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Comparative efficacy and safety of statins for osteoporosis: a study protocol for a systematic review and network meta-analysis

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ABSTRACT

Introduction Osteoporosis (OP) is a prevalent skeletal disease with high mortality and morbidity, followed by acute and chronic back pain, severe spinal deformity and dysfunction. First-line drugs for OP work through antiresorptive or anabolic mechanisms. Although with good efficacy, these drugs still have certain limitations in clinical application due to delivery routes, medication cycles and cost issues. Nowadays, statins (3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors) appear to be potentially promising drugs for OP. Despite the controversy, previous studies have shown the efficacy of statins in treating OP. Other studies have further indicated that the therapeutic effect of OP in statin-treated patients is dose dependent. However, scientists have not yet reached a consensus on the use of statins for the treatment or which statin to choose first. This study aims to review the literature, ascertaining the relative efficacy and safety of statins for patients with OP using a Bayesian network meta-analysis.

Methods and analysis We will systematically search the following databases: MEDLINE, EMBASE, Web of Science, Cochrane Central Register of Controlled Trials, China National Knowledge Infrastructure, Wanfang Database, China Science and Technology Journal Database, Chinese BioMedical Literature Database and preprint servers to include randomised controlled trials that compare different statins for treating OP. Primary outcomes are the incidence of overall fractures and bone mineral density changes. Secondary outcomes contain adverse effects and bone turnover markers. All items of this review will comply with the Cochrane Handbook, and the quality of evidence will be evaluated by Grading of Recommendations Assessment, Development and Evaluation. A traditional pairwise meta-analysis and the Bayesian network meta-analysis will be performed to compare the efficacy of different statins.

Ethics and dissemination Ethical approval is not required since this is a protocol study for meta-analyses. Results will be submitted to a peer-reviewed journal.

PROSPERO registration number CRD42021242619.

Search dates From database inception to February 2022.

Strengths and limitations of this study

⇒ This is the most comprehensive review comparing the efficacy and safety of statins for patients with osteoporosis through a Bayesian network meta-analysis.
⇒ We will use the Grading of Recommendations Assessment, Development and Evaluation approach to evaluate the quality of evidence.
⇒ The results will explore the dosage and potency of statins for osteoporosis and help physicians and patients select appropriate treatments.
⇒ This study is based on the quantity and quality of the trials available for review.

INTRODUCTION

Osteoporosis (OP) is a systemic and silent skeletal disease characterised by low bone mass, and microarchitectural changes in bones and skeletal fragility. These changes contribute to decreased bone strength and increased susceptibility to fractures.[1] Patients with OP, especially the elderly, often suffer from poor life quality because of complications such as back pain, severe spinal deformities and dysfunction. Notably, the incidence of OP is gradually increasing with the ageing of the global population. According to a report, more than half of older people in the USA were at high risk of OP by 2020.[2] Scholars predicted that the number of patients with OP in China would exceed more than 300 million.[3] The high cost of treatment and nursing will place an economic burden on families and society. It is predicted that the cost of osteoporotic fractures will exceed $25 billion by 2025 in the USA, and the accumulated medical expenditure of accidental fractures will reach $228 billion in one decade from 2016 to 2025.[4] Hence, OP may represent one of the most consequential health crises in the world.

First-line drugs for OP are functioning through the antiresorptive or anabolic mechanisms: (1) antiresorptive drugs such as bisphosphonates,[5] denosumab,[6] calcitonin,[7] hormone replacement therapy[8] and raloxifene[9]; and (2) anabolic drugs including parathyroid hormone (PTH),[10] peptide PTH (1–34) (teriparatide)[11] and the full-length molecule PTH (1–84).[12] These drugs are proven to be effective and widely used. However, there are still some problems in clinical use due to medication methods, medication cycle and drug costs. For example, teriparatide has a markable therapeutic effect, but its method of delivery (by subcutaneous injection) brings patients inconvenience. In addition to the administration, hypercalcaemia, a common side effect caused by teriparatide, could also pose a problem. Therefore, it is essential to discover convenient, economical and practical therapies.

Statins (3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors) have become mainstream in preventing and treating cardiovascular disease. There has been a growing interest in the drug due to its working mechanisms associated with bone formation. The use of statins is correlated with a reduced risk of OP and its complications, especially osteoporotic fractures.[13–16] Possible mechanisms might involve the proliferation, differentiation and protection of osteoblasts and the inhibition of osteoclastogenesis.[17] Mundy *et al* first demonstrated that the osteoprotective effects of statins were associated with increased expressions of bone morphogenetic protein-2 (BMP-2, a gene that could regulate bone formation through enhancing the osteoclasts).[18] Moreover, several observational studies exploring associations between statins and OP suggested that, although the conclusion was not consistent,[15 16] the efficacy was dose dependent.[19] According to Leutner *et al*, treating with a high dose of statins might be associated with an increased incidence of OP and a higher risk of fractures.[19] In contrast, another study on the same issue claimed that high-dose statins have a protective effect on hip fracture.[16] However, which and how statin could facilitate bone metabolism better than its counterparts remain unclear. Therefore, it is essential to select the most appropriate statin and explore its dose-dependent effect and potency on OP.

