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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 the good efficacy, drugs still have certain limitations in clinical application due to delivery routes, medication cycles and cost issues. Nowadays, statins (the 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors, HMG-CoA) 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 choose first. This study aims to review the literature, ascertaining the relative efficacy and safety of statins for osteoporotic patients using a Bayesian network meta-analysis.

Methods and Analysis: We will systematically search the following databases: Pubmed, EMBASE, Web of Science, Cochrane Central Register of Controlled Trials (CENTRAL), China National Knowledge Infrastructure (CNKI), Wanfang Database, China Science and Technology Journal Database (VIP) and Chinese Biomedical Literature Database (CBM) to include randomized control trials that compare different statins for treating osteoporosis. Primary outcomes are the incidence of overall fractures and BMD changes. Secondary outcomes contain adverse effects and bone turnover markers. All items of this review will comply with Cochrane Handbook, and the quality of evidence will be evaluated by GRADE. A traditional pairwise meta-analysis and the Bayesian network-meta analysis will be performed to compare the efficacy of different statins.

Ethics and dissemination: Additional formal ethical approval is not required since this is a protocol based on public databases, with no primary data collected. Results will be submitted to a peer-reviewed journal.

Trial registration number: CRD42021242619

Keywords: osteoporosis; statin; network meta-analysis; protocol; systematic review

Article Summary

Strengths and limitations of this study:

1. This is the most comprehensive review comparing the efficacy and safety of statins for patients with osteoporosis through a Bayesian network meta-analysis.
2. We will use the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach to evaluate the quality of evidence.
3. The results will explore the suitable dosage of statins for osteoporosis and help physicians and patients select appropriate treatments.
4. 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 characterized by low bone mass, microarchitectural changes in bones and skeletal fragility. These changes contribute to decreased bone strength and increased susceptibility to fractures[1]. Osteoporotic patients, especially the elderly, often suffer from poor life quality because of its complications such as back pain, severe spinal deformities and dysfunction. Notably, the incidence of OP is gradually increasing with the aging of the global population. According to the report, more than half of older people in the USA would be at high risk for osteoporosis from 2020;[2] meanwhile, scholars predicted that the number of patients with osteoporosis 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 osteoporosis are functioning through the antiresorptive or the anabolic mechanisms: 1)antiresorptive drugs such as bisphosphonates[5], denosumab[6], calcitonin[7], hormone replacement therapy[8] and raloxifene[9], whereas 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 proved to be effective and widely used. However, there are still some problems in clinical use due to medication methods, medication cycles and drug costs. For example, teriparatide has a markable therapeutic effect but can only be injected subcutaneously, bringing many inconveniences. (2-5). In addition to its administration, hypercalcemia could be a common side effect in those treated with teriparatide. Therefore, it is essential to discover convenient, economical and practical therapies.

Statins (HMG-CoA reductase inhibitors) have become mainstream in preventing and treating cardiovascular disease(CVD). 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 osteoporosis and its complications, especially osteoporotic fractures[13]-[14][15][16]. Possible mechanisms might involve the proliferation, differentiation and protection of osteoblasts and the inhibition of osteoclastogenesis.[17] Moreover, certain observational researches exploring associations between statins and osteoporosis suggested that, although the conclusion was not in the agreement[15],[16],[18], the efficacy was dose-dependent[18]. According to Leutner M, treating with a high dose of statins might be associated with an increased incidence of osteoporosis and a higher risk of fractures.[18] To 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 remains unclear. Therefore, it is essential to select statins and explore the dose-dependent effect between statins and osteoporosis.

To date, several systematic reviews and meta-analyses have studied the correlation between statins and osteoporosis from multiple perspectives [19]-[22][23]. Nevertheless, they all had one or more following limitations: (1) Studies included were not comprehensive [19]-[20][23][21], some of which have not mentioned the safety of drugs. (2) No guidelines were supporting an appropriate therapy for OP in terms of statins. [19]-[23](3) Articles included need further updates on this topic [19]-[22][23].

To our knowledge, there has been no network meta-analysis studying the dose-dependent effects of statins on osteoporosis so far. This study aims to conduct a systematic review and network meta-analysis comparing the efficacy and safety of various statins treating osteoporosis at different dose levels. We will elaborate on the variety and dosage distinctions of 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 network-meta analysis based on a Bayesian framework in this study. All items in this review will comply with the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocol (PRISMA-P)[24] and PRISMA extension statement, which develop systematic reviews incorporating a network meta-analysis of healthcare interventions.[25] 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

1.Type of studies

All randomized clinical trials (RCTs) focusing on statins used for osteoporosis treatment, regardless of published or unpublished, will be included without language and data restriction. RCTs focusing on antiosteoporotic drugs such as bisphosphonates will be excluded. Cohort studies, cross-sectional studies, case reports, and reviews will not be taken into consideration. All assignments are ensured to be obtainable.

