.14	1619 (52.2%)	1619 (52.2%)	<0.01
Hyperlipidaemia	762 (11.2%)	527 (17.0%)	0.17	503 (16.2%)	527 (17.0%)	0.02
Ischemic heart disease	1393 (20.4%)	582 (18.7%)	0.04	586 (18.9%)	582 (18.8%)	<0.01
CVD	789 (11.5%)	276 (8.9%)	0.09	274 (8.8%)	276 (8.9%)	<0.01
COPD	565 (8.3%)	252 (8.1%)	0.01	247 (8.0%)	252 (8.1%)	0.01
Chronic renal failure	294 (4.3%)	131 (4.2%)	<0.01	148 (4.8%)	131 (4.2%)	0.03
Cancers	1324 (19.4%)	534 (17.2%)	0.06	579 (18.7%)	534 (17.2%)	0.04
Cataract surgery	903 (13.2%)	307 (9.9%)	0.10	322 (10.4%)	307 (9.9%)	0.02
Type 1 diabetes	34 (0.5%)	17 (0.5%)	0.01	17 (0.5%)	17 (0.5%)	<0.01
Type 2 diabetes	739 (10.8%)	329 (10.6%)	0.01	321 (10.3%)	329 (10.6%)	0.01

Standardised mean difference, SMD; standard deviation, SD; body mass index, BMI; proton pump inhibitor, PPI; non-steroidal anti-inflammatory drug, NSAID; hormone replacement therapy, HRT; selective estrogen receptor modulator, SERM; cardio vascular disease, CVD; chronic obstructive pulmonary disease, COPD. SMD values <0.10 are indicators of good balance and suitability for survival analysis of the matched cohort.

Table 2. AMD events among non-BP and BP-users after matching.

	<b>Non-BP</b>	<b>BP-users</b>	<b><i>P</i>-value</b>
	(n=42)	(n=57)	
Sex			
Women	39 (92.9%)	49 (86.0%)	0.35
Men	3 (7.1%)	8 (14.0%)	
Smoking			1.00
Never	25 (59.5%)	35 (61.4%)	
Former	12 (28.6%)	16 (28.1%)	
Current	5 (11.9%)	6 (10.5%)	
Drinking			0.02
Never	9 (21.4%)	11 (19.3%)	
Former	0 (0.0%)	3 (5.3%)	
Current	33 (78.6%)	43 (75.4%)	
Index year			1.00
1999	2 (4.8%)	5 (8.8%)	
2000	2 (4.8%)	1 (1.8%)	
2001	3 (7.1%)	4 (7.0%)	
2002	4 (9.5%)	6 (10.5%)	
2003	5 (11.9%)	7 (12.3%)	
2004	4 (9.5%)	4 (7.0%)	
2005	4 (9.5%)	6 (10.5%)	
2006	6 (14.3%)	6 (10.5%)	
2007	4 (9.5%)	5 (8.8%)	
2008	3 (7.1%)	6 (10.5%)	
2009	2 (4.8%)	4 (7.0%)	
2010	3 (7.1%)	1 (1.8%)	
2011	0 (0.0%)	2 (3.5%)	
2012	—	—	

Table 2. AMD events among non-BP and BP-users after matching (continued).

	<b>Non-BP</b>	<b>BP-users</b>	<b><i>P</i>-value</b>
	(n=42)	(n=57)	
<b>Region</b>			0.24
North England	21 (50.0%)	30 (52.6%)	
South England	14 (33.3%)	19 (33.3%)	
Northern Ireland	0 (0.0%)	2 (3.5%)	
Scotland	1 (2.4%)	4 (7.0%)	
Wales	6 (14.3%)	2 (3.5%)	
<b>Drug confounders</b>			
Antiarrhythmics	2 (4.8%)	5 (8.8%)	0.70
Antidepressants	13 (31.0%)	17 (29.8%)	1.00
Antiepileptics	0 (0.0%)	5 (8.8%)	0.07
Antiparkinson	2 (4.8%)	3 (5.3%)	1.00
Anxiolytics	8 (19.1%)	6 (10.5%)	0.26
PPI	16 (38.1%)	27 (47.4%)	0.42
NSAIDS	41 (97.6%)	48 (84.2%)	0.04
Systemic HRT	2 (4.8%)	4 (7.0%)	1.00
SERMS	—	—	
Strontium	—	—	
Calcium	4 (9.5%)	4 (7.0%)	0.72
Non-ocular corticoids	5 (11.9%)	3 (5.3%)	0.28
Ocular corticoids	2 (4.8%)	1 (1.8%)	0.57
Insulin	1 (2.4%)	0 (0.0%)	0.42



Table 2. AMD events among non-BP and BP-users after matching (continued).