Several systematic reviews and meta-analyses have studied the correlation between statins and OP from multiple perspectives.[20–24] Nevertheless, they all had one or more following limitations: (1) studies included were not comprehensive,[20–22 24] some of which have not mentioned the safety of drugs; (2) no guidelines supporting an appropriate therapy for OP in terms of statins[20–24]; (3) articles included need further updates on this topic.[20–24]

To our knowledge, there has been no network meta-analysis (NMA) studying the dose-dependent effects of statins on OP so far. This study aims to conduct a systematic review and NMA comparing the efficacy and safety of various statins treating OP at different dose levels. We will elaborate on the dosage and potency distinctions of various statins. Each treatment will be rated in a practical consideration via a Bayesian framework.

METHODS AND ANALYSIS

Design

We will conduct the systematic review and NMA based on a Bayesian framework in this study. This protocol was completed in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocol (PRISMA-P)[25] and PRISMA extension statement, which develop systematic reviews incorporating an NMA of healthcare interventions.[26] Any specific modification to this protocol will be submitted to PROSPERO and published with results.

Registration

We have already registered this protocol at PROSPERO with registration number CRD42021242619 (https://www.crd.york.ac.uk/prospero/).

Eligibility criteria

Type of studies

We will review the Chinese Clinical Trials Registry Platform, WHO International Clinical Trials Registry Platform (ICTRP) and ClinicalTrials.gov for registered published randomised controlled trials (RCTs) and preprint servers (such as medRxiv and Research Square) for unpublished data focusing on statins used for OP treatment, without language and data restriction. RCTs focusing on anti-OP drugs, such as bisphosphonates, will be excluded. Cohort studies, cross-sectional studies, case reports and reviews will not be taken into consideration. The full text of target studies will be accessible for the screening.

Participants

We will search RCTs enrolling participants as follows:

1. Adults aged 18 years and above.
2. Participants with a medical diagnosis of primary OP associated with age/heredity/lifestyles and environmental factors.[1 27]
3. Participants diagnosed with primary OP and treated with statins as main drugs for at least 2 months.
4. Patients with OP having comorbidities not associated with the onset of OP (eg, hyperlipidaemia).

We will also conduct exclusion criteria as follows:

1. Paediatric and adolescent patients.
2. Patients diagnosed with secondary OP (induced by other diseases or drugs).
3. Patients with OP comorbidities associated with the onset of OP (eg, type I and II diabetes).[28]

According to the American National Bone Health Alliance Working Group[29] and the Chinese Society of Osteoporosis and Bone Mineral Research,[3] the diagnosis of osteoporosis was based on the WHO as follows: (1) individuals who experience a low trauma hip or vertebral fracture; (2) T-score of −2.5 or lower at the lumbar spine, femur neck or total hip by bone mineral density (BMD) testing; (3) the occurrence of one or more types of low trauma fractures, such as hip, osteopenia-associated vertebral, proximal humerus, pelvis and some wrist fractures, even the T-score between −2.5 and −1; (4) FRAX (WHO

Fracture Risk Assessment Tool, FRAX) scores with ≥3% (hip) or 20% (central) 10-year fracture risk that also confer an OP diagnosis.

Type of interventions

We will include RCTs using any common statins or HMG-CoA reductase inhibitors (atorvastatin, pravastatin, simvastatin, fluvastatin, atorvastatin, rosuvastatin, pitavastatin and so forth) for the analysis. Complete treatment periods of at least 2 months, regardless of the therapeutic dose and the method of delivery, will be considered. Any combined therapy setting at least one kind of statins as the treatment arm will be included as well. Appropriate treatments containing bone health supplementation and lifestyle modifications, alone or in combination, will be considered. RCTs setting placebo and no pharmacotherapy intervention as control will be included as well.

Outcomes of interest

Our primary outcomes are the incidence of overall fractures and BMD improvements (percentage change and absolute change (in g/cm^3)) at the lumbar spine, the femoral neck and the hip. If studies reported BMD without changes and associated variance, the mean change of BMD between baseline and endpoint values as well as the SD will be measured before and after interventions according to methods outlined in the Cochrane Handbook.[30 31] Based on the intention-to-treat principle, we are supposed to extract and analyse the number of fractures defined as a clinical osteoporotic fracture at the maximum follow-up duration. If there were no fracture events in the treatment arms, a continuity correction factor of 0.5 to studies will be applied. Target RCTs involved in the present study mostly conducted dual-energy X-ray absorptiometry scans to measure BMD.

