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Bisphosphonates and Atrial Fibrillation
Systematic Review and Meta-Analysis

Yoon Kong Loke,[1] *Vinodh Jeevanantham*[2] and *Sonal Singh*[2]

1 School of Medicine, University of East Anglia, Norwich, UK
2 Section on General Internal Medicine, Wake Forest University School of Medicine, Winston-Salem, North Carolina, USA

Abstract

Background: Bisphosphonates are widely used in osteoporosis, but there have been concerns about a potential link between bisphosphonate therapy and atrial fibrillation.

Objective: We aimed to systematically evaluate the risk of atrial fibrillation associated with bisphosphonate use.

Methods: We searched MEDLINE, regulatory authority websites, pharmaceutical company trial registers and product information sheets for randomized controlled trials (RCTs) and controlled observational studies published in English through to May 2008. We selected RCTs of bisphosphonates versus placebo for osteoporosis or fractures, with at least 3 months of follow-up, and data on atrial fibrillation. For the observational studies, we included case-control or cohort studies that evaluated the risk of atrial fibrillation in patients exposed to bisphosphonates compared with non-exposure. Data on atrial fibrillation as the primary outcome, and stroke and cardiovascular mortality as secondary outcomes, were extracted.

Data Synthesis/Results: We calculated pooled odds ratio (OR) using random effects meta-analysis, and estimated statistical heterogeneity with the I^2 statistic. Bisphosphonate exposure was significantly associated with risk of atrial fibrillation serious adverse events in a meta-analysis of four trial datasets (OR 1.47; 95% CI 1.01, 2.14; $p = 0.04$; $I^2 = 46\%$). However, meta-analysis of all atrial fibrillation events (serious and non-serious) from the same datasets yielded a pooled OR of 1.14 (95% CI 0.96, 1.36; $p = 0.15$; $I^2 = 0\%$).

We identified two case-control studies, one of which found an association between bisphosphonate exposure (ever users) and atrial fibrillation (adjusted OR 1.86; 95% CI 1.09, 3.15) while the other showed no association (adjusted OR 0.99; 95% CI 0.90, 1.10). Both studies failed to demonstrate a significant association in 'current' users.

We did not find a significant increase in the risk of stroke (three trial datasets; OR 1.00; 95% CI 0.82, 1.22; $p = 0.99$; $I^2 = 0\%$) or cardiovascular mortality (three trial datasets; OR 0.86; 95% CI 0.66, 1.13; $p = 0.28$; $I^2 = 31\%$).

Conclusion: While there are some data linking bisphosphonates to serious atrial fibrillation, heterogeneity of the existing evidence, as well as paucity of

information on some of the agents, precludes any definitive conclusions on the exact nature of the risk.

Background

Bisphosphonates are effective anti-resorptive agents that reduce the risk of vertebral and non-vertebral fractures.[1-9] Risedronate, alendronate, pamidronate, ibandronate, etidronate, zoledronic acid and tiludronate are the currently approved bisphosphonates in the US. They are widely used mainly in patients with osteoporosis. There were more than 190 million oral bisphosphonate prescriptions dispensed worldwide by 2006.[10,11]

In October 2007,[12] the US FDA announced their ongoing safety review of a potential link between bisphosphonate use and 'serious' atrial fibrillation adverse events, based on data from two randomized trials.[7,8] The FDA communication states, ''Upon initial review, it is unclear how these data on serious atrial fibrillation should be interpreted.''[12] The FDA maintains that the current indications for bisphosphonate use should remain unchanged.[12]

Limited clinical information is currently available on this possible risk of serious atrial fibrillation with long-term bisphosphonate therapy. It is also unclear whether the risk of stroke is affected by any potential increase in the frequency or severity of atrial fibrillation.

We aimed to systematically evaluate the risk of atrial fibrillation with bisphosphonate therapy and to ascertain the rates of stroke and cardiovascular mortality in studies where atrial fibrillation was reported.

Methods

Eligibility Criteria

We selected randomized trials and controlled observational studies that reported on the risk of atrial fibrillation with bisphosphonate therapy.