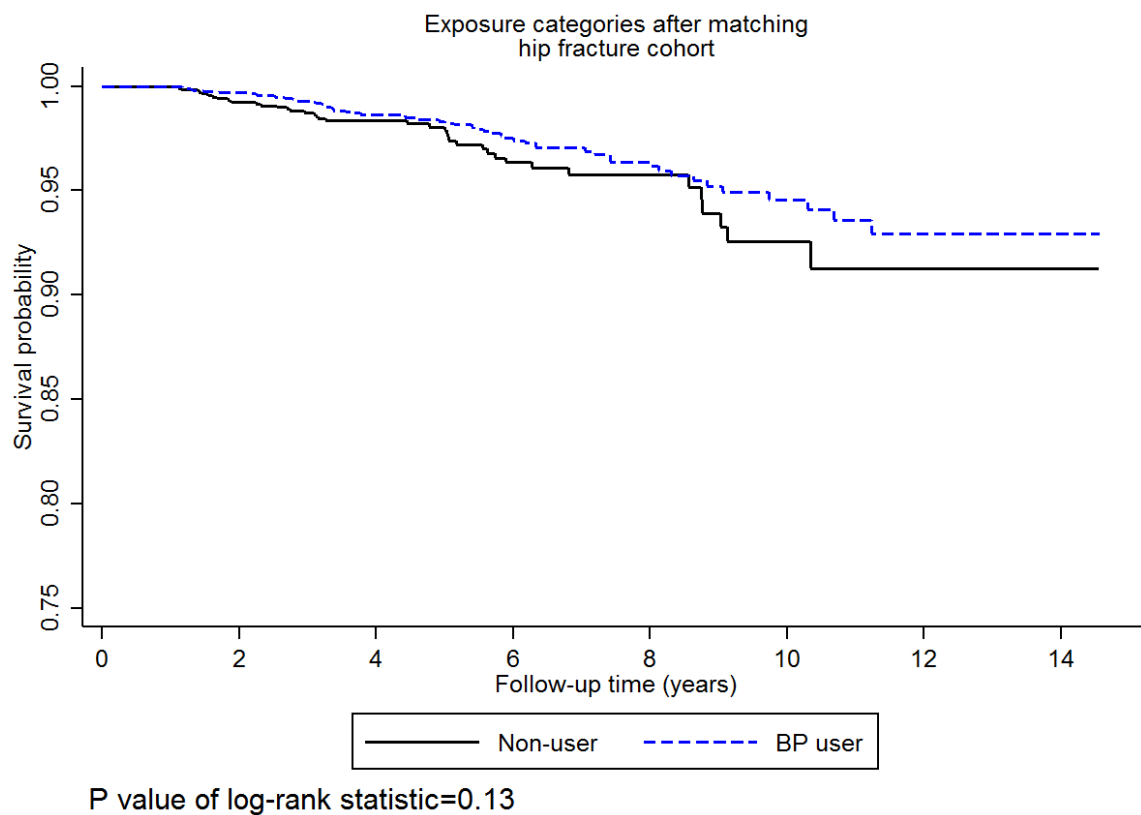
	<b>Non-BP</b>	<b>BP-users</b>	<b>P-value</b>
	(n=42)	(n=57)	
<b>Co-morbidity confounders</b>			
Charlson Comorbidity in previous 5-years			0.86
None	24 (57.1%)	29 (50.9%)	
Mild (1 to 2)	15 (35.7%)	23 (40.3%)	
Moderate (3 to 4)	2 (4.8%)	2 (3.5%)	
Severe (5+)	1 (2.4%)	0 (0.0%)	
Asthma	9 (21.4%)	6 (10.5%)	0.16
Inflammatory bowel disease	1 (2.4%)	1 (1.8%)	1.00
Hypertension	21 (50.0%)	32 (56.1%)	0.68
Hyperlipidaemia	6 (14.3%)	14 (24.6%)	0.31
Ischemic heart disease	5 (11.9%)	11 (19.3%)	0.41
CVD	5 (11.9%)	2 (3.5%)	0.13
COPD	5 (11.9%)	3 (5.3%)	0.28
Chronic renal failure	0 (0.0%)	4 (7.0%)	0.14
Cancers	6 (14.3%)	8 (14.0%)	1.00
Cataract surgery	4 (9.5%)	6 (10.5%)	1.00
Type 1 diabetes	1 (2.4%)	0 (0.0%)	0.42
Type 2 diabetes	3 (7.1%)	8 (14.0%)	0.35

Proton pump inhibitor, PPI; non-steroidal anti-inflammatory drug, NSAID; hormone replacement therapy, HRT; selective estrogen receptor modulator, SERM; cardio vascular disease, CVD; chronic obstructive pulmonary disease, COPD. *P*-values from Fisher's exact of 2 tails.

