

- without hydration or nutrition for patients nearing death in the Netherlands. *Ann Intern Med* 2004;141:178-85.
- 4 Van der Heide A, Onwuteaka-Philipsen BD, Rurup ML, Buiting HM, van Delden JJ, Hanssen-de Wolf JE, et al. End-of-life practices in the Netherlands under the Euthanasia Act. *N Engl J Med* 2007;356:1957-65.
 - 5 Onwuteaka-Philipsen BD, van der Heide A, Koper D, Keij-Deerenberg I, Rietjens JA, Rurup ML, et al. Euthanasia and other end-of-life decisions in the Netherlands in 1990, 1995, and 2001. *Lancet* 2003;362:395-9.
 - 6 Stichting Farmaceutische Kengetallen. De richtlijn palliatieve sedatie. [Palliative sedation directive.] *Pharm Weekbl* 2006;141(3):81.
 - 7 Muller-Busch HC, Andres I, Jehser T. Sedation in palliative care—a critical analysis of 7 years experience. *BMC Palliat Care* 2003;2:2.
 - 8 Fainsinger RL, Waller A, Bercovici M, Bengtson K, Landman W, Hosking M, et al. A multicentre international study of sedation for uncontrolled symptoms in terminally ill patients. *Palliat Med* 2000;14:257-65.
 - 9 Chiu TY, Hu WY, Lue BH, Cheng SY, Chen CY. Sedation for refractory symptoms of terminal cancer patients in Taiwan. *J Pain Symptom Manage* 2001;21:467-72.
 - 10 Stone P, Phillips C, Spruyt O, Waight C. A comparison of the use of sedatives in a hospital support team and in a hospice. *Palliat Med* 1997;11:140-4.
 - 11 Hasselaar JG, Reuzel RP, Verhagen SC, de Graeff A, Vissers KC, Crul BJ. Improving prescription in palliative sedation: compliance with Dutch guidelines. *Arch Intern Med* 2007;167:1166-71.
 - 12 Verkerk M, van Wijlick E, Legemaate J, de Graeff A. A national guideline for palliative sedation in the Netherlands. *J Pain Symptom Manage* 2007;34:666-70.
 - 13 Rietjens JA, van Delden JJ, van der Heide A, Vrakking AM, Onwuteaka-Philipsen BD, van der Maas PJ, et al. Terminal sedation and euthanasia: a comparison of clinical practices. *Arch Intern Med* 2006;166:749-53.

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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 (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 are widely used to treat osteoporosis after the menopause.¹ Recently an international trial reported that the bisphosphonate zoledronic acid substantially reduced the risk of fractures² but unexpectedly was associated with serious atrial fibrillation.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 We investigated whether bisphosphonates are associated with a risk of atrial fibrillation and flutter.

METHODS

We carried out this population based case-control study using databases from four northern Danish counties, with a combined population of 1.7 million (about 30% of the Danish population). We used the personal identifier assigned to each Danish citizen⁵ 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 Danish women.

Cases and population controls

To identify incident cases of atrial fibrillation and flutter we used computerised data from the Danish National Registry of Patients. For each hospital admission since 1977 (since 1995 for hospital outpatient visits and emergency room visits) the registry records the civil registration number of the patient; dates of admission and discharge; surgical procedures, and up to 20 discharge diagnoses, coded by doctors (international classification of diseases, eighth revision until the end of 1993 and the 10th revision thereafter).^{6,7} We searched the registry for patients with discharge codes for atrial fibrillation and flutter. These were coded separately in ICD-8 but together in ICD-10. We therefore studied atrial fibrillation and atrial flutter as one end point.

We chose cases who had a first diagnosis during 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.

For each case we used risk set sampling to select five controls matched on age, sex, and county, and assigned

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

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.

an index date identical to the diagnosis date of atrial fibrillation or flutter for the matched case.⁸ We included 68 054 population controls in the study.

Prescription data

We used the health service's prescription databases^{9,10} to identify prescriptions for bisphosphonates filled by cases and controls before the date of hospital admission (or outpatient visit), with atrial fibrillation of the cases or the index date among controls. We defined current use of bisphosphonates as the filling of at least one prescription within 90 days before admission for atrial fibrillation and 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.¹⁰ Never use of bisphosphonates was 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.¹¹

Data on potential confounding factors¹² were collected from the Danish National Registry of Patients 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.ke.aau.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 cardioversions within one year after the index date. From the prescription databases (codes available at www.ke.aau.dk/doc/biscodes.pdf), we ascertained current use of cardiovascular, pulmonary, antithyroid, thyroid, hormone replacement therapy, and oral glucocorticoid drugs¹² since these 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.⁸ In addition we fitted multiple logistic regression models, controlling for other variables (see bmj.com). We 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 as 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 bisphosphonate use 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 (no prescriptions, 1-3 prescriptions, 4-9 prescriptions, and ≥10 prescriptions). In the inpatient analysis we included only patients who had an outpatient and an inpatient record of atrial fibrillation and flutter at the same time.