Secondary outcomes contain adverse effects as well as bone turnover markers. Side effects including (but not limited to) gastrointestinal symptoms and impaired liver functions caused by treatments will be evaluated. Bone turnover markers contain N-terminal propeptide of type I procollagen, C terminal telopeptide of type I collagen, cross-linked N-telopeptide of type I collagen and alkaline phosphatase. Sources of BTMs (Bone turnover markers, BTMs) will be chosen for their applications in diseases according to included RCTs and the extensive literature.[32]

Data sources and search strategy

Literature retrieval will be mainly carried out in the following nine databases from inception to February 2022: MEDLINE, EMBASE, Web of Science, China National Knowledge Infrastructure, Wanfang Database, SinoMed, and China Science and Technology Journal Database. In the meantime, we will comprehensively search ongoing trials via the Cochrane Central Register of Controlled Trials, WHO ICTRP, Chinese Clinical Trials Registry Platform (http://www.chictr.org.cn/searchprojen.aspx) and ClinicalTrials.gov. Preprint servers (such as medRxiv and Research Square) for unpublished data will be searched as well. Furthermore, we will scan all retrieved trials' bibliographies and existing systematic reviews and meta-analyses relevant to RCTs for further pertinent publications. As for unavailable studies, we will attempt to email authors for permission. Publications not obtaining data will be excluded.

The search is based on the Cochrane checklist.[31] Search terms are defined for Participant (OP), Intervention (statins, HMG-CoA reductase inhibitors), Outcomes (fracture, BMD, adverse event and bone turnover markers) and RCTs. Synonyms of search terms were selected by the 'OR' operator, while the 'AND' operator combined terms from different categories: Participants, Interventions, Outcomes and RCTs. The sample search strategies adapting for databases were detailed in the online supplemental materials. Literary works have no date or language restrictions.

Study selection

Four researchers (MX, WZ, GZ and YX) will work in pairs to complete the study selection. Two will independently review the title and abstract of each study based on the PICO (Population, Intervention, Control and Outcomes) criteria above. After obtaining the full text of papers, we will re-evaluate them according to the above requirements. In case of the inconsistent result given by two researchers, the third one will reassess the part of the article that might be in dispute. To determine the contents of literature published only by abstracts, we will contact those authors for more details. A PRISMA-compliant flow diagram[25] will show the process of study selection (see figure 1).

Data extraction

Two reviewers (MX and YX) will independently and in duplicate extract data using an Excel sheet. For the sake of data conversion, a structured form will be designed through Excel (Microsoft Office Home and Student 2019). Categories are as follows: study information (such as first author, year of publication, country and sponsor), demographic (such as mean age and gender), numbers of participants included and excluded, clinical characteristics (time since diagnosis and treatment, statin type, dose), outcomes of interest (primary outcomes: fractures and BMD; secondary outcomes: adverse events and bone turnover markers), duration of follow-up, and numbers of withdrawals in each group as well as its reasons. If the information was missed in the original articles, we will contact the authors for necessary data.

Risk of bias assessment

Two assessors (ZT and AD) will independently judge the risk of bias in individual studies complying with the revised Cochrane risk of bias tool for randomised trials,[33] then will double check each other to guarantee there is no error. The assessment criteria contain domains list as 'bias arising from the randomisation process', 'bias due to deviations from intended interventions', 'bias due to missing outcome data', 'bias in the measurement of the