### Survival probability of AMD

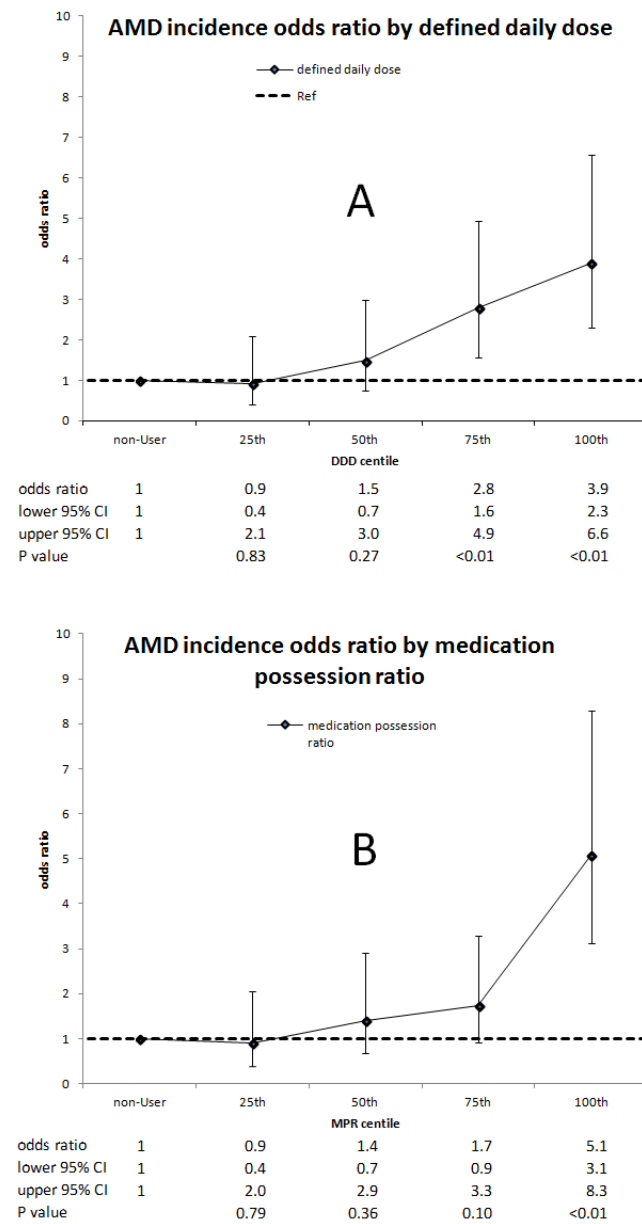
The Kaplan-Meier probability of AMD was not significantly different between non-BP and BP-users ( $P=0.13$ ) (Figure 2). According to the Kaplan-Meier estimator, one in 100 hip-fracture patients would develop AMD in 5 years for non-BP, while this was 2 in 100 for BP-users. Therefore, the probability of not experiencing AMD, some time after 5 years, was 0.986 (95% CI: 0.979 to 0.991) for non-BP and 0.978 (95% CI: 0.968 to 0.984) for BP-users. For 10 years of follow up these probabilities increased to 6 out of 100, 0.942 (95% CI: 0.910 to 0.963) and 0.936 (95% CI: 0.913 to 0.953), for non-BP and BP-users respectively.

**Fig. 2. Kaplan-Meier survival curves.** Survival curves showing probability of age-related macular degeneration for bisphosphonate (BP)-users Vs. non-BP users.  $P$  values were calculated using the log-rank test.



Using multivariable competing risk survival models, there was weak evidence of an increased risk of AMD development among BP-users (sHR: 1.6; CI: 0.9-2.7;  $P=0.08$ ). Conditional logistic regression analysis on DDDs showed a trend increasing across the quartiles, which become significant for the 3<sup>rd</sup> and 4<sup>th</sup> quartiles (OR<sub>75th</sub>:2.8, CI: 1.6-4.9,  $P<0.01$ ; OR<sub>100th</sub>: 3.9, CI: 2.3-6.6,  $P<0.01$ ) (Figure 3). A similar ascending trend was observed for the quartiles of MPR, achieving significance for the highest quartile (OR<sub>100th</sub>: 5.1, 3.1-8.3,  $P<0.01$ ) (Figure 3).

**Fig. 3. Age-related macular degeneration incidence** according to (A) bisphosphonate defined daily dose (DDD) and (B) medication possession ratio (MPR)\*.



\* Odds ratios for AMD incidence (black marker) were obtained from conditional logistic regression. They are presented with their 95% confidence intervals (CI) (error bars) and their *P* values. Non-bisphosphonate (non-BP) odds ratios are compared with odds ratios of increased amount of DDD and MPR categorised in quartiles. Markers or error bars lying into the dotted horizontal line denoted statistically non-significant association.

## DISCUSSION

We found that in an incident hip fracture cohort, oral BP use was not overall significantly associated with increased risk of AMD. After matching, there were 42 (1.4%) vs. 57 (1.8%) AMD cases among non-BP users vs. BP-users, equating to a low and non-significant absolute risk difference of 0.49%, CI: -0.13% to 1.11%;  $P=0.06$ ) (6 more cases per 1000). However, the increased risk became **somewhat greater and** statistically significant among BP-users who had a high MPR. According to our results, one AMD case at five years would be prevented if 12 hip fracture patients in the top quartile of MPR avoided BP treatment longer than one year.

To our knowledge, there is only one previous study analysing the risk of AMD in patients taking oral BP<sup>24</sup>. This study used data from the Food and Drug Administration (FDA) Adverse Event Reporting System (FAERS) database in the USA, which captures spontaneous adverse drug reactions. Two patient cohorts from Canada were also included, covering the period 2009-2013 for the cases and 2000-2007 for the controls. This study found a higher risk of developing wet AMD in BP-users, although a caveat to these findings has to be that the selection of patients was limited to reported cases to FAERS without a clear definition of AMD for a disproportionality analysis. In addition, although this prior study conducted a case-control and a self-controlled case series analysis, this was limited to patients with wet AMD or controls without any type of AMD (dry, wet or unspecified) selected among those visiting the ophthalmologist, and as such was not population-based or inclusive of dry and unspecified AMD cases. Additionally, some concerns can arise when using different time periods for cases vs. controls, and despite the fact that their results reached significance, the magnitude of the effect was marginal<sup>25</sup>.

Several risk factors have been previously identified as being associated with the development of AMD, with age being the strongest one. The pathogenesis however is not well understood. Inflammation may play a significant role and most recently, hydroxyapatite (calcium and phosphate) spherules, which is commonly found in bones and teeth, has been identified as a key player in the development of the disease<sup>8</sup>.