For the trials, specific inclusion criteria were:
1. parallel-group, randomized controlled trials (RCTs) of any bisphosphonate of ≥3 months duration;
2. study participants with either osteoporosis or fractures;
3. bisphosphonates were compared with placebo;
4. studies had to provide numerical data (including zero events) on atrial fibrillation adverse events.

We excluded RCTs of bisphosphonates for the treatment of malignancy, as there may be substantial metabolic and cardiovascular changes in cancer patients that affect their susceptibility to atrial fibrillation.

We included controlled observational studies (case control, or prospective or retrospective cohort design) in patients with osteoporosis reporting on the association between any bisphosphonate exposure and atrial fibrillation.

Primary and Secondary Outcomes

We specified atrial fibrillation adverse events (AEs) as the primary outcome of the meta-analysis, and recorded the rates of atrial fibrillation events overall, as well as atrial fibrillation diagnosed within the category of serious adverse events (SAEs). According to the FDA, SAEs are ''life threatening, or lead to death, or prolongation of hospitalization, or disability, or requiring intervention to prevent permanent damage.''[13] Since none of the trials were primarily designed to estimate the risk of atrial fibrillation, we relied on investigator-recorded categories of 'serious' adverse events in the trials.

Secondary outcomes were stroke and cardiovascular mortality in studies reporting on atrial fibrillation.

Search Strategy

Two reviewers (VJ and YL) independently and in duplicate searched MEDLINE up to May 2008 for published clinical trials of bisphosphonates in osteoporosis using a combination of free text terms [using the following search string in the Ovid interface: (bisphosphonate.mp or ibandronate.mp or

pamidronate.mp or tiludronate.mp or clodronate.mp or etidronate.mp or risedronate.mp or alendronate.mp or zoledronic-acid.mp) AND (clinical-trial.mp) and (osteoporosis.mp)] and MeSH terms (using the following search string: ''Diphosphonates''[Mesh] AND ''Osteoporosis'' [Mesh] AND ''Randomized Controlled Trial ''[Publication Type]).

For additional studies of bisphosphonates and atrial fibrillation we searched PubMed up to May 2008 using the terms 'bisphosphonates' AND 'atrial', and we also registered to receive automated electronic notifications of any new articles on bisphosphonates and atrial fibrillation. We searched the websites of US and European regulatory authorities, manufacturer's product information sheets and pharmaceutical companies' clinical trials registers for unpublished data. We checked the bibliographies of included studies, and used the Web of Science Citation Index to identify relevant cited and citing articles. Our search was limited to English language articles.

Study Selection

From the search, two reviewers (VJ and YL) independently and in duplicate scanned all titles and abstracts against the eligibility criteria. After obtaining full reports of potentially relevant studies the same reviewers independently assessed eligibility for inclusion from full text articles, and reached full agreement on the selected studies following discussion with a third reviewer (SS).

Data Abstraction

Two reviewers (VJ and YL) independently and in duplicate extracted data on atrial fibrillation adverse events, stroke and overall mortality after discussing and reaching consensus on eligible studies. If there were multiple reports available for a particular study, we chose to extract data from the most recent version.

Study Characteristics

The type, dose and duration of bisphosphonate therapy, mean age and sex of participants, and the population studied were recorded. We contacted authors of relevant articles when specific aspects of the data required clarification.

We used a standard form to record information on study type and study population (hospital based or population based), and the methods used to determine bisphosphonate exposure and the outcome of atrial fibrillation in the observational studies.

Validity Assessment

Our assessment of trial quality is listed in Appendix 1 (see supplementary material ['ArticlePlus'] at http://drugsafety.adisonline.com), while Appendix 2 (see also supplementary material) provides details regarding the quality of the observational studies. We assessed the reporting of allocation concealment and use of blinding in the trials. We recorded the methods used in detecting and confirming adverse events, in order to assess the strength of adverse drug reaction reporting as recommended in the *Cochrane Handbook of Systematic Reviews of Interventions*.[14]

The quality assessment of observational studies included information on representativeness of the case/controls, comparability of cases and controls, ascertainment of exposure or outcomes, and adequacy of follow-up and duration.