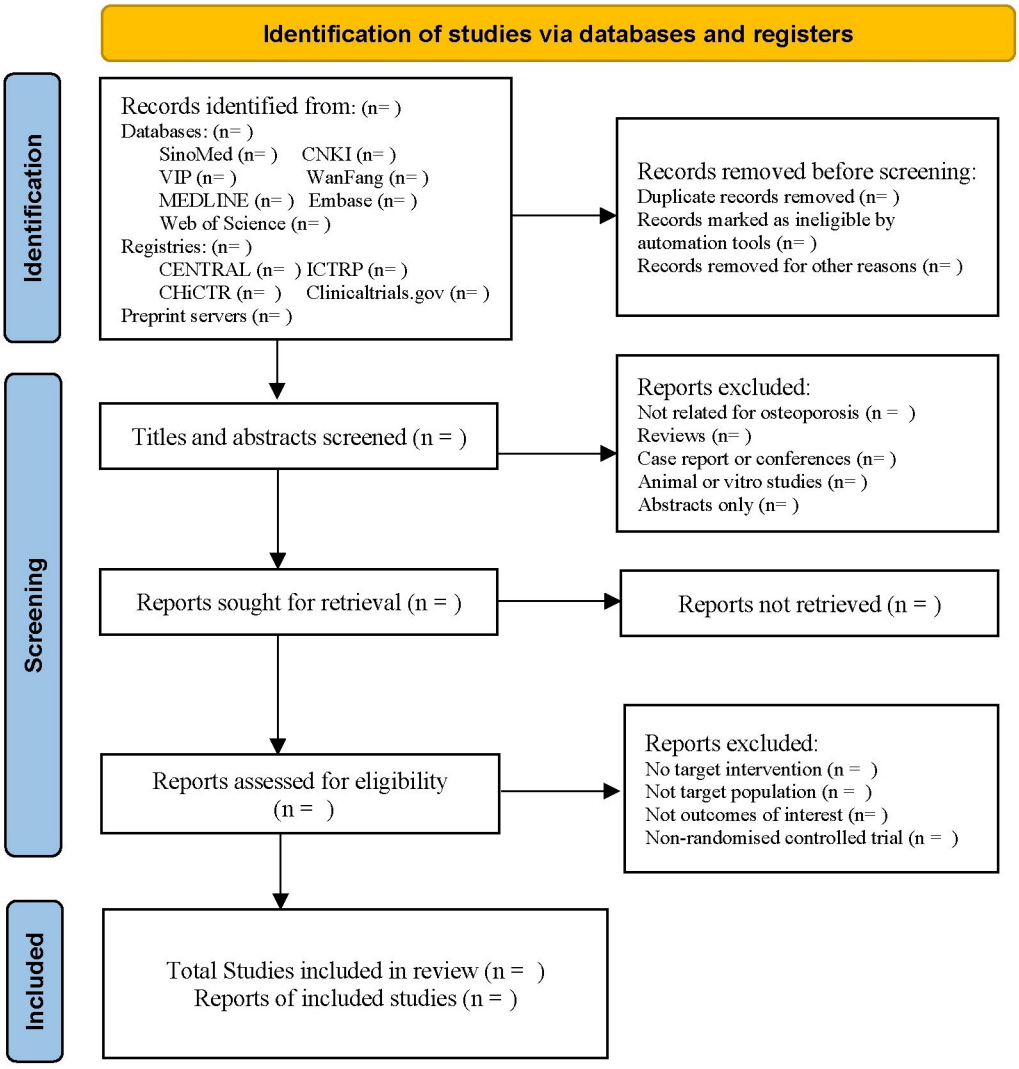

Figure 1 PRISMA 2020 flow diagram for literature selection. CENTRAL, Cochrane Central Register of Controlled Trials; CHiCTR, Chinese Clinical Trials Registry Platform; CNKI, China National Knowledge Infrastructure; ICTRP, WHO International Clinical Trials Registry Platform; PRISMA, Preferred Reporting Items for Systematic Review and Meta-Analysis; SinoMed, Chinese BioMedical Literature Database; VIP, China Science and Technology Journal Database.

outcome' and 'bias in the selection of the reported result'. Each domain will be judged by three levels, which are 'low risk of bias', 'high risk of bias' or 'some concerns'. Trials reaching a judgement of 'low risk of bias' signified those issues addressed have met the criteria, while 'high risk of bias' implied that at least one domain is responsible for this result. If the trial is judged to raise some concerns in at least one domain, it will be deemed 'some concerns'.[34] Any disagreement will be resolved through consulting the research professor (NX).

Statistical analysis

We will first conduct a traditional pairwise meta-analysis on all comparable outcome indicators, checking and evaluating their consistency and heterogeneity. The I^2 statistic and p values will be applied to assess the heterogeneity in all individual studies. To acquire more reliable estimated effects, I^2 >50% as a threshold indicates significant heterogeneity, and p<0.01 as a threshold exposes considerable heterogeneity.[35] Given the expected between-study heterogeneity due to differences in treatments, we will apply a random-effects model. Furthermore, the OR with 95% CIs will be reported for the dichotomous variables, while the continuous variables will be reported by standard mean difference (SMD) with 95% CIs. This process will be run by Stata V.13.0 (Stata Corp, College Station, Texas, USA).

Bayesian Markov chain Monte Carlo (MCMC) framework is applied for conducting the NMA in WINBUGSS software V.1.4 (Medical Research Council Biostatistics Unit, Cambridge, UK).[36] Three chains will be initiated simultaneously with different original values. For the stability of analysis, we will set 150 000 iterations of MCMC after a 50 000 iteration as a burn-in period.[37] The inference parameter of the posterior distribution will come from the summary of its median with SMD or OR and 95% credible intervals. A Bernoulli model will be used for

analysing dichotomous variables, and a Gaussian model will be conducted for the continuous variables. Moreover, trace plots and Brooks-Gelman-Rubin diagnostic plots[38] will be used to evaluate convergence.