In terms of a potential mechanism of effect, ocular inflammatory reactions have been described in patients on bisphosphonate treatment. Inflammatory proteins such as interleukins have also been linked to AMD development<sup>26-31</sup> and BPs could cause systemic release of cytokines and other acute phase proteins. Moreover, a causative link between bisphosphonates and inflammatory ocular events is likely and is based on reports of inflammatory eye reaction relapses after affected patients were re-challenged with the same or another bisphosphonate<sup>32</sup>.

If indeed inflammation is the cause, it begs the question why AMD is not a common complication in patients with inflammatory diseases such as rheumatoid arthritis, inflammatory bowel disease, or sarcoidosis? The explanation could be that the inflammation alone is not sufficient by itself but requires the presence of hydroxyapatite (calcium and phosphate) spherules, which could be the critical factor in the development of AMD. Interestingly, BPs could not only retard the growth but also increase the dissolution of hydroxyapatite crystals<sup>33</sup>, in which case they would be expected to provide some protective effect. Our results did not show any beneficial effects of nitrogen containing oral bisphosphonates on the incidence of AMD. On the other hand, there is no convincing explanation for the increased risk with higher DDDs and MPR. Therefore, if there is an association between their use and AMD, this association may not be a causal one.

Another plausible mechanism, and opposed to our results (increased risk with higher DDDs and MPR), could relate bisphosphonate use to a reduced risk of AMD is their potential antiangiogenic effect especially in the wet form of AMD where anti-vascular endothelial

growth factor (VEGF) intravitreal agents are the first line of treatment. In vitro, administration of BPs (alendronate and etidronate) on cultured retinal pigment epithelial cells reduced the expression of a number of angiogenic factors<sup>34</sup>. Also, in two pilot, non-randomized studies of relatively short duration (6 and 24 months), administration of 5 mg alendronate daily in patients with wet AMD showed promising results<sup>35, 36</sup>.

BPs have been demonstrated to stop bone loss and reduce significantly the occurrence of fractures in individuals with osteoporosis, and consequently, they are the most extensively prescribed antiresorptive drugs<sup>37</sup>. Although they have been associated with some rare and severe adverse effects (atypical femur fractures and osteonecrosis of the jaw), the “real-world” anti-fracture benefit to patients at high risk of fracture far exceeds the potential risks<sup>38</sup>.

### **Strengths and limitations**

There are multiple strengths to our current study. Firstly, we conducted the analysis in a population of hip fracture patients for which BP treatment is recommended for the secondary prevention of fragility fractures. Secondly, we have used an incident user design to minimise biases associated with the inclusion of prevalent BP-users. Thirdly, despite the fact that our study was observational, we show an effect of BP after adjusting for a large number of confounders, including comorbidity, co-medication and other important factors using propensity matching. Furthermore, we used a time dependent exposure variable and conducted a subsequent nested case-control analysis for assessing dose-response. Using a nested case-control analysis gave us an unbiased assessment like the sHR obtained from the time to event analysis in the matched cohort, almost free of immortal time bias<sup>39</sup>.

Included in the *limitations* is the fact that prescriptions in the CPRD may have been misclassified in terms of BP exposure due to data entry errors by GPs and other potential sources of error in the use of electronic systems<sup>40</sup>. Nevertheless, given that we only included patients into the BP-user cohort if they were newly treated, misclassification is probably low given that CPRD is nowadays well known and established in the routine of health personnel. Another limitation is that the study is observational in nature and unmeasured or unknown factors may have resulted in residual confounding, e.g. genetic risk factors<sup>41</sup>. Furthermore, deprivation index, ethnicity<sup>42</sup> and measurements of the marker of inflammation C reactive protein were in the dataset but were not used due to high level of missingness and/or inaccuracy. Misclassification of AMD cannot be ruled out, as well as the further subdivision between wet and dry categories with many patients included in the category of unspecific. For this reason we have not made distinctions between types of AMD. Furthermore, we may have potentially overestimated BP use as the analyses were based only on prescription data given that information on adherence is not captured in CPRD. However, the nested case-control design did allow us to estimate the effect of BP dose in AMD occurrence. Finally, there is the possibility of detection bias given that BP use is associated with one eye condition, therefore giving rise to the possibility that BP-users were more likely than non-BP users to have an eye exam where early AMD could be diagnosed, although this is unlikely given that eye examination is not routine for patients on BPs or in those with a hip fracture.

## **Conclusion**

Our study of incident hip fracture patients offers an external validation showing that overall, oral BP use was not associated with increased risk of AMD in a cohort of hip fracture



patients. However we found increased risk with higher DDDs and MPR. More data are needed to confirm these findings.

