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Use of bisphosphonates among women and risk of atrial fibrillation and flutter: population based case-control study

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ABSTRACT

Objective To assess the association between atrial fibrillation and flutter and use of bisphosphonates for osteoporosis among women.

Design Population based case-control study, using medical databases from Denmark.

Setting Northern Denmark.

Participants 13 586 patients with atrial fibrillation and flutter and 68 054 population controls, all with complete hospital and prescription history.

Main outcome measure Adjusted relative risk of atrial fibrillation and flutter.

Results 435 cases (3.2%) and 1958 population controls (2.9%) were current users of bisphosphonates for osteoporosis. Etidronate and alendronate were used with almost the same frequency among cases and controls. The adjusted relative risk of current use of bisphosphonates compared with non-use was 0.95 (95% confidence interval 0.84 to 1.07). New users had a relative risk of 0.75 (95% confidence interval 0.49 to 1.16), broadly similar to the estimate for continuing users (relative risk 0.96, 95% confidence interval 0.85 to 1.09). The relative risk estimates were independent of number of prescriptions and the position of the atrial fibrillation and flutter diagnosis in the discharge record, and were similar for inpatients and outpatients.

Conclusion No evidence was found that use of bisphosphonates increases the risk of atrial fibrillation and flutter.

INTRODUCTION

Bisphosphonates, widely used for the treatment of established osteoporosis after the menopause, increases bone density and reduces the risk of fractures.[1] Recently an international multicentre clinical trial reported that the intravenously administered bisphosphonate zoledronic acid, used annually, substantially reduced the risk of vertebral, hip, and other fractures.[2] Unexpectedly the study also found that serious atrial fibrillation occurred more often among participants randomised to zoledronic acid than among those given placebo.[2] A reanalysis of an earlier placebo controlled clinical trial of zoledronic acid showed similar rates of atrial fibrillation in the two groups,[3] but a reanalysis of a third trial found a trend towards an increased risk of atrial fibrillation among patients treated with oral alendronate compared with placebo.[4] Thus, overall, the data on the effects of bisphosphonates on risk of atrial fibrillation are conflicting.

Atrial fibrillation is common and potentially serious: the lifetime risk of having at least one episode of the arrhythmia is over 20% in the general population,[5] and it is a major risk factor for stroke, thromboembolism, and heart failure.[6] Since osteoporosis is also a major cause of morbidity and mortality, any association between use of bisphosphonates and atrial fibrillation has major public health implications. We investigated whether use of bisphosphonates is associated with a risk of atrial fibrillation and flutter.

METHODS

We carried out this population based case-control study using medical databases from the counties of North Jutland, Ringkjobing, Viborg, and Aarhus, Denmark, which have a combined population of 1.7 million (about 30% of the total Danish population). We used the personal identifier assigned uniquely to each Danish citizen[7] at birth to link records to people across all the Danish medical registries and databases. Because bisphosphonates are primarily used by women we focused our study on the female Danish population.

Cases with atrial fibrillation and flutter

To identify incident cases of atrial fibrillation and flutter in women we used computerised data from the Danish National Registry of Patients. For each hospital admission since 1977 (since 1995 for all hospital outpatient visits and emergency room visits) the registry records the civil registration number of the patient; dates of admission and discharge; surgical procedures carried out, and up to 20 discharge diagnoses, coded by doctors, classified according to the International Classification of Diseases, eighth revision until the end of 1993 and the 10th revision thereafter.[8 9] We searched the Danish National Registry of Patients for patients who had discharge codes

for atrial fibrillation and flutter. These two arrhythmias were coded separately in ICD-8 (codes 427.93 and 427.94), but in ICD-10 atrial fibrillation and flutter have the same code (I48.9). We therefore studied atrial fibrillation and atrial flutter as one combined end point. None the less, the cases were probably mostly atrial fibrillation: in a previous study of patients recorded in the Danish National Registry of Patients with an incident diagnosis of atrial fibrillation or flutter, only about 5% had pure atrial flutter.[10]

We chose cases who had a first diagnosis during the years 1999-2005 because the availability of computerised prescription data for people living in the four counties has been complete since 1998. In this way we had at least a year of prediagnosis prescription history for all cases.