2. Participants

We will search RCTs enrolling participants as follows: (1) Adults aged at least 18 years with a medical diagnosis of osteoporosis and treated with statins as main drugs. (2)Participants who were healthy or asymptomatic will be excluded. (3)Patients with osteoporosis caused by other diseases or drugs will also be excluded.

According to the American National Bone Health Alliance Working Group[26] and the Chinese Society of Osteoporosis and Bone Mineral Research,[3] the diagnosis of osteoporosis was based on the World Health Organization(WHO) as follows i) an individual who experiences a low-trauma hip fracture or vertebral fracture. ii) T-score of −2.5 or lower at the lumbar spine, femur neck, or total hip by bone mineral density testing. iii) the occurrence of one or more of several types of low-trauma fractures, like hip fractures, osteopenia-associated vertebral, proximal humerus, pelvis, or some wrist fractures, even the T-score between -2.5 and -1. iv) FRAX scores with ≥3 % (hip) or 20 % (central) 10-year fracture risk also confer an osteoporosis diagnosis.

3. Type of interventions

Universal statins or HMG-CoA reductase inhibitors (atorvastatin, pravastatin, simvastatin, fluvastatin, atorvastatin, rosuvastatin, pitavastatin and so forth) were evaluated in RCTs. Complete treatment periods of at least two months, regardless of the therapeutic dose and the conduction. Adjuvant therapy such as placebo or calcium or vitamin D, no intervention will be set as a control.

4. Outcomes of interest

Our primary outcomes are the incidence of overall fractures and the improvement of BDM (percentage change and absolute change [in g/cm^2]) of the lumbar, the spine, the femoral neck, and the hip. Based on the intention-to-treat principle, we are supposed to extract and analyze the number of fractures defined as a clinical osteoporotic fracture at the maximum follow-up duration. Dual-energy X-ray absorptiometry (DEXA) scans were conducted to check BDM.

Secondary outcomes contain adverse effects as well as bone turnover markers. We intend to record and compare but not limited to gastrointestinal or liver side effects causing by active treatments. Bone turnover markers contain N-terminal propeptide of type I procollagen (PINP), C terminal telopeptide of type I collagen (CTX), cross-linked N-telopeptide of type I collagen (NTX), alkaline phosphatase(A.P.).

Data sources and search strategy

Literature retrieval will be mainly carried out in the following nine databases: Pubmed, EMBASE, Web of Science, Cochrane Central Register of Controlled Trials (CENTRAL), China National Knowledge Infrastructure (CNKI), Wanfang Database, China Science and Technology Journal Database (VIP), and Chinese Biomedical Literature Database (CBM). In the meantime, we will comprehensively search ongoing trials via the Chinese Clinical Trials Registry Platform(http://www.chictr.org.cn/searchprojen.aspx) and ClinicalTrials.gov (https://ClinicalTrials.gov/) as well. Futhermore, 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.[27] Search terms are defined for Participant (Osteoporosis), Intervention (Statins, HMG-CoA reductase inhibitors), Outcomes (Fracture, BDM, adverse event, and bone turnover markers), and RCTs (randomized controlled trials). Synonyms of search terms were selected by the "OR" operator, whilst the "AND" operator combined terms from different categories: Participants, Interventions, Outcomes, and RCTs. The search strategy adapting for each database was detailed in Table.1. Literary works have no date or language restrictions.

Table.1 Central Search Strategy

Number	Search Terms
#1	osteoporosis [Mesh]
#2	fracture [Title/Abstract] OR low bone mineral density [Title/Abstract]
#3	statins [All Felids] OR HMG-CoA reductase inhibitors [All Felids]
#4	lovastatin [Title/Abstract] OR pravastatin [Title/Abstract] OR simvastatin [Title/Abstract] OR Fluvastatin [Title/Abstract] OR atorvastatin [Title/Abstract] OR rosuvastatin

	[Title/Abstract] OR pitavastatin [Title/Abstract]
#5	#1 OR #2 AND #3 OR #4
#6	BDM [All Felids] OR adverse events [All Felids] OR bone turnover marker [All Felids]
#7	randomized controlled trial [Mesh]
#8	#5 AND #6 AND #7

Study selection

Four researchers (X-MX, Z-W, Z-GW and X-YJ) will work in pairs to complete the study selection. Two will independently review the title and abstract of each study based on the PICO 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 re-assess 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 integrated details. The process of study selection will be exhibited in a PRISMA-compliant [24] flow chart (figure 1).