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Oral bisphosphonate use and age-related macular degeneration: retrospective cohort and nested case-control study

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Table 1. Baseline characteristics among non-BP and BP-users: before and after matching.

	before matching Non-BP	BP-users	SMD	after matching 1 to 1 Non-BP	BP-users	SMD
	(n=6834)	(n=3105)		(n=3104)	(n=3104)	
Age, mean (SD), years	81.04 (10.15)	79.93 (9.34)	0.11	80.28 (10.78)	79.94 (9.34)	0.03
Women	4730 (69.2%)	2552 (82.2%)	0.31	2500 (80.5%)	2551 (82.2%)	0.04
BMI, mean (SD), kg/m <sup>2</sup>	24.30 (4.68)	24.50 (4.64)	0.04	24.59 (4.81)	24.50 (4.64)	0.02
Smoking			0.07			0.02
Never	4184 (61.2%)	1864 (60.0%)		1867 (60.1%)	1864 (60.1%)	
Former	1531 (22.4%)	783 (25.2%)		795 (25.6%)	782 (25.2%)	
Current	1119 (16.4%)	458 (14.8%)		442 (14.2%)	458 (14.8%)	
Drinking			0.06			0.02
Never	2073 (30.3%)	912 (29.4%)		922 (29.7%)	912 (29.4%)	
Former	223 (3.3%)	74 (2.4%)		81 (2.6%)	74 (2.4%)	
Current	4538 (66.4%)	2119 (68.2%)		2101 (67.7%)	2118 (68.2%)	
Index year			0.53			0.06
1999	733 (10.7%)	153 (4.9%)		138 (4.4%)	153 (4.9%)	
2000	684 (10.0%)	135 (4.3%)		121 (3.9%)	135 (4.3%)	
2001	646 (9.5%)	149 (4.8%)		156 (5.0%)	149 (4.8%)	
2002	632 (9.2%)	187 (6.0%)		198 (6.4%)	187 (6.0%)	
2003	626 (9.2%)	205 (6.6%)		218 (7.0%)	205 (6.6%)	
2004	574 (8.4%)	194 (6.2%)		202 (6.5%)	194 (6.2%)	
2005	460 (6.7%)	259 (8.3%)		268 (8.6%)	259 (8.3%)	
2006	460 (6.7%)	289 (9.3%)		309 (10.0%)	289 (9.3%)	
2007	435 (6.4%)	286 (9.2%)		288 (9.3%)	286 (9.2%)	
2008	403 (5.9%)	269 (8.7%)		282 (9.1%)	269 (8.7%)	
2009	347 (5.1%)	287 (9.2%)		272 (8.8%)	287 (9.2%)	
2010	346 (5.1%)	270 (8.7%)		259 (8.3%)	269 (8.7%)	
2011	302 (4.4%)	272 (8.8%)		250 (8.1%)	272 (8.8%)	
2012	186 (2.7%)	150 (4.8%)		143 (4.6%)	150 (4.8%)	

Table 1. Baseline characteristics among non-BP and BP-users: before and after matching

(continued).

	before matching Non-BP	BP-users	SMD	after matching 1 to 1 Non-BP	BP-users	SMD
Region			0.09			0.02
North England	3310 (48.4%)	1469 (47.3%)		1477 (47.6%)	1468 (47.3%)	
South England	2413 (35.3%)	1053 (33.9%)		1055 (34.0%)	1053 (33.9%)	
Northern Ireland	303 (4.4%)	199 (6.4%)		190 (6.1%)	199 (6.4%)	
Scotland	334 (4.9%)	157 (5.1%)		148 (4.8%)	157 (5.1%)	
Wales	474 (6.9%)	227 (7.3%)		234 (7.5%)	227 (7.3%)	
<b>Drug confounders</b>						
Antiarrhythmics	483 (7.1%)	209 (6.7%)	0.01	206 (6.6%)	209 (6.7%)	<0.01
Antidepressants	2446 (35.8%)	1139 (36.7%)	0.02	1169 (37.7%)	1139 (36.7%)	0.02
Antiepileptics	429 (6.3%)	212 (6.8%)	0.02	220 (7.1%)	212 (6.8%)	0.01
Antiparkinson	366 (5.4%)	118 (3.8%)	0.07	124 (4.0%)	118 (3.8%)	0.01
Anxiolytics	1325 (19.4%)	601 (19.4%)	<0.01	610 (19.7%)	601 (19.4%)	0.01
PPI	2207 (32.3%)	1166 (37.6%)	0.11	1176 (37.9%)	1165 (37.5%)	0.01
NSAIDS	5585 (81.7%)	2671 (86.0%)	0.12	2652 (85.4%)	2671 (86.1%)	0.02
Systemic HRT	374 (5.5%)	344 (11.1%)	0.21	285 (9.2%)	344 (11.1%)	0.06
SERMS	2 (0.0%)	4 (0.1%)	0.04	1 (0.0%)	3 (0.1%)	0.03
Strontium	10 (0.1%)	2 (0.1%)	0.03	3 (0.1%)	2 (0.1%)	0.01
Calcium	718 (10.5%)	438 (14.1%)	0.11	443 (14.3%)	437 (14.1%)	0.01
Non-ocular corticoids	440 (6.4%)	265 (8.5%)	0.08	245 (7.9%)	265 (8.5%)	0.02
Ocular corticoids	160 (2.3%)	85 (2.7%)	0.03	90 (2.9%)	85 (2.7%)	0.01
Insulin	100 (1.5%)	28 (0.9%)	0.05	33 (1.1%)	28 (0.9%)	0.02

Table 1. Baseline characteristics among non-BP and BP-users: before and after matching

(continued).

