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Bisphosphonates for cardiovascular risk reduction: A systematic review and meta-analysis

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ABSTRACT

Background and aims: Bisphosphonates might be effective in reducing cardiovascular events due to their ability to reduce calcification in arterial walls. We aimed to investigate the effects of treatment with bisphosphonates on the prevention of atherosclerotic processes and cardiovascular disease.
Methods: Pubmed, Embase and the Cochrane Library were systematically reviewed by two independent investigators for randomized controlled studies published up to January 2016, in which the effect of bisphosphonates on arterial wall disease, cardiovascular events, cardiovascular mortality or all-cause mortality were reported. There was no restriction for the type of population used in the trials. Random-effects models were used to calculate the pooled estimates.
Results: 61 trials reporting the effects of bisphosphonates on the outcomes of interest were included. Bisphosphonates had beneficial effects on arterial wall disease regarding arterial calcification (pooled mean percentage difference of 2 trials −11.52 (95% CI -16.51 to −6.52, $p < 0.01$, I^2 13%), but not on arterial stiffness (pooled mean percentage difference of 2 trials −2.82; 95% CI -10.71−5.07; $p = 0.48$, I^2 59%). No effect of bisphosphonate treatment on cardiovascular events was found (pooled RR of 20 trials 1.03; 95% CI 0.91−1.17, I^2 16%), while a lower risk for cardiovascular mortality was observed in patients treated with bisphosphonates (pooled RR of 10 trials 0.81; 95% CI 0.64−1.02; I^2 0%) although not statistically significant. Patients treated with bisphosphonates had a reduced risk of all-cause mortality (pooled RR of 48 trials 0.90; 95% CI 0.84−0.98; I^2 53%).
Conclusions: In this systematic review and meta-analysis it is shown that bisphosphonates reduce arterial wall calcification but have no effect on arterial stiffness or on cardiovascular events. Bisphosphonates tend to reduce the risk of cardiovascular mortality and reduce all-cause mortality in various patient groups, including osteoporosis and cancer patients.

1. Introduction

Despite improvements in treatment of cardiovascular risk factors cardiovascular disease still results in an immense disease burden [1]. New treatment targets could further reduce the risk for first and subsequent cardiovascular events. As vascular calcifications are related to an increased cardiovascular risk, preventing or reducing arterial calcification might be an important target for further cardiovascular risk reduction [2]. Arterial calcifications are observed in several common conditions such as diabetes mellitus, renal failure and aging, all conditions known to be related to a high cardiovascular risk [3].

Osteoporosis is related to a 2-fold increased risk of cardiovascular mortality, also known as the 'bone-vascular axis' [4–8]. The process of arterial calcification might play an important role in this relation [9]. Arterial calcification is regulated through a network of inhibitory (and promoting) pathways, such as vitamin K dependent pathways, the Klotho protein, Fetuin-A and pyrophosphate [10]. Pyrophosphate is a strong inhibitor of arterial calcification [11,12]

Abbreviations: 95% CI, 95% confidence interval; HORIZON, Health Outcomes and Reduced Incidence with Zolendronic Acid Once Yearly; LDL, low-density lipoprotein; RR, relative risk.

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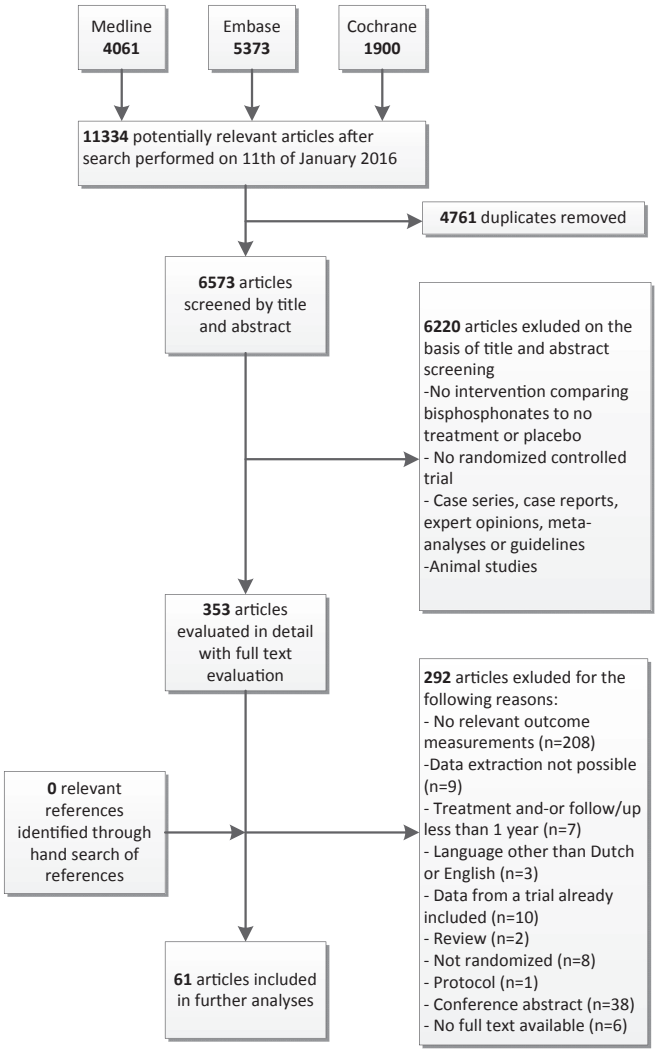