RESULTS

We identified 13 586 women with atrial fibrillation and flutter and 68 054 controls; 11 994 patients (88.3%) were inpatients. A total of 996 (8.3%) had cardioversion within one year after 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 (see bmj.com).

Bisphosphonate use was uncommon in both cases and controls: around 2% were former users and 3% current users (see bmj.com). The relative risk for current use of bisphosphonates was 0.95 (95% confidence interval 0.84 to 1.07), and for former use it was similar (table). 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, 0.52 to 1.35). For new and continuing users the relative risks

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

were 0.75 (0.49 to 1.16) and 0.96 (0.85 to 1.09). Etidronate and alendronate were used with almost the same frequency among cases and controls.

The relative risks for current use of bisphosphonates were similar in patients with and without a previous hospital diagnosis of cardiovascular disease (table). 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 inpatient discharge diagnosis listed first in the registry record, the relative risk estimate was 0.92 (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, 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 reanalysis of a 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% in the 2.5 mg risedronate group and 1.4% in the 5 mg risedronate group.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).¹³ In contrast, Black et al reported a significant increase in the risk of "serious" atrial fibrillation among patients treated with zoledronic acid,² and another study reported a trend towards an increased risk of atrial fibrillation among patients treated with alendronate.⁴ The events in Black et al's trial were uniformly distributed over the year after treatment. Most 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 play a part.¹⁴

Strength and limitations

The strengths of our study include the population based design within a free tax healthcare system with a complete hospital prescription history and access to population controls. This reduces the risk of biases from referral, diagnosis, and information.⁶ In addition our analysis adjusted for the most important risk factors for atrial fibrillation.¹² Although some hospital discharge diagnoses may not be accurate,⁶ the specificity of the diagnosis of atrial fibrillation and flutter is reported to be high.¹⁵ The accuracy of most of the other hospital discharge diagnoses we used in this study is likewise high.⁶ The universal provision of health care 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.¹⁶ As zoledronic acid was not used by outpatients and risedronate use was limited our results do not necessarily hold for those bisphosphonates.

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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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- 1 Woolf AD, Akesson K. Preventing fractures in elderly people. *BMJ* 2003;327:89-95.
- 2 Black DM, Delmas PD, Eastell R, Reid IR, Boonen S, Cauley JA, et al. Once-yearly zoledronic acid for treatment of postmenopausal osteoporosis. *N Engl J Med* 2007;356:1809-22.
- 3 Karam R, Camm J, McClung M. Yearly zoledronic acid in postmenopausal osteoporosis. *N Engl J Med* 2007;357:712-3.
- 4 Cummings SR, Schwartz AV, Black DM. Alendronate and atrial fibrillation. *N Engl J Med* 2007;356:1895-6.
- 5 Frank L. When an entire country is a cohort. *Science* 2000;287:2398-9.
- 6 Sørensen HT. Regional administrative health registers as a resource in clinical epidemiology. A study of options, strengths, limitations and data quality provided with examples of use. *Int J Risk Safety Med* 1997;10:1-22.
- 7 Andersen TF, Madsen M, Jørgensen J, Møller-Jensen L, Olsen JH. The Danish National Hospital Register. A valuable source of data for modern health sciences. *Dan Med Bull* 1999;46:263-8.
- 8 Rothman KJ, Greenland S. *Modern epidemiology*. Philadelphia: Lippincott-Raven, 1998.
- 9 Thomsen RW, Johnsen SP, Olesen AV, Mortensen JT, Bøggild H, Olsen J, et al. Socioeconomic gradient in use of statins among Danish patients: population-based cross-sectional study. *Br J Clin Pharmacol* 2005;60:534-42.
- 10 Sørensen HT, Jacobsen J, Nørgaard M, Pedersen L, Johnsen SP, Baron JA. Newer cyclooxygenase-2 selective inhibitors, other nonsteroidal anti-inflammatory drugs, and risk of acute pancreatitis. *Aliment Pharmacol Ther* 2006;24:111-6.