	before matching Non-BP	BP-users	SMD	after matching 1 to 1 Non-BP	BP-users	SMD
<b>Co-morbidity confounders</b>						
Charlson Comorbidity in previous 5-years			0.11			0.03
None	3614 (52.9%)	1808 (58.2%)		1774 (57.2%)	1807 (58.2%)	
Mild (1 to 2)	2160 (31.6%)	884 (28.5%)		899 (29.0%)	884 (28.5%)	
Moderate (3 to 4)	707 (10.3%)	272 (8.8%)		275 (8.9%)	272 (8.8%)	
Severe (5+)	353 (5.2%)	141 (4.5%)		156 (5.0%)	141 (4.5%)	
Asthma	825 (12.1%)	456 (14.7%)	0.08	440 (14.2%)	456 (14.7%)	0.02
Inflammatory bowel disease	81 (1.2%)	41 (1.3%)	0.01	39 (1.3%)	41 (1.3%)	0.01
Hypertension	3075 (45.0%)	1619 (52.1%)	0.14	1619 (52.2%)	1619 (52.2%)	<0.01
Hyperlipidaemia	762 (11.2%)	527 (17.0%)	0.17	503 (16.2%)	527 (17.0%)	0.02
Ischemic heart disease	1393 (20.4%)	582 (18.7%)	0.04	586 (18.9%)	582 (18.8%)	<0.01
CVD	789 (11.5%)	276 (8.9%)	0.09	274 (8.8%)	276 (8.9%)	<0.01
COPD	565 (8.3%)	252 (8.1%)	0.01	247 (8.0%)	252 (8.1%)	0.01
Chronic renal failure	294 (4.3%)	131 (4.2%)	<0.01	148 (4.8%)	131 (4.2%)	0.03
Cancers	1324 (19.4%)	534 (17.2%)	0.06	579 (18.7%)	534 (17.2%)	0.04
Cataract surgery	903 (13.2%)	307 (9.9%)	0.10	322 (10.4%)	307 (9.9%)	0.02
Type 1 diabetes	34 (0.5%)	17 (0.5%)	0.01	17 (0.5%)	17 (0.5%)	<0.01
Type 2 diabetes	739 (10.8%)	329 (10.6%)	0.01	321 (10.3%)	329 (10.6%)	0.01

Standardised mean difference, SMD; standard deviation, SD; body mass index, BMI; proton pump inhibitor, PPI; non-steroidal anti-inflammatory drug, NSAID; hormone replacement therapy, HRT; selective estrogen receptor modulator, SERM; cardio vascular disease, CVD; chronic obstructive pulmonary disease, COPD. SMD values <0.10 are indicators of good balance and suitability for survival analysis of the matched cohort.

**MANUSCRIPT TITLE:**

Oral bisphosphonate use and age-related macular degeneration: retrospective cohort and nested case-control study

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Table 2. AMD events among non-BP and BP-users after matching.

	<b>Non-BP</b>	<b>BP-users</b>	<b><i>P</i>-value</b>
	(n=42)	(n=57)	
Sex			
Women	39 (92.9%)	49 (86.0%)	0.35
Men	3 (7.1%)	8 (14.0%)	
Smoking			1.00
Never	25 (59.5%)	35 (61.4%)	
Former	12 (28.6%)	16 (28.1%)	
Current	5 (11.9%)	6 (10.5%)	
Drinking			0.02
Never	9 (21.4%)	11 (19.3%)	
Former	0 (0.0%)	3 (5.3%)	
Current	33 (78.6%)	43 (75.4%)	
Index year			1.00
1999	2 (4.8%)	5 (8.8%)	
2000	2 (4.8%)	1 (1.8%)	
2001	3 (7.1%)	4 (7.0%)	
2002	4 (9.5%)	6 (10.5%)	
2003	5 (11.9%)	7 (12.3%)	
2004	4 (9.5%)	4 (7.0%)	
2005	4 (9.5%)	6 (10.5%)	
2006	6 (14.3%)	6 (10.5%)	
2007	4 (9.5%)	5 (8.8%)	
2008	3 (7.1%)	6 (10.5%)	
2009	2 (4.8%)	4 (7.0%)	
2010	3 (7.1%)	1 (1.8%)	
2011	0 (0.0%)	2 (3.5%)	
2012	—	—	

Table 2. AMD events among non-BP and BP-users after matching (continued).