Table 1 | Characteristics of cases with atrial fibrillation and flutter and population controls

Characteristic	No (%) of cases (n=13 586)	No (%) of controls (n=68 054)
Bisphosphonate exposure		
Current	435 (3.2)	1958 (2.9)
Former	289 (2.1)	1180 (1.7)
Never	12 862 (94.7)	64 781 (95.4)
Current users:		
New	32 (0.2)	156 (0.2)
Continuing	403 (3.0)	1802 (2.6)
No of prescriptions for bisphosphonates, current users:		
1-3	54 (0.4)	240 (0.4)
4-9	144 (1.1)	606 (0.9)
≥10	238 (1.8)	1112 (1.6)
Covariates		
Age (years):		
≤70	3573 (26.3)	17 834 (26.3)
71-80	4579 (33.7)	23 034 (33.7)
>80	5434 (40.0)	27 141 (39.9)
Previous hospital diagnoses:		
Cardiovascular disease	3582 (26.4)	9121 (13.4)
Diabetes	904 (6.7)	2679 (3.9)
Renal failure	211 (1.6)	342 (0.5)
Pulmonary disease	2270 (16.7)	6816 (10.0)
Cancer	1908 (14.0)	7827 (11.5)
Liver disease	1261 (9.3)	3606 (5.3)
Hyperthyroidism	842 (6.2)	2574 (3.8)
Osteoporosis	1209 (8.9)	5329 (7.8)
Hip or wrist fracture	2096 (15.4)	9472 (13.9)
Current use of drugs (prescription):		
Cardiovascular	11 087 (81.6)	41 816 (61.4)
Antithyroid	788 (5.8)	2273 (3.3)
Thyroid replacement	897 (6.6)	4128 (6.1)
Hormone replacement	2717 (20.0)	14 198 (20.9)
Oral glucocorticoids	1783 (13.1)	6030 (8.9)
Respiratory	2923 (21.5)	9913 (14.6)
Hospital diagnosis and current use of drugs (prescription):		
Alcoholism	131 (0.9)	386 (0.6)
Hospital diagnosis concurrent with index date:		
Acute alcohol intoxication	44 (0.3)	115 (0.2)

According to Danish guidelines the first diagnosis in the discharge record is the main reason for the admission to hospital. However, as arrhythmias may precipitate other important medical events that may become the immediate reason for admission to hospital (for example, stroke, heart failure), we included cases with a discharge diagnosis of atrial fibrillation and flutter at any position on the hospital discharge or diagnosis list.

Population controls

For each case with atrial fibrillation and flutter we selected five population controls matched on age, sex, and county, each selected from the population registries of the four counties. These registries, updated daily, have maintained records on vital status (dead or alive), date of death, and the residence of all Danish citizens since 1 April 1968.[7] The controls were selected using risk set sampling and assigned an index date identical to the diagnosis date of atrial fibrillation or flutter for the matched case.[11] We included a total of 68 054 population controls in the study.

The four counties are served by pharmacies equipped with electronic accounting systems that are primarily used to secure reimbursement from the national health service.[8 12] The health service provides tax supported free health care for all inhabitants of Denmark and refunds part of the cost of prescribed drugs such as bisphosphonates for osteoporosis, which have been available in Denmark since 1984 (etidronate), 1995 (alendronate), and 1997 (etidronate with calcium). No cases and just five controls used risedronate (introduced to Denmark in 2004). For each filled prescription the patient's civil registration number, the type and amount of drug prescribed according to the Anatomical Therapeutic Chemical (ATC) classification system, and the date of the drug dispensed are transferred from the pharmacies to the prescription databases.

Prescription data

We used the population based prescription databases in the four counties[12 13] to identify all prescriptions for bisphosphonates filled by cases and population controls before the date of hospital admission (or outpatient visit), with atrial fibrillation of the cases or the index date among population controls. We defined current use of bisphosphonates as the filling of at least one prescription within 90 days before admission for atrial fibrillation or flutter or the corresponding date for controls, and former use as the absence of recorded prescriptions within 90 days before admission or the index date and the filling of at least one prescription after 1997 up to 91 days before the diagnosis or index date.[13] Never use of bisphosphonates was used as the reference category. We defined new users to be women who had the first recorded prescription three months before the index date and continuing users to be women with more than one recorded prescription.[14]

Data on potential confounding factors[6] were collected from the Danish National Registry of Patients

Table 2 | Crude and adjusted relative risk (95% confidence intervals) for atrial fibrillation and flutter among current and former users of bisphosphonates