To check whether an NMA model fit is satisfying, we are supposed to calculate the posterior mean residual deviance, which is an absolute measure fit.[39] Afterwards, we will assess if the model is appropriate via contradistinguishing the posterior mean residual deviance value from the number of independent data points.[39] The random-effects models with vague priors for multiarm trials will be used. The deviance information criterion (DIC) will be used to measure the model fit to penalise model complexity. The result turns out that the lower the DIC is, the better the fit is.[40] Differences more than or equivalent to three units indicate the significance.[40] If both models report a similar DIC, the fixed-effects model is preferred in the case the pairwise comparison has no significant heterogeneity. Otherwise, the random-effects model will be selected. If the data are insufficient for the NMA, the pairwise meta-analysis will be possible, in which case the random-effects model will be performed.

We will evaluate each treatment and choose the best three of all. The ranking of different treatments will be based on the results of every single iteration of the Markov chain. After that, the level of evidence will be graded, and results will be reported by the surface under the cumulative ranking area (SUCRA), which is the numerical summary and estimation more precise than other methods, both for the magnitude and uncertainty of the estimated effect for each intervention.[41] In general, SUCRA scores ranging from 0 to 1 represent the treatment from the worst to the best, a more considerable SUCRA value indicates a more efficacious treatment.[42] If the results are not sufficient for the analysis, we will describe those pieces of evidence and then make a summary. Previous studies[15 16 19] have demonstrated that the efficacy of statins was dose dependent. Therefore, subgroup meta-analysis will be further performed by the dosage (only separated as low, moderate and high dosage) because of the differences in treatment arms. Specific cut-offs depend on different kinds of statin.[43] Moreover, subgroup analyses will also be conducted based on different kinds of primary OP (postmenopausal vs age-related vs others).

We will use the network and network graphs packages in Stata (V.14.0) to produce the graphs.[44] The result will be figured by ggplot2 3.3.5 packages in R (V.4.1.0).[45] NMAs of the primary outcomes were duplicated using the geMTC 1.0-1 package in R (V.4.1.0).[45 46]

Publication bias

We will conduct the comparison-adjusted funnel plots to assess the small-study effects in the network. If there is the absence of small-study effects, the funnel plot will be around the zero line; otherwise, researchers will explore this further by appropriate network meta-regression and models.[47]

Quality of evidence

We will assess the quality of evidence for the primary and secondary outcomes from our NMA adhering to the Grading of Recommendations Assessment, Development and Evaluation (GRADE).[48] The process will follow the classic GRADE four-step approach and the results will be presented in the form of the GRADE Summary of Findings.[49] The four steps are as follows: (1) list direct and indirect comparisons of effect estimates and CIs, respectively; (2) rate the quality of each comparison effect estimate; (3) determine and present the quality of evidence base on each direct and indirect comparison; (4) check whether the results of direct and indirect comparisons are inconsistent by different qualitative models and methods. Depending on the option of each parameter (risk of bias, inconsistency, indirectness, imprecision and publication bias), the quality of effect estimates will be rated as high, moderate, low and very low. GRADE pro V.3.6 software (http://www.gradeworkinggroup.org/) is applied to accomplish the evaluation processes.

Patient and public involvement

This systematic review and NMA will only publish anonymous data and will not recruit new patients. We have already consulted physicians specialising in orthopaedics and experts in evidence-based medicine to refine our study protocol as well as research questions; nevertheless, they did not draft and design this protocol.

ETHICS AND DISSEMINATION

Ethical consideration

Ethical approval is not necessary for this review as no primary data collected. The study is in accordance with the PRISMA-P and the PRISMA extension statement.

Publication plan

The findings of our review will be submitted to a peer-reviewed journal. In addition, we will widely disseminate current findings within electronic files or brochures to patients with OP and researchers in similar areas.

DISCUSSION

The incidence of diseases including OP, hyperlipidaemia and coronary artery disease increases dramatically with age. Lipid metabolism in bone cells has long been appreciated among various metabolic pathways. The ‘lipid hypothesis of OP’ suggested that lipid oxidation was a contributing factor to OP.[50] Bone marrow mesenchymal cells can selectively differentiate into osteoblasts or adipocytes. Once the lipid oxidation occurs, its products subsequently stimulate peroxisome proliferator-activated receptors gamma, preventing the osteogenic differentiation and promoting adipocyte expansion, which leads to bone loss.[51] Lipids, especially cholesterol, can impact the phenotype of osteoclasts and osteoblasts in such pathological conditions.[52]

