Bisphosphonates to reduce bone fractures in stage 3B+ chronic kidney disease: a propensity score-matched cohort study

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Scientific summary

Bisphosphonates for bone fractures in CKD

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Scientific summary

Background

Bisphosphonates are the most commonly prescribed anti-osteoporosis therapies worldwide and are the most common frontline therapy. Their antifracture efficacy has been demonstrated in pivotal trials including thousands of post-menopausal women and hundreds of men. Given their low cost and the high-quality evidence of benefits, they are widely recommended for preventing fragility fractures by the National Institute for Health and Care Excellence guidelines [National Institute for Health and Care Excellence. *Raloxifene for the Primary Prevention of Osteoporotic Fragility Fractures in Postmenopausal Women*. Technology Appraisal Guidance [TA160]. URL: www.nice.org.uk/guidance/ta160 (accessed 12 July 2012)].

However, there are few data on bisphosphonate risks and benefits in patients with moderate or severe chronic kidney disease. Despite the high risk of fractures in chronic kidney disease patients, bisphosphonates are contraindicated in late-stage (stage 4+) chronic kidney disease. Alternative, more costly, therapies such as denosumab (Prolia®; Amgen Inc. Thousand Oaks, CA, USA)] are increasingly used for these patients. However, these therapies have safety concerns, including severe hypocalcaemia.

Research aims

This research aimed to study the risk–benefit of bisphosphonate therapies in patients with stage 3B+ chronic kidney disease. The specific aims were as follows:

- Work package 1 – to study the association between bisphosphonate use and chronic kidney disease progression. Progression was defined as stage worsening (based on estimated renal function, quantified as the estimated glomerular filtration rate) or the requirement for renal replacement therapy (primary outcome). The association between bisphosphonate use and renal decline was also assessed, estimated as annualised rates of renal function loss, quantified as estimated glomerular filtration rate loss over time (secondary outcome).
- Work package 2 – to study the association between bisphosphonate exposure and fragility-related clinical (symptomatic) fractures.
- Work package 3 – to determine the relationship between bisphosphonate use and the adverse events hypocalcaemia, hypophosphataemia, acute kidney injury and upper gastrointestinal events (i.e. symptomatic esophagitis, ulcer, perforation, or upper gastrointestinal bleeding).
- Work package 4 – to investigate the association between bisphosphonate use and femoral neck bone mineral density changes over time, quantified as the annualised loss in percentage change compared with baseline.

Methods

Study design and data sources

A new-user cohort design was chosen for all four work packages. The study was conducted using pseudonymised routinely collected data.

Work packages 1–3 used UK NHS primary care records linked to hospital inpatient data obtained from the Clinical Practice Research Datalink GOLD and admitted patient care records in Hospital Episode Statistics. Work package 4 used data from the Danish Odense University Hospital Databases, which comprise all

bone mineral density and biochemistry measurements from the Funen region, linked to hospital inpatient and outpatient records and pharmacy dispensations.

Participants and follow-up

Patients recorded in the Clinical Practice Research Datalink GOLD (work packages 1–3) or the Odense University Hospital Databases (work package 4) who were aged ≥ 40 years and had at least one estimated glomerular filtration rate value of < 45 ml/minute/1.73 m^2 were eligible. A second estimated glomerular filtration rate measure of < 45 ml/minute/1.73 m^2 within 12 months after the first one was further required for work packages 1 and 3. Patients were excluded if they had received a bisphosphonate prescription in the previous year, had ever previously used a non-bisphosphonate anti-osteoporosis therapy, or had no outcome data (i.e. follow-up estimated glomerular filtration rate measurements for work package 1 and repeat bone mineral density testing for work package 4).

All participants initially joined the unexposed cohort. They contributed to the bisphosphonate user cohort from their first prescription of bisphosphonate in a time-varying exposure fashion. All participants were followed up until the earliest of occurrence of the event of interest, the end of treatment or switching (for bisphosphonate users only), or the end of enrolment as a result of migration or death.

Exposure

Bisphosphonate use was the main exposure, ascertained from primary care prescriptions (work packages 1–3) or pharmacy dispensation data (work package 4). Prespecified, previously validated lists of *British National Formulary* codes (work packages 1–3) and mapped Anatomic Therapeutic Classification codes (work package 4) were used to identify bisphosphonate therapies. Bisphosphonate use was modelled as a time-varying exposure to avoid immortal time bias.