Data extraction

Researchers will also extract comprehensive information from the original studies. 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 BDM; 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 (T-ZK and D-Al) will independently judge the risk of bias in individual studies complying with the Cochrane Handbook (https://training.cochrane.org/handbook)[27], following by the re-check with each other to guarantee there is no mistake. The assessment criteria contain domains list as "bias arising from the randomization process", "bias due to deviations from intended interventions", "bias due to missing outcome data", "bias in the measurement of the 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 judgment of "low risk of bias" signified that 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, they will be deemed "some concerns". [28] Any disagreement will be resolved through consulting the research professor (XN).

Statistical analysis

We will first conduct a 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 indicating significant heterogeneity, and $P < 0.01$ as a threshold exposing considerable heterogeneity. [29] If there is an evident heterogeneity, we will apply a random-effects model; otherwise, we will use the fixed-effects model. Furthermore, the odds ratio (OR) with 95% Confidence Interval (CI) will be reported for the dichotomous variables, while the continuous variables will be reported by Standard mean difference (SMD) with 95% CI. 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 network meta-analysis in R V.3.2.4 software (https://cran. r-project.org/src/base/R-3/). 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.[30] The inference parameter of the posterior distribution will come from the summary of its median with SMD or OR and 95% CI. 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[31] will be used to appraise convergence.

To check whether a model fit is satisfying, we are supposed to calculate the posterior mean residual deviance, which is an absolute measure fit.[32] Afterwards, we will assess if the model is appropriate via contradistinguishing the posterior mean residual deviance value from the number of independent data points.[32] The fixed- and random-effects models with vague priors for multi-arm trials will be used. The deviance information criterion (DIC) will be used to measure the model fit to penalize model complexity. The result turns out that the lower DIC is, the better the fit is.[33] Differences more than or equivalent to three units indicate the significance. [33] If both models report a similar DIC, the fixed-effects model is preferred in the case of the pairwise comparison has no significant heterogeneity. Otherwise, the random-effect model will be selected.

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), whose scores ranging from 0 to 100 represents the treatment from the worst to the best.[34] 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],[18] have demonstrated that the efficacy of statins was dose-dependent. Therefore, further subgroup meta-analyses on the dosage will be performed.

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).[35] 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 (SoF).[36] Four steps are as below: 1) List direct and indirect comparisons of effect estimates and confidence intervals, respectively. 2) Rate the quality of each comparison effect estimate. 3) Determine and present the quality of evidence-based 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 network-meta analysis will only publish anonymous data and will not recruit new patients. We have already consulted physicians specialized in orthopedics 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 was not necessary for this review as no primary data collected. The study will comply 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 osteoporosis and researchers in similar areas.

DISCUSSION

The incidence of diseases including osteoporosis (O.P.), hyperlipidemia and Coronary artery disease (CAD) increases dramatically with age. Lipid metabolism in bone cells has long been appreciated among various metabolic pathways. The "lipid hypothesis of osteoporosis" suggested that lipid oxidation was a contributing factor to osteoporosis.[37] Bone marrow mesenchymal cells (BMSCs) can selectively differentiate into osteoblasts or adipocytes. Once the lipid oxidation occurs, its products subsequently stimulate peroxisome proliferator-activated receptors gamma (PPARγ), preventing the osteogenic differentiation and promoting adipocyte expansion, which leads to bone loss.[38] Lipids, especially cholesterol, can impact the phenotype of osteoclasts and osteoblasts in such pathological conditions.[39]

Statins are FDA-approved drugs for hypercholesterolemia [40],[41] and have been proved to increase BDM and reduce the risk of fracture.[42]-[43][44] Previous clinical trials[13]-[16], [18] and pairwise meta-analyses [19]-[22][23] have also certified that. The positive outcome might be that statins could promote osteogenic activity through activating and improving the expression of bone morphogenetic protein-2 (BMP-2) and osteocalcin[45] by suppressing farnesylation and geranylgeranylation of Rho/Ras small G proteins in osteoblasts.[46] Statins could additionally increase osteoprotegerin (OPG) that antagonizing RANKL [46][47]and inhibited osteoclast activity.[47][48] Furthermore, clinical studies have proposed a dose-dependent effect of statins on bone health, though those findings have not been scientifically consistent.[15],[16],[18] However, it remains unknown whether different statins have similar function and efficacy for the sake of

treating OPThus, 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 attempt to evaluate the relative effects of variable statins and dosages in patients with osteoporosis 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 analyze RCTs concerning statins therapies. This search strategy will contain all available treatment arms, including a variety of generations and dosage. In the final, we will use tools (The 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 osteoporosis patients. The results of this study might help patients and therapists choose the best treatment to improve bone health and provide convincing evidence for guidelines.