Variable	Crude relative risk (95% CI)	Adjusted relative risk* (95% CI)
Bisphosphonate use		
Current	1.10 (0.98 to 1.23)	0.95 (0.84 to 1.07)
Former	1.24 (1.08 to 1.41)	1.04 (0.90 to 1.21)
Never	1 (reference)	1 (reference)
New *v* continuing use:		
New current users	0.90 (0.59 to 1.37)	0.75 (0.49 to 1.16)
Continuing users	1.12 (1.00 to 1.25)	0.96 (0.85 to 1.09)
Never users	1 (reference)	1 (reference)
No of prescriptions for bisphosphonates, current users		
1-3	1.27 (1.06 to 1.52)	1.05 (0.86 to 1.27)
4-9	1.24 (1.07 to 1.43)	1.07 (0.92 to 1.25)
≥10	1.05 (0.93 to 1.19)	0.90 (0.79 to 1.03)
Stratified on cardiovascular disease†		
Previous hospital diagnoses of cardiovascular disease, bisphosphonate use:		
Current	1.25 (0.90 to 1.74)	1.13 (0.78 to 1.64)
Former	1.21 (0.81 to 1.79)	1.07 (0.70 to 1.65)
Never	1 (reference)	1 (reference)
No previous hospital diagnoses of cardiovascular disease, bisphosphonate use:		
Current	1.06 (0.92 to 1.21)	0.93 (0.80 to 1.07)
Former	1.11 (0.94 to 1.32)	0.97 (0.81 to 1.16)
Never	1 (reference)	1 (reference)

*Adjusted for cardiovascular disease; renal failure; diabetes; pulmonary diseases; cancer, liver diseases; alcoholism; acute alcohol intoxication; hyperthyroidism; osteoporosis; hip or wrist fracture; use of cardiovascular drugs, antithyroid drugs, hormone replacement therapy, respiratory drug use, use of oral glucocorticoids.
†Defined as previous hospital diagnosis of cardiovascular disease.

and the prescription databases. We searched hospital registry files for discharge or (since 1995 outpatient) records before the index dates containing diagnoses of cardiovascular disease, diabetes, cancer, pulmonary disease, liver disease, hyperthyroidism, renal failure, osteoporosis, and alcoholism (codes available at www.kea.au.dk/doc/biscodes.pdf). A diagnosis of acute alcohol intoxication was included in the analysis if it occurred during the index outpatient visit or admission to hospital, or index date among controls. As a measure of severity of the atrial fibrillation and flutter we also obtained information on all cardioversions within one year after the index date. From the prescription databases (codes available at www.kea.au.dk/doc/biscodes.pdf), we ascertained current use of cardiovascular, pulmonary, antithyroid, thyroid, hormone replacement therapy, and oral glucocorticoid drugs[6] since these drugs (or the diseases that are indications for the drugs) have been linked to a risk of atrial fibrillation and flutter.

Statistical analysis

We calculated odds ratios and 95% confidence intervals, using conditional logistic regression, as measures of relative risk. Since we used risk set sampling of controls, these odds ratios are unbiased estimates of the corresponding rate ratios.[11] In addition we fitted multiple logistic regression models, controlling for other variables listed in table 1. We then repeated the analysis with osteoporosis and fractures excluded. We also did an analysis limited to patients with an inpatient diagnosis of atrial fibrillation and flutter and their controls as well an analysis limited to patients who underwent cardioversion within one year after the first episode of atrial fibrillation and flutter and their controls.

Finally, we examined the association between duration of use of bisphosphonates and risk of atrial fibrillation and flutter by assessing the risk of atrial fibrillation and flutter according to the number of prescriptions filled after 1997 up to the diagnosis or index date—that is, no prescriptions, 1-3 prescriptions, 4-9 prescriptions, and 10 or more prescriptions. Patients who had an outpatient and inpatient diagnosis of atrial fibrillation or flutter registered on the same date were included in the inpatient analysis only.

RESULTS

We identified 13 586 women with atrial fibrillation and flutter and 68 054 population controls; 11 994 of the patients (88.3%) were inpatients. A total of 996 (8.3%) had cardioversion within one year after the diagnosis. About 74% of cases and controls were aged more than 70 years. Overall, 26.4% of the cases had a hospital diagnosis of cardiovascular disease and 81.6% had received a prescription for cardiovascular drugs compared with 13.4% and 61.4% among controls (table 1).

Bisphosphonate use was uncommon in both cases and controls: around 2% were former users and 3% current users (table 1). For current use of bisphosphonates the relative risk was 0.95 (95% confidence interval 0.84 to 1.07); the relative risk for former use was similar (table 2). If osteoporosis and fractures were excluded from the regression model the relative risk estimates were virtually unchanged (adjusted relative risk 0.96, 95% confidence interval 0.86 to 1.08). Restriction to cases who underwent cardioversion showed a similar relative risk estimate (0.84, 95% confidence interval 0.52 to 1.35). For new and continuing users the relative risks were 0.75 (95% confidence interval 0.49 to 1.16) and 0.96 (0.85 to 1.09), respectively. Etidronate and alendronate were used with almost the same frequency among cases and controls; 163 cases (1.2%) used etidronate and 264 (1.9%) used alendronate.