Fig. 1. Flowchart.

and bisphosphonates, well-established drugs for the treatment of bone diseases associated with excessive bone resorption including osteoporosis and bone metastasis, are pyrophosphate analogues and could thus stimulate the inhibitory effects of pyrophosphate on arterial calcification [13,14]. In fact, bisphosphonates were first shown to reduce arterial calcification and soft tissues calcification in rats [15].

Therefore it is conceivable that bisphosphonates interfere in the arterial calcification process and might be able to reduce the risk of cardiovascular disease [16]. Support for this hypothesis is growing as cohort studies show that the use of bisphosphonates in patients with maximum adherence is associated with a 20% lower risk of acute myocardial infarction [17] and randomized controlled trials such as the Health Outcomes and Reduced Incidence with Zolendronic Acid Once Yearly (HORIZON) trial show an 11% reduction of risk of cardiovascular events and a 31% reduction of cardiovascular deaths was found after treatment with bisphosphonates compared to placebo [18].

To investigate the effects of treatment with bisphosphonates on arterial wall calcification and stiffness, cardiovascular events, cardiovascular mortality and all-cause mortality, we performed a systematic review of randomized controlled trials with no restrictions on populations and summarized the results in a meta-analysis.

2. Materials and methods

2.1. Search strategy

A systematic literature search of Medline, Embase and the Cochrane Library was performed reviewing articles published up to January 2016. A search filter was designed using synonyms for the determinant (bisphosphonates) and outcome (surrogate markers of cardiovascular disease such as arterial stiffness and arterial calcification, cardiovascular events, cardiovascular mortality, survival and mortality) and using synonyms for determinant (bisphosphonates) and randomized controlled trials. A full search string is provided in Supplemental Table 1. All articles were screened on title and abstract by two independent researchers (GK and JB) and subsequently the full text was independently evaluated on eligibility by both researchers. Consensus was achieved by discussion, if needed with another independent investigator (WS). Additionally, a manual search through the references of selected articles was performed to identify additional relevant studies. Authors were contacted when a publication was not available or when not all the required information could be retrieved from a study.

2.2. Study selection

Studies were considered eligible if they investigated the effects of bisphosphonates, if at least one outcome of interest was reported and if the study was a randomized controlled trial performed in human subjects. As we assumed that some duration of exposure to bisphosphonate treatment was needed for effects on the cardiovascular system, studies in which participants were treated less than one year were excluded for further analyses. Articles providing insufficient data for the analyses were excluded.

2.3. Data extraction and quality assessment

Two authors (GK and JB) extracted data from the included studies independently. Discrepancies between the authors were discussed and resolved. From each study the following information was extracted: surname of first author, year of publication, country, number of patients in the treatment and control group, type of bisphosphonate, dosage, duration of bisphosphonate treatment, treatment in control group, gender distribution, age distribution, outcome of interest and eventually absolute numbers of the dichotomous outcome and mean and standard deviation for continuous outcomes. In studies where cardiovascular mortality or cardiovascular events were reported the definition of these outcomes were extracted. For the HORIZON trial [18,19] the total number of cardiovascular events was calculated by summing up the individual reported numbers of non-fatal stroke, non-fatal myocardial infarction and death due to a vascular cause, as the follow-up was ended after a serious adverse event in these trials. For the continuous outcomes the mean percentage change in aortic calcification or pulse wave velocity and the standard deviation were calculated using the absolute numbers at baseline and after treatment.

The methodological quality of each included study was evaluated based on the Cochrane risk assessment tool for randomized controlled trials, using the following items: random sequence generation, allocation concealment, similarity of groups, blinding of outcome assessment, completeness of trial and intention to treat analysis [20]. A summary score can be calculated from 0 to 7 points with higher scores indicating a lower risk of bias.