Author Contributions

X-N and Z-GW devised the study, designed the analysis plan, and will carry out the statistical analyses. X-MX and X-YJ drafted the protocol; they will assist with the data extraction and analysis and draft the results and discussion sections. X-MX designed and conducted the search strategies. X-MX, Z-W, Z-GW, and X-YJ assisted with study design and data extraction and will carry out most of the data collection. T-ZK, D-AL will assist with the data collection and provided input on the working of the manuscript.

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Competing interests None declared.

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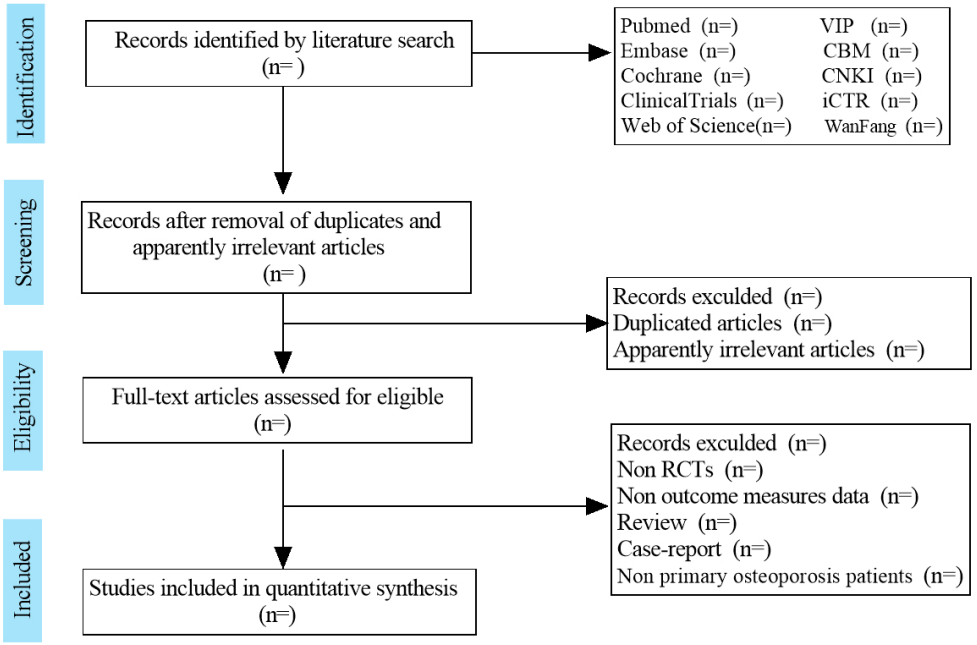

Figure 1. Literature screening process. VIP: China Science and Technology Journal Database; CNKI: China National Knowledge Infrastructure; CBM: Chinese Biomedical Literature Database; iCTR: ClinicalTrials.gov; RCT: randomized controlled trial

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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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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 the good efficacy, drugs still have certain limitations in clinical application due to delivery routes, medication cycles and cost issues. Nowadays, statins (the 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors, HMG-CoA) 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 choose first. This study aims to review the literature, ascertaining the relative efficacy and safety of statins for osteoporotic patients 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 (CENTRAL), China National Knowledge Infrastructure (CNKI), Wanfang Database, China Science and Technology Journal Database (VIP), Chinese BioMedical Literature Database (SinoMed) and preprint servers to include randomized control trials that compare different statins for treating osteoporosis. Primary outcomes are the incidence of overall fractures and BMD (Bone mineral density, BMD) changes. Secondary outcomes contain adverse effects and bone turnover markers. All items of this review will comply with Cochrane Handbook, and the quality of evidence will be evaluated by GRADE. 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.

Trial registration number: CRD42021242619

Dates of search: 24-Feb-2022

Keywords: osteoporosis; statin; network meta-analysis; protocol; systematic review

Article Summary

Strengths and limitations of this study:

1. This is the most comprehensive review comparing the efficacy and safety of statins for patients with osteoporosis through a Bayesian network meta-analysis.
2. We will use the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach to evaluate the quality of evidence.
3. The results will explore the dosage and potency of statins for osteoporosis and help physicians and patients select appropriate treatments.
4. 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 characterized by low bone mass, microarchitectural changes in bones and skeletal fragility. These changes contribute to decreased bone strength and increased susceptibility to fractures.[1] Osteoporotic patients, especially the elderly, often suffer from poor life quality because of its complications such as back pain, severe spinal deformities and dysfunction. Notably, the incidence of OP is gradually increasing with the aging of the global population. According to the report, more than half of older people in the USA would be at high risk for osteoporosis from 2020[2]; meanwhile, scholars predicted that the number of patients with osteoporosis 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 osteoporosis are functioning through the antiresorptive or the anabolic mechanisms: 1)antiresorptive drugs such as bisphosphonates,[5] denosumab,[6] calcitonin,[7] hormone replacement therapy[8] and raloxifene,[9] whereas 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 proved to be effective and widely used. However, there are still some problems in clinical use due to medication methods, medication cycles and drug costs. For example, teriparatide has a markable therapeutic effect but can only be injected subcutaneously, bringing many inconveniences. In addition to its administration, hypercalcemia could be a common side effect in those treated with teriparatide. Therefore, it is essential to discover convenient, economical and practical therapies.