- 11 Ray WA. Evaluating medication effects outside of clinical trials: new-user designs. *Am J Epidemiol* 2003;158:915-20.
- 12 Kannel WB, Benjamin EJ. Status of the epidemiology of atrial fibrillation. *Med Clin North Am* 2008;92:17-40.
- 13 Poole KE, Kaptoge S, Reeve J. Yearly zoledronic acid in postmenopausal osteoporosis. *N Engl J Med* 2007;357:711-2.
- 14 Lyles KW, Colón-Emeric CS, Magaziner JS, Adachi JD, Pieper CF, Mautalen C, et al. Zoledronic acid and clinical fractures and mortality after hip fracture. *N Engl J Med* 2007;357:1799-809.
- 15 Frost L, Vestergaard P. Alcohol and risk of atrial fibrillation or flutter: a cohort study. *Arch Intern Med* 2004;164:1993-8.
- 16 Tankó LB, Christiansen C, Cox DA, Geiger MJ, McNabb MA, Cummings SR. Relationship between osteoporosis and cardiovascular disease in postmenopausal women. *J Bone Miner Res* 2005;20:1912-20.

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Effect of high throughput *RHD* typing of fetal DNA in maternal plasma on use of anti-RhD immunoglobulin in RhD negative pregnant women: prospective feasibility study

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ABSTRACT

Objectives To assess the feasibility of applying a high throughput method, with an automated robotic technique, for predicting fetal RhD phenotype from fetal DNA in the plasma of RhD negative pregnant women to avoid unnecessary treatment with anti-RhD immunoglobulin.

Design Prospective comparison of fetal *RHD* genotype determined from fetal DNA in maternal plasma with the serologically determined fetal RhD phenotype from cord blood.

Setting Antenatal clinics and antenatal testing laboratories in the Midlands and north of England and an international blood group reference laboratory.

Participants Pregnant women of known gestation identified as RhD negative by an antenatal testing laboratory. Samples from 1997 women were taken at or before the 28 week antenatal visit.

Main outcome measures Detection rate of fetal RhD from maternal plasma, error rate, false positive rate, and the odds of being affected given a positive result.

Results Serologically determined RhD phenotypes were obtained from 1869 cord blood samples. In 95.7% (n=1788) the correct fetal RhD phenotype was predicted by the genotyping tests. In 3.4% (n=64) results were either unobtainable or inconclusive. A false positive result was obtained in 0.8% (14 samples), probably because of unexpressed or weakly expressed fetal *RHD* genes. In only three samples (0.2%) were false negative results obtained. If these results had been applied as a guide to treatment, only 2% of the women would have received anti-RhD unnecessarily, compared with 38% without the genotyping.

Conclusions High throughput *RHD* genotyping of fetuses in all RhD negative women is feasible and would substantially reduce unnecessary administration of anti-RhD immunoglobulin to RhD negative pregnant women with an RhD negative fetus.

INTRODUCTION

In 2002 the National Institute for Health and Clinical Excellence (NICE) recommended that all RhD negative pregnant women should be offered anti-RhD immunoglobulin at 28 and 34 weeks' gestation.¹ It also

“endorsed studies into the feasibility of mass testing antenatally for fetal blood group by analysis of fetal DNA in maternal plasma.”¹ Benefits would be twofold. Firstly, a substantial reduction in the use of anti-RhD immunoglobulin, an expensive blood product in short supply and, secondly, women with an RhD negative fetus would be spared unnecessary exposure to this pooled human blood product. The antigens of the Rh blood group system are located on two proteins encoded by two homologous genes, *RHD* and *RHCE*.² The most immunogenic of the Rh antigens, RhD, is encoded by *RHD* and the RhD negative phenotype usually results from homozygosity for a complete deletion of *RHD* (see bmj.com for further details).

In 2001 the International Blood Group Reference Laboratory of the English National Blood Service introduced fetal *RHD* genotyping from fetal DNA in maternal plasma as a service. Maternal plasma has now almost replaced fetal cells, obtained by amniocentesis or chorionic villus sampling, as the source of fetal DNA. The method currently used routinely for fetal *RHD* genotyping is labour intensive and expensive and therefore not suitable for the mass screening of all RhD negative women. Recent developments in technology and the introduction of automated robotic techniques have brought down costs and increased the potential for higher throughput.

We validated a high throughput *RHD* fetal genotyping technique by comparing the results obtained with the RhD serological phenotype obtained from cord blood taken at delivery.

METHODS

Blood samples—Anticoagulated blood samples were chosen for fetal genotyping from any RhD negative pregnant women attending antenatal clinics that use the Birmingham and Sheffield centres of the National Blood Service for routine ABO and RhD blood grouping and antibody screening. This did not involve taking additional blood samples to those collected for routine testing. The blood samples were collected at the women's 28 week visit to the antenatal clinic. Ethnicity was 55% white, 8% Asian, 1.5% black, 0.5% Caribbean

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