Quantitative Data Synthesis and Sensitivity Analysis

Review Manager (RevMan®) version 5.016 (The Nordic Cochrane Center, Copenhagen, Denmark) was used to calculate pooled odds ratio (OR) and 95% CIs for atrial fibrillation and stroke using a random effects model. All reported p-values are two-sided. Statistical heterogeneity was assessed using I^2, with values of 30–60% indicating a moderate level of heterogeneity.[15] If heterogeneity >60%, we planned to conduct additional sensitivity analyses to explore individual study characteristics and those of subgroups of the main body of evidence.

Prespecified sensitivity analyses were conducted to explore the influence on effect size of the statistical model and of trials that had to be excluded owing to insufficient detail in the reports.

Results

We identified four datasets from clinical trials, and two datasets from observational studies that were eligible for inclusion in our meta-analysis (figure 1). Three individual RCTs[7-9,16] provided data on atrial fibrillation, while one pharmaceutical company analysis (published as a journal letter)[17] yielded pooled rates of atrial fibrillation from six RCTs of risedronate.[1-5,18] Characteristics of RCTs that reported on atrial fibrillation events and stroke are shown in table I. Data on atrial fibrillation, stroke and cardiovascular mortality in the included RCTs are shown in table II. We did not find any information on atrial fibrillation in trials of ibandronate, pamidronate, tiludronate, clodronate and etidronate.

We found two case-control studies of bisphosphonate use and atrial fibrillation,[20,21] and extracted crude and adjusted ORs according to category of exposure (table III).

Atrial Fibrillation Adverse Effects

Randomized Controlled Trials

Meta-analysis of four datasets from clinical trials showed that bisphosphonates significantly increased the risk of atrial fibrillation SAEs (139/13 172 vs 91/13 180; OR 1.47; 95% CI 1.01, 2.14; p = 0.04; $I^2 = 46\%$) compared with placebo.[7-9,16,17,19] Only one trial showed significant findings on its own, with a relative risk (RR) of 2.33 (95% CI 1.41, 3.85) [figure 2] and number-needed-to-harm of 118 over a 3-year period.[8,19]

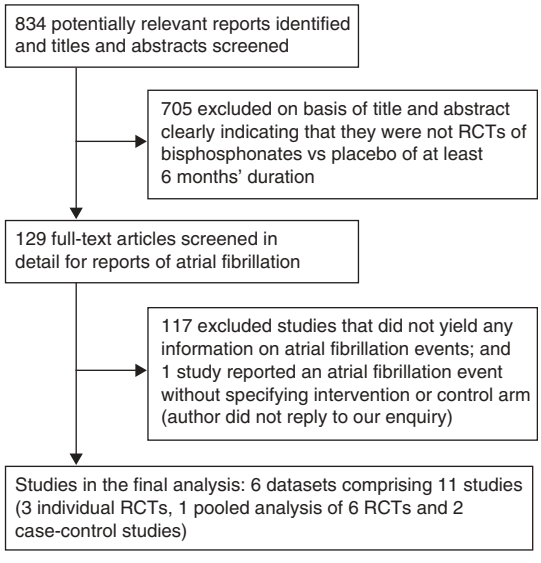

Fig. 1. Study selection from MEDLINE search. **RCTs** = randomized controlled trials.

In contrast, meta-analysis of atrial fibrillation events overall (serious and non-serious) from the same datasets yielded a pooled OR of 1.14 (95% CI 0.96, 1.36; p = 0.15; $I^2 = 0\%$).

Atrial fibrillation SAEs were subject to independent adjudication in three trials, whereas the inclusion of non-serious atrial fibrillation in the overall analysis relied on non-adjudicated events.

Case-Control Studies

Both studies gave contrasting results, with one showing a significant association between any bisphosphonate exposure ('ever' users) and atrial fibrillation,[21] whereas the other study found no association.[22] In both instances, the association was not statistically significant when restricted to current users (table III).