Statins (HMG-CoA reductase inhibitors) have become mainstream in preventing and treating cardiovascular disease (CVD). 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 osteoporosis and its complications, especially osteoporotic fractures.[13]-[14][15][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 was associated with increased expressions of bone morphogenetic protein–2 (BMP-2: a gene could regulate the bone formation through enhancing the osteoclasts).[18] Moreover, certain observational researches exploring associations between statins and osteoporosis suggested that, although the conclusion was not in the agreement[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 osteoporosis and a higher risk of fractures.[19] To 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 remains unclear. Therefore, it is essential to select statins and explore the dose-dependent effect between statins and osteoporosis.

To date, several systematic reviews and meta-analyses have studied the correlation between statins and osteoporosis from multiple perspectives.[20]-[23][24] Nevertheless, they all had one or more following limitations: (1) Studies included were not comprehensive,[20]-[21][24][22] some of which have not mentioned the safety of drugs. (2) No guidelines were supporting an appropriate therapy for OP in terms of statins.[20]-[24] (3) Articles included need further updates on this topic.[20]-[23][24]

To our knowledge, there has been no network meta-analysis studying the dose-dependent effects of statins on osteoporosis so far. This study aims to conduct a systematic review and network meta-analysis comparing the efficacy and safety of various statins treating osteoporosis 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 network meta-analysis based on a Bayesian framework in this study. This review 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 a network meta-analysis 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

1.Type of studies

We will review the Chinese Clinical Trials Registry Platform (CHiCTR), WHO International Clinical Trials Registry Platform (ICTRP) and ClinicalTrials.gov for registered published randomized clinical trials (RCTs) and preprint servers (such as medRxiv and Research Square) for unpublished data focusing on statins used for osteoporosis treatment, without language and data restriction. RCTs focusing on antiosteoporosis 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.

2. Participants

We will search RCTs enrolling participants as follows:

(1) Adults aged at 18 years and above.

(2) Participants with a medical diagnosis of primary osteoporosis associated with age/heredity/life-styles 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 osteoporosis having comorbidities not associated with the onset of OP will be included (e.g., hyperlipidemia).

We will also conduct exclusion criteria as follows:

(1) Pediatric and adolescent patients.

(2) Patients diagnosed with secondary osteoporosis (induced by other diseases or drugs) will be excluded.

(3) Patients with osteoporosis comorbidities associated with the onset of OP will be excluded (e.g., 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 World Health Organization(WHO) as follows i) an individual who experiences a low-trauma hip fracture or vertebral fracture. ii) T-score of −2.5 or lower at the lumbar spine, femur neck, or total hip by bone mineral density testing. iii) the occurrence of one or more of several types of low-trauma fractures, like hip fractures, osteopenia-associated vertebral, proximal humerus, pelvis, or some wrist fractures, even the T-score between -2.5 and -1. iv) FRAX scores with ≥3 % (hip) or 20 % (central) 10-year fracture risk also confer an osteoporosis diagnosis.

3. 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 two

months, regardless of the therapeutic dose and the method of delivery, will be considered. Any combined therapy setting at least on kind of statins as the treatment arm will be included as well. Appropriate treatments containing bone health supplementations and lifestyle modifications, alone or in combination, will be considered. RCTs setting placebo and no pharmacotherapy intervention as control will be included as well.

4. 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 standard deviations (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 analyze 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 (DEXA) 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 causing by treatments will be evaluated. Bone turnover markers contain N-terminal propeptide of type I procollagen (PINP), C terminal telopeptide of type I collagen (CTX), cross-linked N-telopeptide of type I collagen (NTX), alkaline phosphatase (A.P.). Sources of 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: MEDLINE, EMBASE, Web of Science, Cochrane Central Register of Controlled Trials (CENTRAL), China National Knowledge Infrastructure (CNKI), Wanfang Database, SinoMed and China Science and Technology Journal Database (VIP). In the meantime, we will comprehensively search ongoing trials via the WHO International Clinical Trials Registry Platform (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 (Osteoporosis), Intervention (Statins, HMG-CoA reductase inhibitors), Outcomes (Fracture, BMD, adverse event, and bone turnover markers), and RCTs (randomized controlled trials). Synonyms of search terms were selected by the "OR" operator, whilst the "AND" operator combined terms from different categories: Participants, Interventions, Outcomes, and RCTs. The sample search strategies adapting for databases were detailed in the supplement materials. Literary works have no date or language restrictions.