Outcomes

The main study outcome in work package 1 was chronic kidney disease progression, defined by either stage worsening (based on repeated estimated glomerular filtration rate measurements) or the requirement for renal replacement therapy (i.e. dialysis or transplant). Secondary analyses included stage improvement and continuous change in estimated glomerular filtration rate over time. In work package 2, clinical (recorded by general practitioners) hip fractures were the primary outcome. General practitioner-recorded non-hip and all osteoporotic (except face, skull and digits) fractures were secondary outcomes. Work package 3 studied severe adverse events: hospital admissions for hypocalcaemia, hypophosphataemia or acute kidney injury; and recorded gastrointestinal events. For work package 4, annualised percentage change in bone mineral density after 1–3 years at the femoral neck was the primary outcome, and at the lumbar spine and total hip were the secondary outcomes.

Statistical analyses

Propensity score matching minimised confounding by indication. Propensity scores represent the predicted probability of treatment, conditional on baseline characteristics. Propensity scores were estimated using logistic regression modelling and included prespecified confounders and risk factors. One propensity score was created per outcome of interest. Propensity score calliper matching was then used to obtain cohorts of bisphosphonate users and non-users of similar observed characteristics. Post hoc analyses using multivariable adjustment (for the same confounders) was used for work packages 1–3 and covariate adjustment using the estimated propensity score was used for work package 4.

Most of the analyses for work packages 1 and 3 were conducted using Fine and Gray regression to account for competing risks due to differential mortality; work package 2 was conducted using Cox proportional hazards regression. The secondary analysis of decline in estimated glomerular filtration rate over time was modelled using random-effects models. The analysis of bone mineral density change in work package 4 used linear regression. When significant associations were seen, array bias analyses were performed to measure the likelihood that unobserved confounders could account for the observed effects.

Results

Work package 1

A total of 2613 bisphosphonate users and 53,986 non-users were included. Users contributed time to both cohorts. Propensity score matching reduced the observed imbalance in confounders between the two groups, leaving 2447 users and 8931 matched non-users. Bisphosphonate users had a higher incidence of chronic kidney disease progression than matched non-users in the primary analysis, with incidence rates of 89.07 per 1000 person-years (95% confidence interval 82.06 to 96.67 per 1000 person-years) and 85.64 per 1000 person-years (95% confidence interval 81.97 to 89.47 per 1000 person-years), respectively. Survival analyses confirmed a subdistribution hazard ratio of 1.12 (95% confidence interval 1.02 to 1.24). The observed excess risk was higher in those with better compliance to bisphosphonate therapy (dose–response gradient). Sensitivity analyses confirmed the robustness of these findings.

Work package 2

Despite severe confounding, propensity score matching produced cohorts of 11,118 bisphosphonate users and 43,999 non-users with similar observed features. The incidence rates of hip fracture (the primary outcome) were 20.70 per 1000 person-years (95% confidence interval 20.14 to 21.28) for users and 16.41 (95% confidence interval 16.2 to 16.62) for non-users. The resulting Cox-derived hazard ratio was 1.25 (95% confidence interval 1.13 to 1.39) and higher for non-hip and all osteoporotic fractures.

Sensitivity analyses suggested that the observed associations were due to unresolved confounding, probably from a lack of information on baseline bone mineral density. Bone mineral density is a key driver for bisphosphonate treatment and a key predictor of hip and other osteoporotic fracture risk. The dose–response analysis found no increased risk with higher cumulative exposure. A restricted time frame analysis showed a peak in effect size in the first 3–6 months of treatment, when trial data (Black DM, Thompson DE, Bauer DC, Ensrud K, Musliner T, Hochberg MC, *et al.* Fracture risk reduction with alendronate in women with osteoporosis: the Fracture Intervention Trial. FIT Research Group. *J Clin Endocrinol Metab* 2000;**85**:4118–24) have shown that bisphosphonates have no effect on bone strength. An array analysis suggested that the estimated hazard ratio was prone to unobserved confounding, as a prevalence of 60% in bisphosphonate users and 38% in non-users would attenuate the observed risk. This is the prevalence of osteoporosis observed among bisphosphonate users in work package 4.