Stroke and Cardiovascular Mortality

Bisphosphonates did not significantly increase the risk of stroke (n = 203/9936 vs 203/9957; RR 1.00; 95% CI 0.82, 1.22; p = 0.99; $I^2 = 0\%$) or cardiovascular mortality (n = 155/9936 vs 181/9957; OR 0.86; 95% CI 0.66, 1.13; p = 0.28; $I^2 = 0\%$) in a meta-analysis of 19 893 patients in three trials[8,9,17] (figure 3).

Sensitivity Analysis

Statistical Model

Fixed effects meta-analysis yielded an OR of 1.53 (95% CI 1.18, 2.00; p = 0.002) for atrial fibrillation SAEs in the four trial datasets. For overall atrial fibrillation, the fixed effects pooled OR was unchanged at 1.14 (95% CI 0.96, 1.36; p = 0.14; $I^2 = 0\%$).

Unpublished Data

An additional unpublished pooled analysis of 28 alendronate trials involving 9300 patients was available from the Merck website as a press release.

Table I. Characteristics of randomized controlled trials (RCTs) of bisphosphonate included in the analysis

Dataset (y)	Design	Mean study duration (mo)	Mean age (y)	Women (%)	Drug	Participants	Monitoring of adverse events
Black et al.[8] (2007)	Double-blind. Allocation concealment unclear	36	73	100	Zoledronic acid 5 mg once a year	Postmenopausal, osteoporosis (n = 7714)	Investigator enquiry and physical examination. CV events adjudicated based on medical records review by blinded committee
Cummings et al.[7,16] (1998)	Double-blind. Adequate allocation concealment	50	69	100	Alendronate 5–10 mg daily	Postmenopausal, osteoporosis (n = 6459)	Investigator enquiry and physical examination about AEs (including minor illnesses) at each visit. AF events verified by 'blinded' independent physician
Lyles et al.[9] (2007)	Double-blind. Adequate allocation concealment	22 (median)	74.5	76.1	Zoledronic acid 5 mg once a year	Patients after operation for hip fracture (n = 2111)	Investigator recorded AEs at each visit. Independent blinded committee adjudicated serious cardiac arrhythmias
Karam et al.[17]a (2007)	Double-blind. Allocation concealment adequate in one trial;[2] unclear in others	24	73	98	Risedronate 5 mg daily	Osteoporosis[b] (n = 10 068)	Investigators recorded AEs at each visit, irrespective of severity or causality. Physical examination and recording of vital signs regularly. Extent of adjudication not described

a Pooled analysis of six RCTs.[1-5,18]

b Five RCTs included participants with postmenopausal osteoporosis, except Reid et al.,[4] which included patients with corticosteroid-induced osteoporosis.

AEs = adverse events; **AF** = atrial fibrillation; **CV** = cardiovascular.

However, these data had to be excluded from our review because the press release did not provide any description of the trials, the population involved or the exact nature of the intervention arms.[22] The event rate from these trials was very low (total of only eight atrial fibrillation SAEs in 5201 alendronate patients across 28 trials) and, unlike the alendronate Fracture Intervention Trial, the atrial fibrillation events had not been adjudicated. If these data of uncertain quality were included in our meta-analysis, we would have a pooled OR of 1.38 (95% CI 0.98, 1.95; $p = 0.06$; $I^2 = 33\%$) for atrial fibrillation SAEs and pooled OR of 1.14 (95% CI 0.96, 1.35; $p = 0.14$; $I^2 = 0\%$) for atrial fibrillation overall.

Discussion

While we found that atrial fibrillation SAEs were significantly more common in bisphosphonate users than placebo (OR 1.47; 95% CI 1.01, 2.14; $p = 0.04$), there are still considerable uncertainties surrounding the evidence overall. The findings of an association are dominated by two large trials (only one trial showed significant risk on its own),[7,8] and there are still dozens of trials with missing outcome data. Moreover, no significant association was found when we analysed all atrial fibrillation events, as opposed to 'serious' events only. The observational studies also yielded heterogeneous results, and reached opposing conclusions. Nevertheless, the existing signal of risk (from two trials – covering zoledronic acid and alendronate,[7,8] and one case-control study involving alendronate[21]) deserves further consideration.