Statins are FDA (Food and Drug Administration)-approved drugs for hypercholesterolaemia[53 54] and have been proven to increase BMD and reduce the risk of fracture.[55–57] Previous clinical trials[13–16 19] and pairwise meta-analyses[21–24] have also certified that. The positive outcome might be that statins could promote osteogenic activity through activating and improving the expression of BMP-2 and osteocalcin[18] by suppressing farnesylation and geranylgeranylation of Rho/Ras small G proteins in osteoblasts.[58] Statins could additionally increase osteoprotegerin that antagonised RANKL[59] and inhibited osteoclast activity.[59 60] Furthermore, clinical studies have proposed a dose-dependent effect of statins on bone health, though those findings have not been scientifically consistent. Lin *et al* concluded that use of high-dose statin daily was associated with a significant protective effect preventing osteoporotic fractures.[15] However, Leutner *et al* conducted a cross-sectional retrospective study consisting of 7 897 449 patients which explored the correlation of different types and dosages of statins with OP.[19] Results showed that statins might also have a negative effect on bone health especially in high-dose statin-treated patients. This might due to the mechanism of statins, that is, by inhibiting the endogenous synthesis of cholesterol thus relating to the lower serum level of testosterone, which was positively correlated with BMD.[61] Though there was a connection between statin use and OP treatment and prophylaxis, it remains unknown whether different statins have similar function and efficacy for the sake of treating OP. Thus, further research is needed to explore the selection of proper statins for various indications and the accuracy of the dosage used clinically.

To our knowledge, this is the first study attempting to evaluate the relative effects of variable statins and dosages in patients with OP using an NMA approach. In this study, we will search for literature comprehensively and systematically in public databases. We include RCTs as the only type of study which is eligible. We will not cover retrospective studies because BMD in such studies was not measured daily, making it difficult to evaluate the impact of statins and their dosage on BMD. On the contrary, RCTs can explore whether the dosage or the potency of statins would affect BMD.

Furthermore, we will perform a Bayesian NMA framework to analyse RCTs concerning statin therapies. This search strategy will contain all available treatment arms, including a variety of generations and dosages. Finally, we will use tools (Cochrane Handbook, GRADE, SUCRA and so forth) to evaluate the quality of included papers and NMAs.

In summary, by comparing the effectiveness and safety of treatments, this NMA is expected to rank statins for patients with OP. The results of this study might help patients and therapists choose the best treatment to improve bone health and provide convincing evidence for guidelines.

Contributors NX and WZ supervised and designed the study, and will carry out the statistical analyses. MX and YX drafted and revised the protocol, designed and conducted the search strategies. MX, WZ, GZ and YX assisted with the study design and data extraction, and will carry out most of the data collection. ZT, AD and GZ will assist with the data collection and provided input to the manuscript. MX and YX contributed equally to this study.

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Competing interests None declared.

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Supplementary Material: Sample Search Strategy

February 24, 2022

Supplementary 1: MEDLINE search strategy

#	Searches
1.	Osteoporosis/
2.	(Osteoporoses or "Osteoporosis, Senile" or "Senile Osteoporoses" or "Osteoporoses, Senile" or "Senile Osteoporoses" or "Senile Osteoporosis" or "Osteoporosis, Involutional").mp.
3.	("Osteoporosis, Age-Related" or "Osteoporosis, Age Related" or "Bone Loss, Age-Related" or "Age-Related Bone Loss" or "Age-Related Bone Losses" or "Bone Loss, Age Related").mp.
4.	("Bone Losses, Age-Related" or "Age-Related Osteoporosis" or "Age Related Osteoporosis" or "Age-Related Osteoporoses" or "Osteoporoses, Age-Related").mp.
5.	Postmenopausal Osteoporosis/
6.	("Perimenopausal Bone Loss" or "Bone Loss, Postmenopausal" or "Bone Losses, Postmenopausal" or "Postmenopausal Bone Losses" or "Osteoporosis, Post-Menopausal" or Osteoporoses, Post-Menopausal" or "Osteoporosis, Post Menopausal" or "Post-Menopausal Osteoporoses" or "Post-Menopausal Osteoporosis" or "Postmenopausal Osteoporosis" or "Osteoporoses, Postmenopausal" or "Postmenopausal Osteoporoses" or "Bone Loss, Perimenopausal" or "Bone Losses, Perimenopausal" or "Perimenopausal Bone Losses" or "Postmenopausal Bone Loss").mp.
7.	or /1-6
8.	Hydroxymethylglutaryl CoA Reductase Inhibitors/
9.	("Inhibitors, Hydroxymethylglutaryl-CoA Reductase" or "Reductase Inhibitors, Hydroxymethylglutaryl-CoA" or "HMG-CoA Reductase Inhibitor" or "HMG CoA Reductase Inhibitor").mp.
10.	8 or 9
11.	Statin/
12.	("Statins" or "Statins, HMG-CoA" or "HMG-CoA Statins" or "Statins, HMG CoA").mp.
13.	("Inhibitors, HMG-CoA Reductase" or "Inhibitors, HMG CoA Reductase" or "Reductase Inhibitors, HMG-CoA" or "HMG-CoA Reductase Inhibitors" or "HMG