Study selection

Four researchers (X-MX, Z-W, Z-GW and X-YJ) will work in pairs to complete the study selection. Two will independently review the title and abstract of each study based on the PICO 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 re-assess 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 (XMX and XYJ) 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 (T-ZK and D-Al) will independently judge the risk of bias in individual studies complying with the revised Cochrane risk of bias tool for randomized trials (RoB.2),[33] then will double check each other to guarantee there is no error. The assessment criteria contain domains list as “bias arising from the randomization process”, “bias due to deviations from intended interventions”, “bias due to missing outcome data”, “bias in the measurement of the 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 judgment 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, they will be deemed “some concerns”.[34] Any disagreement will be resolved through consulting the research professor (XN).

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 indicating significant heterogeneity, and P < 0.01 as a threshold exposing considerable heterogeneity.[35] Given that the expected between-study heterogeneity due to differences in treatments, we will apply a random-effects model. Furthermore, the odds ratio (OR) with 95% confidence Intervals (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 network meta-analysis in WINBUGSS software version 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 (CrIs). A Bernoulli model will be used for analyzing 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 a 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 multi-arm trials will be used. The deviance information criterion (DIC) will be used to measure the model fit to penalize model

complexity. The result turns out that the lower 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 of the pairwise comparison has no significant heterogeneity. Otherwise, the random-effect model will be selected. If the data is insufficient for the NMA, the pairwise meta-analysis will be possible, in which case the random-effect 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 represents 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 be also conducted based on different kinds of primary osteoporosis (post-menopausal vs age-related vs others).

We will use the network and network graphs packages in Stata (version 14.0) to produce the graphs.[44] The result will be figured by ggplot2 3.3.5 packages in R (version 4.1.0).[45] Network meta-analyses of the primary outcomes were duplicated using the geMTC 1.0-1 package in R (version 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 (SoF).[49] Four steps are as below: 1) List direct and indirect comparisons of effect estimates and confidence intervals, respectively. 2) Rate the quality of each comparison effect estimate. 3) Determine and present the quality of evidence-based 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 network meta-analysis will only publish anonymous data and will not recruit new patients. We have already consulted physicians specialized in orthopedics 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 osteoporosis and researchers in similar areas.

DISCUSSION

The incidence of diseases including osteoporosis (O.P.), hyperlipidemia and coronary artery disease (CAD) increases dramatically with age. Lipid metabolism in bone cells has long been appreciated among various metabolic pathways. The "lipid hypothesis of osteoporosis" suggested that lipid oxidation was a contributing factor to osteoporosis.[50] Bone marrow mesenchymal cells (BMSCs) can selectively differentiate into osteoblasts or adipocytes. Once the lipid oxidation occurs, its products subsequently stimulate peroxisome proliferator-activated receptors gamma (PPARγ), 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-approved drugs for hypercholesterolemia [53],[54] and have been proved to increase BMD and reduce the risk of fracture.[55]-[56][57] Previous clinical trials[13]-[16], [19] and pairwise meta-analyses [20]-[23][24] have also certified that. The positive outcome might be that statins could promote osteogenic activity through activating and improving the expression of bone morphogenetic protein-2 (BMP-2) and osteocalcin[18] by suppressing farnesylation and geranylgeranylation of Rho/Ras small G proteins in osteoblasts.[58] Statins could additionally increase osteoprotegerin (OPG) that antagonizing RANKL [58] 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 high-dosage statin use 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-dosage 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 statins 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 osteoporosis 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 analyze RCTs concerning statins therapies. This search strategy will contain all available treatment arms, including a variety of generations and dosage. In the final, we will use tools (The 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 osteoporosis patients. The results of this study might help patients and therapists choose the best treatment to improve bone health and provide convincing evidence for guidelines.

Contributorship Statement

X-N and Z-GW supervised and designed the study, and will carry out the statistical analyses. X-MX and X-YJ drafted the protocol and revised the manuscript; they will assist with the data extraction and analysis and draft the results and discussion sections. X-MX and X-YJ designed and conducted the search strategies. X-MX, Z-W, Z-GW, and X-YJ assisted with study design and data extraction and will carry out most of the data collection. T-ZK, D-AL and Z-QC will assist with the data collection and provided input on the working of the manuscript. X-MX and X-YJ contributed equally to this study.

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Competing interests None declared.