There are a few potential explanations for the inconsistencies in the evidence. As there were no changes in cardiovascular mortality, stroke or non-serious atrial fibrillation events, it is possible that the observed differences in atrial fibrillation

Table II. Atrial fibrillation, stroke and cardiovascular mortality in randomized controlled trials of bisphosphonates

Study (y)	Treatment groups	All atrial fibrillation events (%)	Atrial fibrillation serious adverse events (%)	Stroke (%)	Cardiovascular mortality (%)
Black et al.[8,19][a] (2007)	Zoledronic acid (n = 3862)	96 (2.5)[a]	51(1.3)[a]	87 (2.2)	39 (1.0)
	Placebo (n = 3852)	75 (1.8)[a]	22 (0.6)[a]	88 (2.2)	33 (0.86)
Cummings et al.[7,16] (1998)	Alendronate (n = 3236)	81 (2.5)	47 (1.4)	Not reported	Not reported
	Placebo (n = 3223)	71 (2.2)	31 (1)	Not reported	Not reported
Lyles et al.[9] (2007)	Zoledronic acid (n = 1054)	29 (2.7)	12 (1.1)	46 (4.3)	36 (3.4)
	Placebo (n = 1057)	27 (2.5)	14 (1.3)	38 (3.5)	52 (4.9)
Karam et al.[17][b] (2007)	Risedronate (n = 5020)	70 (1.3)[b]	29 (0.5)[b]	70 (1.3)	80 (1.6)
	Placebo (n = 5048)	70 (1.3)[b]	24 (0.4)[b]	77 (1.5)	96 (1.9)

a Updated data on overall atrial fibrillation and serious atrial fibrillation were extracted from the European prescribing information.[19]

b Data extracted on the licensed therapeutic dose of risedronate 5 mg daily.

SAEs stem from increased hospitalizations. Bisphosphonates may have caused deterioration in the rhythm or rate control of certain susceptible patients, potentially leading to more medical interventions or hospitalizations, which were recorded as 'serious' atrial fibrillation events in the trials. Cardiovascular conditions may be important susceptibility factors: in a subgroup analysis of the zoledronic acid trial by Black et al.[8] a history of tachyarrhythmias appeared to be the strongest risk factor for atrial fibrillation SAEs (hazard ratio [HR] 6.01; 95% CI 3.23, 11.2; $p < 0.001$) compared with past antihypertensive medication use (HR 1.81; 95% CI 1.05, 3.13; $p = 0.034$) or congestive heart failure (HR 2.86; 95% CI 1.12, 7.25; $p = 0.028$).[23]

It is not clear how bisphosphonates may precipitate atrial fibrillation, but possible mechanisms include the release of cytokines,[24] the development of hypomagnesaemia in patients undergoing treatment of hypercalcaemia[25] or alterations in calcium metabolism.[26-28] However, serum calcium levels measured 9–11 days after infusion of zoledronic acid did not change significantly from baseline in the trial by Black et al.[8] and most serious atrial fibrillation events were noted >30 days after the infusion. In view of the distant temporal nature of the adverse effect following drug administration, we selected trials that were of at least 3 months' duration to ensure that trial participants had sufficient long-term follow-up.

Our study has several limitations, mainly from the paucity and quality of the original trial data. The pooled effect size could be considerably altered in either direction if the substantial amount of missing data eventually becomes available for independent academic scrutiny. None of the trials were designed to prospectively monitor for atrial fibrillation or stroke, which were recorded as treatment-emergent adverse events. However, the incidence rates for atrial fibrillation events in the placebo and bisphosphonate arms of the trials (table II) were consistent with the rates found in the general population, which gives us some idea of the appropriateness of trial surveillance in capturing adverse events.[29] There may have been a potential imbalance between the intervention and control arms with regard to risk factors for atrial fibrillation, such as thyroid disorders. We also do not know if the atrial fibrillation SAEs in the trials were incident atrial fibrillation events or whether they were severe exacerbations in participants with existing prevalent atrial fibrillation.