	CoA Reductase Inhibitors" or "Inhibitors, Hydroxymethylglutaryl-Coenzyme A" or "Hydroxymethylglutaryl-Coenzyme A Inhibitors" or "Inhibitors, Hydroxymethylglutaryl Coenzyme A" or "Inhibitors, Hydroxymethylglutaryl-CoA" or "Hydroxymethylglutaryl-CoA Inhibitors" or "Inhibitors, Hydroxymethylglutaryl CoA" or "Hydroxymethylglutaryl-CoA Reductase Inhibitor" or "Hydroxymethylglutaryl CoA Reductase Inhibitor" or "Reductase Inhibitor, Hydroxymethylglutaryl-CoA").mp.
14.	or/11-13
15.	Lovastatin/
16.	("Mevinolin" or "Monacolin K" or "6-Methylcompactin" or "6 Methylcompactin" or "MK-803" or "MK 803" or "MK803" or "Mevacor" or "Lovastatin, (1 alpha(S*))-Isomer" or "Lovastatin, 1 alpha-Isomer" or "1 alpha-Isomer Lovastatin" or "Lovastatin, 1 alpha Isomer" or "alpha-Isomer Lovastatin, 1").mp.
17.	15 or 16
18.	Pravastatin/
19.	("Eptastatin" or "Vasten" or "CS-514" or "CS 514" or "CS514" or "Lin-Pravastatin" or "Lin Pravastatin" or "Lipemol" or "Liplat" or "Nu-Pravastatin" or "Nu Pravastatin" or "Prareduct" or "Pravachol" or "Elisor" or "Selektine" or "Lipostat" or "Pravacol" or "Pravasin" or "Pravastatin Monosodium Salt, (6 beta)-Isomer" or "Pravastatin Sodium" or "Pravastatin Sodium Salt" or "Sodium Salt, Pravastatin" or "Pravastatin tert-Octylamine Salt" or "Pravastatin tert Octylamine Salt" or "Pravastatin, (6 beta)-Isomer" or "RMS-431" or "RMS 431" or "RMS431" or "SQ-31000" or "SQ 31000" or "SQ31000" or "SQ-31,000" or "SQ 31,000" or "SQ31,000"Apo-Pravastatin" or "Apo Pravastatin" or "Bristacol").mp.
20.	18 or 19
21.	Simvastatin/
22.	("Zocor" or "MK-733" or "MK 733" or "MK733" or "Synvinolin").mp.
23.	21 or 22
24.	Fluvastatin /
25.	("Fluvastatin Sodium" or "Fluvastatin Sodium Salt" or "Fluindostatin" or "Lescol" or "XU 62-320" or "XU 62 320" or "XU-62320" or "XU62320" or "XU 62320" or "7-(3-(4-Fluorophenyl)-1-(1-methylethyl)-1H-indol-2-yl)-3,5-dihydroxy-6-heptenoate").mp.
26.	24 or 25

27.	Atorvastatin/
28.	("(3R,5R)-7-(2-(4-Fluorophenyl)-5-isopropyl-3-phenyl-4-(phenylcarbamoyl)-1H-pyrrol-1-yl)-3,5-dihydroxyheptanoic acid" or "Atorvastatin Calcium" or "Atorvastatin, Calcium Salt" or "Liptonorm" or "Lipitor" or "Atorvastatin Calcium Hydrate" or "Atorvastatin Calcium Anhydrous" or "CI 981" or "CI-981" or "CI981" or "Atorvastatin Calcium Trihydrate").mp.
29.	27 or 28
30.	Rosuvastatin Calcium /
31.	("Calcium, Rosuvastatin" or "Crestor" or "Rosuvastatin" or "ZD4522" or "ZD 4522").mp.
32.	30 or 31
33.	Pitavastatin/
34.	("itavastatin" or "(E,3R,5S)-7-(2-cyclopropyl-4-(4-fluorophenyl)quinolin-3-yl)-3,5-dihydroxyhept-6-enoic acid" or "P 872441" or "P-872441" or "NK 104" or "NK-104" or "pitavastatin calcium" or "itavastatin calcium" or "pitavastatin lactone" or "nisvastatin").mp.
35.	33 or 34
36.	10 or 14 or 17 or 20 or 23 or 26 or 29 or 32 or 35
37.	Placebo/
38.	36 or 37
39.	Fracture/
40.	("Bone Densities" or "Density, Bone" or "Bone Mineral Density" or "Bone Mineral Densities" or "Density, Bone Mineral" or Bone Mineral Content" or "Bone Mineral Contents").mp.
41.	adverse events/
42.	Bone turnover marker/
43.	N-terminal propeptide of type I procollagen/
44.	("P-I-P peptide" or "Type I procollagen N-terminal peptide" or "P1NP peptide" or "amino terminal propeptide of type I collagen" or "PINP peptide" or "fetal antigen 2, human" or "foetal antigen 2, human" or "FA2 antigen, human" or "aminoterminal propeptide of type I collagen, human" or "collagen type I, amino-propeptide, human").mp.
45.	C terminal telopeptide of type I collagen