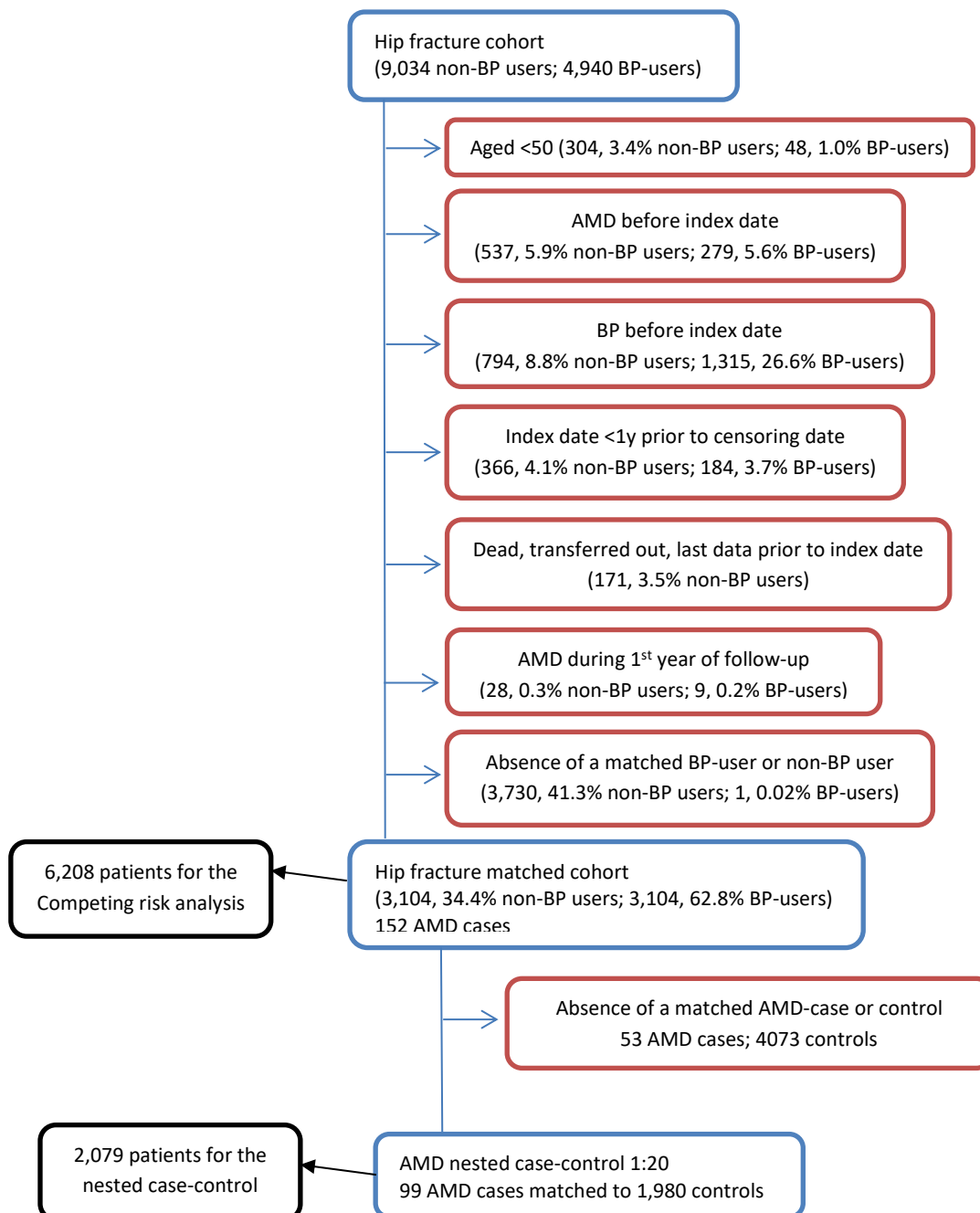
	<b>Non-BP</b>	<b>BP-users</b>	<b><i>P</i>-value</b>
	(n=42)	(n=57)	
<b>Region</b>			0.24
North England	21 (50.0%)	30 (52.6%)	
South England	14 (33.3%)	19 (33.3%)	
Northern Ireland	0 (0.0%)	2 (3.5%)	
Scotland	1 (2.4%)	4 (7.0%)	
Wales	6 (14.3%)	2 (3.5%)	
<b>Drug confounders</b>			
Antiarrhythmics	2 (4.8%)	5 (8.8%)	0.70
Antidepressants	13 (31.0%)	17 (29.8%)	1.00
Antiepileptics	0 (0.0%)	5 (8.8%)	0.07
Antiparkinson	2 (4.8%)	3 (5.3%)	1.00
Anxiolytics	8 (19.1%)	6 (10.5%)	0.26
PPI	16 (38.1%)	27 (47.4%)	0.42
NSAIDS	41 (97.6%)	48 (84.2%)	0.04
Systemic HRT	2 (4.8%)	4 (7.0%)	1.00
SERMS	—	—	
Strontium	—	—	
Calcium	4 (9.5%)	4 (7.0%)	0.72
Non-ocular corticoids	5 (11.9%)	3 (5.3%)	0.28
Ocular corticoids	2 (4.8%)	1 (1.8%)	0.57
Insulin	1 (2.4%)	0 (0.0%)	0.42