The relative risks for current use of bisphosphonates were similar in patients with and without a previous hospital diagnosis of cardiovascular disease (table 2). If analysis was restricted to patients with an inpatient diagnosis of atrial fibrillation and flutter only, the relative risk for current use was almost identical to the overall result of 0.97 (95% confidence interval 0.86 to 1.09). For an inhospital and first listed diagnosis, the relative risk estimate was 0.92 (95% confidence interval 0.76 to 1.12). More generally, the relative risks were independent of the position of atrial fibrillation and flutter in the discharge record. The adjusted relative risk did not differ for current users of etidronate (0.94,

95% confidence interval 0.78 to 1.13) and alendronate (0.96, 0.82 to 1.12).

No association was found between number of prescriptions and risk of atrial fibrillation and flutter. The relative risk estimate for 1-3 prescriptions was 1.05 (95% confidence interval 0.86 to 1.27), for 4-9 prescriptions was 1.07 (0.92 to 1.25), and for 10 or more prescriptions was 0.90 (0.79 to 1.03).

DISCUSSION

In this large case-control study we found no evidence of an increased risk of atrial fibrillation and flutter associated with use of the bisphosphonates etidronate and alendronate.

Our data are consistent with a recent reanalysis of a clinical placebo controlled trial of about 15 000 patients followed up for up to three years. In that study the cumulative incidence of atrial fibrillation was 1.4% in the placebo group compared with 1.3% among patients treated with 2.5 mg risedronate and 1.4% among patients treated with 5 mg risedronate.[3] Similarly, in a recent trial of patients with hip fracture, participants assigned to intravenous zoledronic acid had a rate of serious atrial fibrillation similar to that in participants given placebo (14 of 1065 *v* 12 of 1062).[15] In contrast, Black et al reported a significant increase in the risk of atrial fibrillation, classified as a "serious" event among patients treated with intravenous zoledronic acid,[2] and another study reported a trend towards an increased risk of atrial fibrillation among patients treated with oral alendronate.[4]

The events in Black et al's zoledronic acid trial were uniformly distributed over time in the year after treatment. The majority of events occurred more than 30 days after infusion, by which time zoledronic acid is not detectable in the circulation.[2] The mechanisms that might explain such an association are not clear but it has been suggested that hypocalcaemia and associated secondary hyperparathyroidism might be responsible for the arrhythmia.[16]

Thus an increase in risk of atrial fibrillation has been observed with potent nitrogen containing bisphosphonates, alendronate and zoledronic acid. Some side effects of bisphosphonates have been attributed to the nitrogen containing moiety—for example, a flu-like syndrome.[17] Alendronate is a nitrogen containing bisphosphonate but etidronate is not. We found, however, no difference between etidronate and alendronate, despite their different structure and potency.

Strengths and limitations

The strengths of our study include the population based design within a free tax supported universal healthcare system with a complete hospital prescription history and access to appropriate population controls. This reduces the risk of referral, diagnostic, and information bias.[8] In addition our analysis adjusted for the most important risk factors for atrial fibrillation.[6] Although it is well known that some hospital discharge diagnoses are not accurate,[8] the specificity of the diagnosis of atrial fibrillation and flutter is reported to be high, and less than 5% of the patients with atrial fibrillation have only atrial flutter.[10] The accuracy of most of the other hospital discharge diagnoses we used in this study is likewise high.[8 18] The universal provision of health care (including support for prescription drugs) considerably reduced the likelihood that our null finding was due to selection bias or unmeasured confounding. In particular since osteoporosis and cardiovascular disease share risk factors such as smoking and obesity and evidence is increasing that osteoporosis in itself is a risk factor for cardiovascular disease in post-menopausal women.[19] Zoledronic acid was not used by outpatients and risedronate use was limited. Therefore our results do not necessary hold for those bisphosphonates.

In conclusion, in this large population based study we did not find that use of etidronate or alendronate for osteoporosis was associated with an increased risk of atrial fibrillation and flutter.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Bisphosphonates are widely used in the treatment of osteoporosis

Data from clinical trials have reported that bisphosphonates may increase the risk of atrial fibrillation but data on their potential toxicity are scanty and conflicting

WHAT THIS STUDY ADDS

Patients with atrial fibrillation and flutter had a similar frequency of use of etidronate and alendronate as population controls

No evidence was found that use of bisphosphonates increases the risk of atrial fibrillation and flutter

Contributors: HTS and SRC conceived the study. HTS, SC, FM, LP, and JAB designed the study and collected and analysed the data. All authors interpreted the findings. HTS, RDC, and SRC reviewed the literature. HTS wrote the first draft and all authors edited the manuscript. HTS is the guarantor.

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Ethical approval: This study was approved by the Danish Data Protection Agency (record No 2004-41-4693) and the Aarhus University Hospital registry board.

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