We could not investigate within-class differences in the risk of atrial fibrillation SAEs, as the number of studies was limited, although the drugs vary in potency and degree of affinity for bone. Heterogeneity is an important issue in our meta-analysis, with the two zoledronic acid trials yielding contrasting estimates for the risk of atrial fibrillation. The study by Black et al.[8] showed a significant increase (RR 2.31; 95% CI 1.41, 3.80), while the study by Lyles et al.[9] showed a non-significant decrease (RR 0.86; 95% CI 0.40, 1.85) in atrial fibrillation SAEs. This is possibly due to the imbalance in the baseline distribution of participants with active tachyarrhythmias in the

Table III Observational studies of bisphosphonate exposure and association with atrial fibrillation

Study (y)	Study type and data source	Study population	Ascertainment of drug exposure	Outcome ascertainment	Exposure to bisphosphonates	Crude risk ratio (95% CI)	Adjusted risk ratio (95% CI)[a]
Sørensen et al.[20] (2008)	Case-control. Medical databases from four counties in Denmark	13 586 women with atrial fibrillation and flutter and 68 054 population controls – with complete hospital and prescription claims data, 1999–2005	Population-based prescription database. Current users received bisphosphonates within 90 days, while former users had bisphosphonates up to 91 days before diagnosis or index date. Almost all exposed patients were on alendronate or etidronate	ICD codes from Danish National Registry for discharge diagnosis of atrial fibrillation and flutter (not necessarily main diagnosis, and unclear if this is newly diagnosed). Controls (matched on age, sex and county) selected from population registries, with data collected on 16 possible confounding factors	Cases: 13 586 with 435 current users and 289 former users Controls: 68 054 with 1958 current users and 1180 former users	Current 1.10 (0.98, 2.23) Former: 1.24 (1.08, 1.41) Ever: 1.17 (1.07, 1.27)	Current 0.95 (0.84, 1.07) Former 1.04 (0.90, 1.21) Ever: 0.99 (0.90, 1.10)
Heckbert et al.[21] (2008)	Case control. Group Health – an integrated healthcare delivery system in Washington state	719 women with atrial fibrillation and flutter and 966 controls without atrial fibrillation from population-based Group Health Atrial Fibrillation Study between 1 October 2001 and 31 December 2004	Alendronate exposure through Group Health pharmacy database – 95.5% of Group Health members reported filling all or almost all prescriptions through this scheme. Ever users had at least two prescriptions redeemed at Group Health pharmacies; current users were those who had received enough pills to last until index date	ICD codes for atrial fibrillation and flutter used to identify cases with inpatient or outpatient visits. Cases confirmed with evidence from electrocardiogram and clinical diagnosis by a physician, with no previous record of atrial fibrillation in medical notes. Controls chosen at random from enrolment lists, with matching for age, hypertension and heart disease	Overall, 47/719 cases had been exposed, while 40/966 controls were exposed. Of the 466 cases treated in emergency care or hospital, 31 had history of exposure	Current: 1.22 (0.72, 2.07) Ever: 1.62 (1.05, 2.50)	Current: 1.42 (0.78, 2.59) Ever: 1.86 (1.09, 3.15) Former: 3.27 (1.43, 7.47)

a Sorenson et al. adjusted for cardiovascular disease and drugs, renal failure, diabetes mellitus, cancer, liver, alcoholism, hyperthyroidism, osteoporosis, fractures, hormone replacement therapy and use of corticosteroids and respiratory drugs, while the analysis by Heckbert et al. adjusted for age, hypertension, year of osteoporosis diagnosis and cardiovascular disease.

ICD = International Statistical Classification of Diseases and Related Health Problems.

latter study, which was 5.8% in the zoledronic acid arm versus 7.5% in the placebo arm. In contrast, a total of 559 patients in the former study had electrocardiography before, and shortly after the infusion, and the prevalence of atrial fibrillation was 2.1% in the zoledronic acid group compared with 2.8% in controls. However, the recruitment of patients with fractures rather than just osteoporosis, a higher proportion of men, and a shorter duration of follow-up in the Lyles et al.[9] trial may also explain some of the divergent findings (table I).[8]

The observational data were based primarily on patients taking alendronate, and agents such as risedronate and zoledronic acid were not properly evaluated. Confounding is a particular problem, with the US study failing to adjust for hyperthyroidism, and there may well be unknown residual confounding factors that cannot be accounted for.[21] Given the absence of a clear biological mechanism, we remain uncertain why this observational study only found a significant association with 'ever' users, but not with current users, perhaps suggesting either a false positive, or an adverse effect that occurs temporally distant from the drug administration.