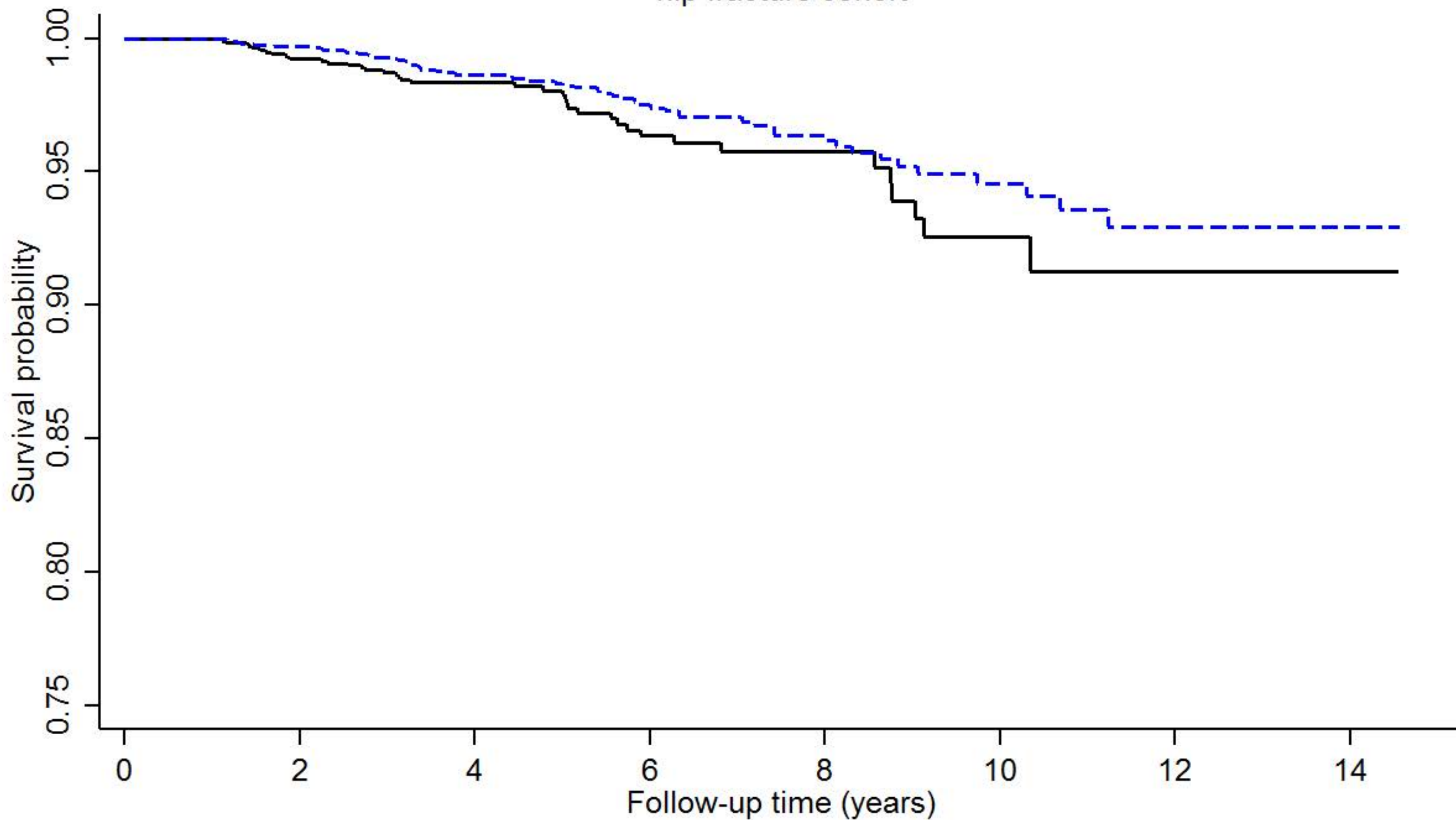
Table 2. AMD events among non-BP and BP-users after matching (continued).

	<b>Non-BP</b>	<b>BP-users</b>	<b>P-value</b>
	(n=42)	(n=57)	
<b>Co-morbidity confounders</b>			
Charlson Comorbidity in previous 5-years			0.86
None	24 (57.1%)	29 (50.9%)	
Mild (1 to 2)	15 (35.7%)	23 (40.3%)	
Moderate (3 to 4)	2 (4.8%)	2 (3.5%)	
Severe (5+)	1 (2.4%)	0 (0.0%)	
Asthma	9 (21.4%)	6 (10.5%)	0.16
Inflammatory bowel disease	1 (2.4%)	1 (1.8%)	1.00
Hypertension	21 (50.0%)	32 (56.1%)	0.68
Hyperlipidaemia	6 (14.3%)	14 (24.6%)	0.31
Ischemic heart disease	5 (11.9%)	11 (19.3%)	0.41
CVD	5 (11.9%)	2 (3.5%)	0.13
COPD	5 (11.9%)	3 (5.3%)	0.28
Chronic renal failure	0 (0.0%)	4 (7.0%)	0.14
Cancers	6 (14.3%)	8 (14.0%)	1.00
Cataract surgery	4 (9.5%)	6 (10.5%)	1.00
Type 1 diabetes	1 (2.4%)	0 (0.0%)	0.42
Type 2 diabetes	3 (7.1%)	8 (14.0%)	0.35

Proton pump inhibitor, PPI; non-steroidal anti-inflammatory drug, NSAID; hormone replacement therapy, HRT; selective estrogen receptor modulator, SERM; cardio vascular disease, CVD; chronic obstructive pulmonary disease, COPD. *P*-values from Fisher's exact of 2 tails.



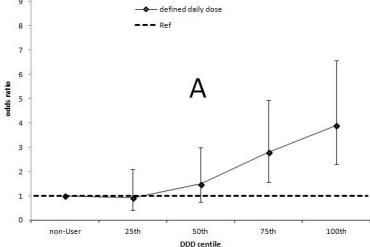
Exposure categories after matching  
hip fracture cohort



— Non-user      - - - BP user

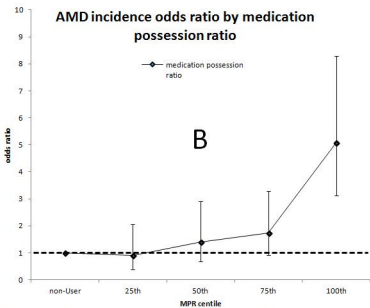
P value of log-rank statistic=0.13

## AMD incidence odds ratio by defined daily dose



odds ratio	1	0.9	1.5	2.8	3.9
lower 95% CI	1	0.4	0.7	1.6	2.3
upper 95% CI	1	2.1	3.0	4.9	6.6
P value		0.83	0.27	<0.01	<0.01

## AMD incidence odds ratio by medication possession ratio



odds ratio	1	0.9	1.4	1.7	5.1
lower 95% CI	1	0.4	0.7	0.9	3.1
upper 95% CI	1	2.0	2.9	3.3	8.3
P value		0.79	0.36	0.10	<0.01