Work package 3

The same number of participants were analysed for work packages 1 and 3. Severe acute kidney injury leading to hospital admission was relatively common. A total of 480 acute kidney injury events in the propensity-matched cohorts were identified and similar (non-significantly different) incidence rates were found in bisphosphonate users (12.02 per 1000 person-years, 95% confidence interval 9.66 to 14.94) and non-users (15.23, 95% confidence interval 13.80 to 16.80). Gastrointestinal events were less common, with 168 unexposed and 37 exposed participants affected. Incidence rates were again similar: 6.39 (95% confidence interval 5.49 to 7.43) per 1000 person-years in users and 5.45 (95% confidence interval 3.95 to 7.52) per 1000 person-years in non-users. Only 31 episodes of severe hypocalcaemia and seven episodes of hypophosphataemia leading to hospital admission were identified. No association was observed between bisphosphonate use and any of the safety events, with subdistribution hazard ratios of 0.86 (95% confidence interval 0.66 to 1.10) for acute kidney injury, 0.96 (95% confidence interval 0.66 to 1.40) for gastrointestinal events and 0.33 (95% confidence interval 0.08 to 1.45) for hypocalcaemia. Post hoc multivariable analyses confirmed these findings.

Work package 4

Fewer participants were identified than initially expected, reflecting the low use of bisphosphonates in moderate to severe chronic kidney disease and the rational use of repeat bone mineral density testing in the Danish health care system. Of the > 36,000 patients in the Odense University Hospital Databases, only 71 bisphosphonate users and 1492 non-users fulfilled the inclusion criteria and had outcome data. Propensity score matching reduced this number further to 40 users and 142 comparable non-users.

In the primary analysis using propensity-matched cohorts, bisphosphonate users increased their femoral neck bone mineral density by an average of 1.07% per year of therapy. In contrast, matched non-users lost an average of 1.59% of their baseline bone mineral density per year. The resulting mean difference in percentage annual change in femoral neck bone mineral density between users and non-users favoured bisphosphonate users by 2.65% (95% confidence interval 1.32% to 3.99%) per year of bisphosphonate exposure. Similar beneficial effects were seen for lumbar spine and total hip bone mineral density.

Sensitivity analyses obtained similar results, with a multivariable-adjusted beta coefficient (mean difference between groups) of 2.14% (95% confidence interval 1.22% to 3.05%) and a propensity score-adjusted beta of 2.15% (95% confidence interval 0.97% to 3.34%) per year.

Conclusions

To our knowledge, this is the largest study to date on the risks and benefits of bisphosphonate therapy for patients with moderate to severe chronic kidney disease. The analyses included > 200,000 participants with stage 3B+ chronic kidney disease, of whom > 10,000 were bisphosphonate users, and up to 10 years of follow-up of each participant.

The results of work package 1 suggested a 12% excess risk of chronic kidney disease progression among users of bisphosphonates compared with matched non-users. The observed effect appeared stronger in those exposed to higher doses. Sensitivity analyses confirmed the robustness of these findings. Fortunately, work package 3 did not demonstrate any other safety concerns, as no association was found between bisphosphonate use and the risk of acute kidney injury, gastrointestinal events, or severe hypocalcaemia or hypophosphataemia.

The work package 2 findings on the benefits of bisphosphonates are worrying. Bisphosphonate users had a 25% increased risk of hip fracture. These findings must be interpreted with caution, as sensitivity analyses suggested that this counterintuitive result may have been due to unresolved bias. Work package 4 showed that bisphosphonate use had a beneficial effect on femoral neck, lumbar spine and total hip bone mineral density, which are known, valid surrogates for fracture risk.

In summary, it has been demonstrated that bisphosphonate therapy has a potential renal toxicity for patients with moderate to severe chronic kidney disease, and the research team have failed to demonstrate antifracture effectiveness other than on surrogate outcomes using bone mineral density. These results should lead to a cautious use of bisphosphonates in chronic kidney disease stage 3B+. More research is needed to understand the safety of bisphosphonates in earlier stages of chronic kidney disease (e.g. 3A) and to characterise the antifracture efficacy of bisphosphonates in patients with more severe renal impairment.

Ethics and scientific approval

No additional ethics approval was required as this study used anonymised, routinely collected data from the UK's Clinical Practice Research Datalink GOLD, with linked Hospital Episode Statistics data and the Danish Odense University Hospital Databases. To access these data sets, an application was submitted to, and approval obtained from, the Independent Scientific Advisory Committee for Clinical Practice Research Datalink GOLD–Hospital Episode Statistics (for work packages 1–3) (Independent Scientific Advisory Committee protocol number 15_153R2) and the Region of Southern Denmark (reference number 15/37999), the health trust accountable to the Data Protection Agency for oversight of research data at Odense University Hospital under the Danish Health Act (for work package 4).

Study registration

This study is registered as EUPAS10029.

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This report

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