For most women with osteoporosis, the benefits of fracture prevention with the bisphosphonates outweigh the possibility of an increased risk of atrial fibrillation. The number-needed-to-harm for atrial fibrillation SAEs was 118 in the zoledronic acid trial by Black et al.,[8] compared with the number-needed-to-treat of 91 for hip fracture over 3 years. However, clinicians should carefully consider these risks of bisphosphonate therapy in those patients who have a low risk of fractures but may be particularly susceptible to atrial fibrillation (e.g. past history of tachyarrhythmia or congestive heart failure).

We now have a signal from different sources that atrial fibrillation may be linked to bisphosphonate exposure in some circumstances. This signal could be usefully clarified if bisphosphonate manufacturers made all their results

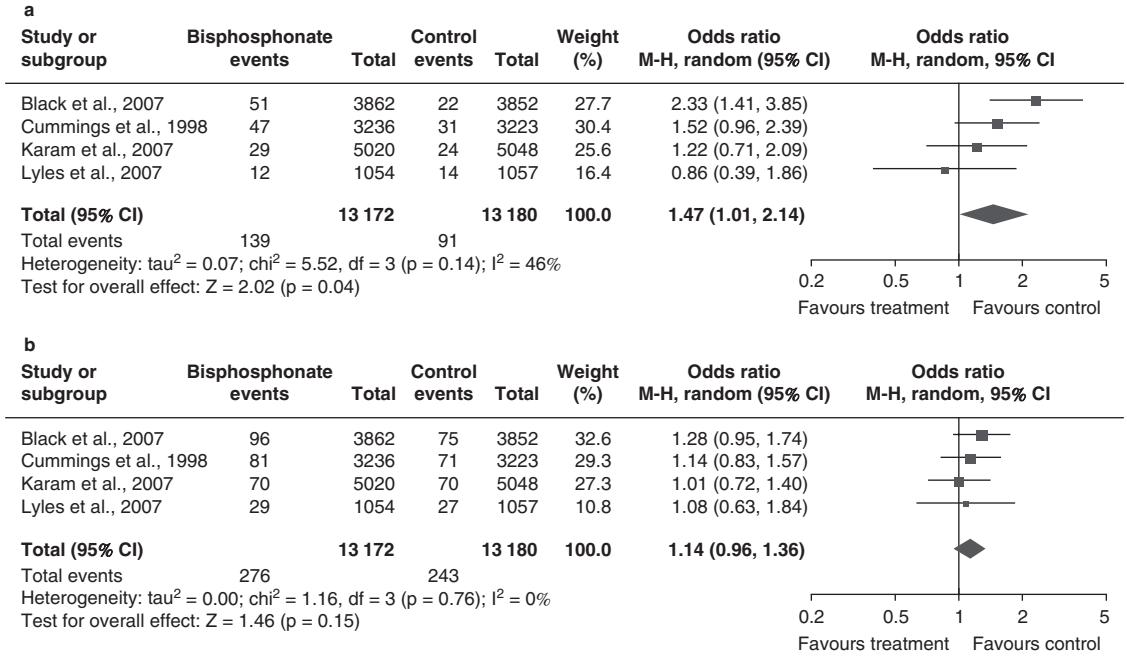

Fig. 2. Meta-analysis of odds ratio for (**a**) atrial fibrillation serious adverse events and (**b**) all atrial fibrillation adverse events (serious and non-serious) with bisphosphonates. Studies: Black et al.,[8] Cummings et al.,[7,16] Karam et al.,[17] and Lyles et al.[9] **df** = degrees of freedom; **M-H** = Mantel-Haenszel.