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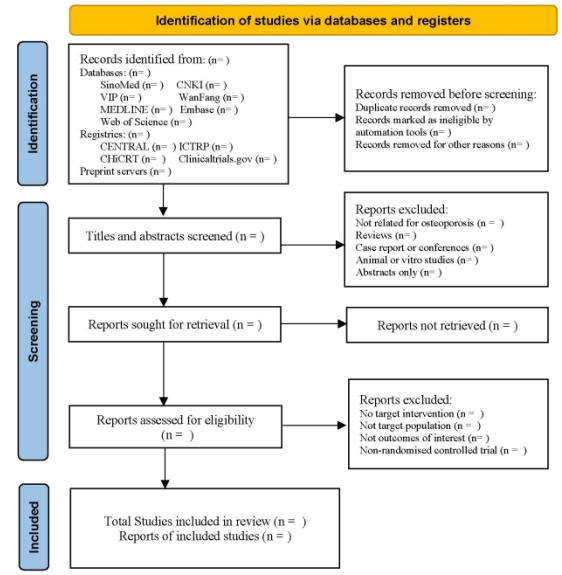

SinoMed: Chinese BioMedical Literature Database; CNKI: China National Knowledge Infrastructure; VIP: China Science and Technology Journal Database; Wang Fang: Wang Fang database; CENTRAL: Cochrane Central Register of Controlled Trials; CHiCRT: Chinese Clinical Trials Registry Platform;ICTRP: WHO International Clinical Trials Registry Platform.

Figure 1 PRISMA 2020 flow diagram for literature selection

SinoMed: Chinese BioMedical Literature Database; CNKI: China National Knowledge Infrastructure; VIP: China Science and Technology Journal Database; Wang Fang: Wang Fang database; CENTRAL: Cochrane Central Register of Controlled Trials; CHiCRT: Chinese Clinical Trials Registry Platform;ICTRP: WHO International Clinical Trials Registry Platform.
Figure 1 PRISMA 2020 flow diagram for literature selection

210x297mm (300 x 300 DPI)

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

PRISMA-P 2015 Checklist

This checklist has been adapted for use with protocol submissions to *Systematic Reviews* from Table 3 in Moher D et al: Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Systematic Reviews* 2015 **4**:1

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
ADMINISTRATIVE INFORMATION					
Title					
Identification	1a	Identify the report as a protocol of a systematic review	☒	☐	Page 1, Line 1 to Line 2
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	☐	☒	
Registration	2	If registered, provide the name of the registry (e.g., PROSPERO) and registration number in the Abstract	☒	☐	Page 2, Line 28
Authors					
Contact	3a	Provide name, institutional affiliation, and e-mail address of all protocol authors; provide physical mailing address of corresponding author	☒	☐	Page 1, Line 3 to Line 10
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	☒	☐	Page 16, Line 6 to Line 13
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	☐	☒	
Support					
Sources	5a	Indicate sources of financial or other support for the review	☒	☐	Page 16, Line 15 to Line 19
Sponsor	5b	Provide name for the review funder and/or sponsor	☒	☐	Page 16, Line 7
Role of sponsor/funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	☒	☐	Page 16, Line 6 to Line 13
INTRODUCTION					
Rationale	6	Describe the rationale for the review in the context of what is already known	☒	☐	Page 4, Line 1 to Page 5, Line 16
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	☒	☐	Page 9, Line 24 to Line 25
METHODS					

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
Eligibility criteria	8	Specify the study characteristics (e.g., PICO, study design, setting, time frame) and report characteristics (e.g., years considered, language, publication status) to be used as criteria for eligibility for the review	☒	☐	Page 6, Line 4 to Line 11; Page 10, Line 7 to Line 13
Information sources	9	Describe all intended information sources (e.g., electronic databases, contact with study authors, trial registers, or other grey literature sources) with planned dates of coverage	☒	☐	Page 6, Line 19 to Line 23; Page 9, Line 1 to Line 12
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	☒	☐	Page 9, Line 13 to Line 20; Supplementary 1 and 2
STUDY RECORDS					
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	☒	☐	Page 11, Line 2 to Line 22
Selection process	11b	State the process that will be used for selecting studies (e.g., two independent reviewers) through each phase of the review (i.e., screening, eligibility, and inclusion in meta-analysis)	☒	☐	Page 9, Line 22 to Page 10, Line 2
Data collection process	11c	Describe planned method of extracting data from reports (e.g., piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	☒	☐	Page 10, Line 5 to Line 14
Data items	12	List and define all variables for which data will be sought (e.g., PICO items, funding sources), any pre-planned data assumptions and simplifications	☒	☐	Page 9, Line 13 to Line 20
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	☒	☐	Page 8, Line 7 to Line 25
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	☒	☐	Page 10, Line 16 to Line 28
DATA					
Synthesis	15a	Describe criteria under which study data will be quantitatively synthesized	☒	☐	Page 11, Line 3 to Line 4; Line 13 to Line 14
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data, and methods of combining data from studies, including any planned exploration of consistency (e.g., I^2, Kendall's tau)	☒	☐	Page 11, Line 3 to Line 22
	15c	Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-regression)	☒	☐	Page 12, Line 17 to Line 21
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	☒	☐	Page 12, Line 5 to