46.	(“trimeric cross-linked peptide collagen type I” or “C-terminal type I collagen telopeptide” or “CTCLP” or “CTx telopeptide” or “serum carboxyterminal telopeptide type I collagen” or “ICTP peptide” or “C-terminal telopeptide of type I collagen” or “COOH-terminal telopeptide of type I collagen” or “C-terminal cross-linking telopeptide, collagen type I” or “N-telopeptide” or “N-terminal type I collagen telopeptide” or “NTx telopeptide” or “pyridinoline cross-linked carboxy-terminal telopeptide, collagen type I” or “C-telopeptide” or “i-ICTP”).mp.
47.	cross-linked N-telopeptide of type I collagen
48.	(“trimeric cross-linked peptide collagen type I” or “C-terminal type I collagen telopeptide” or “CTCLP” or “CTx telopeptide” or “serum carboxyterminal telopeptide type I collagen” or “ICTP peptide” or C-terminal telopeptide of type I collagen” or “COOH-terminal telopeptide of type I collagen” or “C-terminal cross-linking telopeptide, collagen type I” or “N-telopeptide” or “N-terminal type I collagen telopeptide” or “NTx telopeptide” or “pyridinoline cross-linked carboxy-terminal telopeptide, collagen type I” or “C-telopeptide” or “i-ICTP”).mp.
49.	alkaline phosphatase/
50.	or/39-49
51.	randomized controlled trial
52.	7 and 36 and 50 and 51

Supplementary 2: CBM search strategy

#	Searches
1.	"骨质疏松"[不加权:扩展] OR "骨质疏松，绝经后"[不加权:扩展] OR "骨质疏松,绝经后"[不加权:扩展] OR "骨质疏松"[不加权:扩展] OR "骨质疏松"[不加权:扩展] OR "骨质疏松"[不加权:扩展] OR "骨质疏松性骨折"[不加权:扩展] OR "骨质疏松"[不加权:扩展] OR "骨质疏松"[不加权:扩展]
2.	"羟甲基戊二酰基 CoA 还原酶抑制剂"[不加权:扩展]
3.	"阿托伐他汀钙"[不加权:扩展] OR "阿托伐他汀钙"[不加权:扩展] OR "阿托伐他汀钙"[不加权:扩展] OR "阿托伐他汀钙"[不加权:扩展] OR "阿托伐他汀钙"[不加权:扩展] OR "阿托伐他汀钙"[不加权:扩展]
4.	"瑞舒伐他汀钙"[不加权:扩展]
5.	"匹伐他汀钙"[不加权:扩展]
6.	“洛伐他汀钙"[不加权:扩展]

7.	“辛伐他汀钙"[不加权:扩展]
8.	“氟伐他汀钙"[不加权:扩展]
9.	安慰剂对照
10.	OR/2-9
11.	"骨折"[不加权:扩展] OR "骨折"[不加权:扩展] OR "骨折"[不加权:扩展] OR "脊柱骨折"[不加权:扩展] OR "胫骨骨折"[不加权:扩展] OR "胫骨骨折"[不加权:扩展] OR "Monteggia 骨折"[不加权:扩展] OR "Colles 骨折"[不加权:扩展] OR "Bankart 损伤"[不加权:扩展] OR "踝骨折"[不加权:扩展] OR "骨折, 应力性"[不加权:扩展] OR "骨折, 应力性"[不加权:扩展] OR "肩骨折"[不加权:扩展] OR "眶骨折"[不加权:扩展] OR "颌骨折"[不加权:扩展] OR "髋骨折"[不加权:扩展] OR "脊柱骨折"[不加权:扩展] OR "胫骨骨折"[不加权:扩展] OR "Salter-Harris 骨折"[不加权:扩展] OR "骨折"[不加权:扩展]
12.	骨转换标志物
13.	“I 型前胶原的 N 端前肽”
14.	PINP
15.	I 型胶原的 C 端端肽
16.	CTX
17.	I 型胶原的交联 N 端肽
18.	NTX
19.	碱性磷酸酶
20.	ALP
21.	OR/11-20
22.	"随机对照试验"[不加权:扩展]
23.	1 AND 10 AND 21