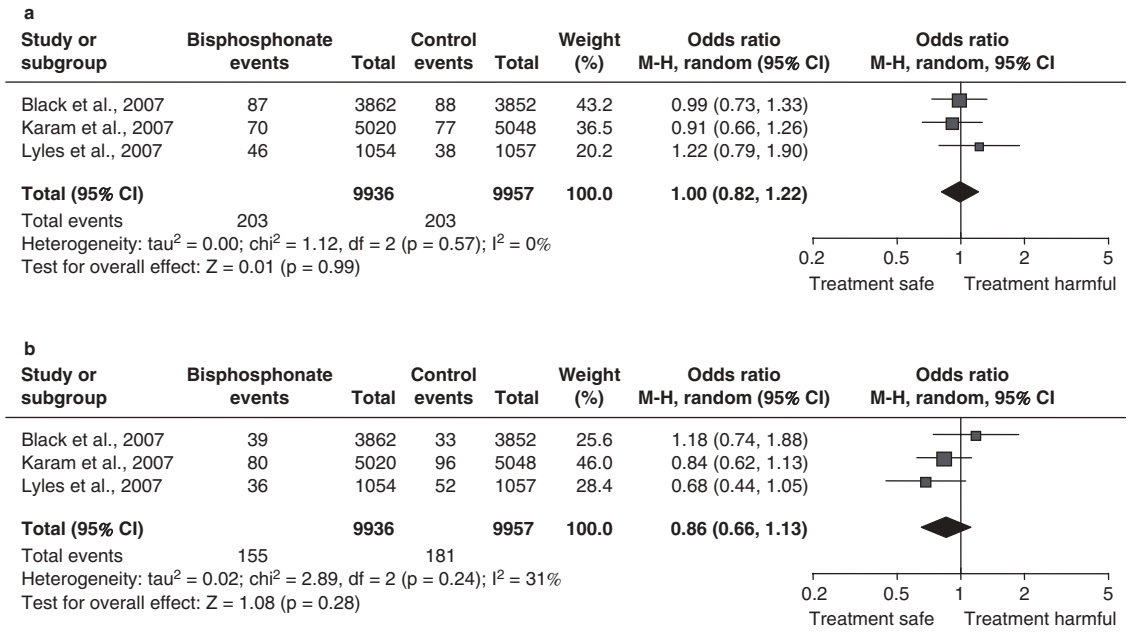

Fig. 3. Meta-analysis of stroke, and death from cardiovascular causes with bisphosphonate versus placebo. Studies: Black et al.,[8] Karam et al.,[17] and Lyles et al.[9] **df** = degrees of freedom; **M-H** = Mantel-Haenszel.

available for individual patient data meta-analysis, with examination of subgroups to evaluate potential sources of the existing heterogeneity. Any potential cellular mechanisms will need to be clarified in bench studies. Future and ongoing trials of bisphosphonates must implement rigorous monitoring for atrial fibrillation so that any risk can be identified early.

Conclusion

Physicians and patients who use bisphosphonates should remain vigilant for episodes of atrial fibrillation, and any such events should be reported to national pharmacovigilance centres.

Acknowledgements

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Note in Proof

In November 2008, the FDA reported their own evaluation of placebo-controlled clinical trials covering 19 687 patients receiving bisphosphonates (alendronate, ibandronate, risedronate and zoledronic acid) and 18 358 placebo-treated patients.[30] The FDA analysis did not provide any further details regarding the individual trials or the method of analysis, but stated that across all studies, no clear association between overall bisphosphonate exposure and the rate of serious or non-serious atrial fibrillation was observed. In contrast, another Danish cohort study found an adjusted hazard ratio of 1.29 (1.17, 1.41) for probable atrial fibrillation (initiation of cardiac glycoside and/or hospital diagnostic code for atrial fibrillation) among fracture patients exposed to bisphosphonates compared to age and sex matched controls.[31] The adjusted hazard ratio for hospitalization for atrial fibrillation was 1.18 (1.08, 1.29) with bisphosponate exposure.

The divergent findings of these updates reinforce our conclusions that the risk of atrial fibrillation with bisphosphonates needs to be investigated with more robust studies.

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Correspondence: Dr *Yoon Kong Loke*, Senior Lecturer in Clinical Pharmacology, University of East Anglia, Earlham Rd, Norwich, NR4 7TJ, UK.
E-mail: y.loke@uea.ac.uk