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Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
					Line 6; Line 14 to Line 16
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective reporting within studies)	☒	☐	Page 13, Line 1 to Line 4
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (e.g., GRADE)	☒	☐	Page 13, Line 7 to Line 19

BMJ Open

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

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2021-054158.R2
Article Type:	Protocol
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Complete List of Authors:	Xiong, Mengxin; Hubei University of Chinese Medicine, Clinical College of Chinese Medicine Xue, Yaojun; Hubei University of Chinese Medicine, Clinical College of Chinese Medicine Zhu, Wei; Wuhan University, College of Public Health Deng, Ali; Hubei University of Chinese Medicine, First Clinical College Tan, Zhangkui; Hubei University of Chinese Medicine, Clinical College of Chinese Medicine Zhou, Guangwen; Hubei University of Chinese Medicine, College of Acupuncture and Orthopedics Xiang, Nan; Hubei University of Chinese Medicine, First Clinical College
Primary Subject Heading:	Diabetes and endocrinology
Secondary Subject Heading:	Research methods
Keywords:	General endocrinology < DIABETES & ENDOCRINOLOGY, Lipid disorders < DIABETES & ENDOCRINOLOGY, Calcium & bone < DIABETES & ENDOCRINOLOGY, Protocols & guidelines < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, STATISTICS & RESEARCH METHODS

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 the good efficacy, drugs still have certain limitations in clinical application due to delivery routes, medication cycles and cost issues. Nowadays, statins (the 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors, HMG-CoA) 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 choose first. This study aims to review the literature, ascertaining the relative efficacy and safety of statins for osteoporotic patients 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 (CENTRAL), China National Knowledge Infrastructure (CNKI), Wanfang Database, China Science and Technology Journal Database (VIP), Chinese BioMedical Literature Database (SinoMed) and preprint servers to include randomized control trials that compare different statins for treating osteoporosis. Primary outcomes are the incidence of overall fractures and BMD (Bone mineral density, BMD) changes. Secondary outcomes contain adverse effects and bone turnover markers. All items of this review will comply with Cochrane Handbook, and the quality of evidence will be evaluated by GRADE. 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.

Trial registration number: CRD42021242619

Search dates: From databases inception to February 2022

Keywords: osteoporosis; statin; network meta-analysis; protocol; systematic review

Article Summary

Strengths and limitations of this study:

1. This is the most comprehensive review comparing the efficacy and safety of statins for patients with osteoporosis through a Bayesian network meta-analysis.
2. We will use the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach to evaluate the quality of evidence.
3. The results will explore the dosage and potency of statins for osteoporosis and help physicians and patients select appropriate treatments.
4. 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 characterized by low bone mass, microarchitectural changes in bones and skeletal fragility. These changes contribute to decreased bone strength and increased susceptibility to fractures.[1] Osteoporotic patients, 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 the report, more than half of older people in the USA would be at high risk for osteoporosis by 2020[2]. Scholars predicted that the number of patients with osteoporosis 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 osteoporosis 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]. 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 proved to be effective and widely used. However, there are still some problems in clinical use due to medication methods, medication cycles and drug costs. For example, teriparatide has a markable therapeutic effect, but its method of delivery (by subcutaneous injection) brings patients inconveniences. In addition to the administration, hypercalcemia, a common side effect caused by teriparatide, also could be problematic. Therefore, it is essential to discover convenient, economical and practical therapies.

Statins (HMG-CoA reductase inhibitors) have become mainstream in preventing and treating cardiovascular disease (CVD). 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 osteoporosis and its complications, especially osteoporotic fractures.[13]-[14][15][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 osteoporosis 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 osteoporosis 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 remains unclear. Therefore, it is essential to select the most appropriate statin and explore its dose-dependent effect and potency on osteoporosis.

Several systematic reviews and meta-analyses have studied the correlation between statins and osteoporosis from multiple perspectives.[20]-[23][24] Nevertheless, they all had one or more following limitations: (1) Studies included were not comprehensive,[20]-[21][24][22] some of which have not mentioned the safety of drugs. (2) No guidelines were supporting an appropriate therapy for OP in terms of statins.[20]-[24] (3) Articles included need further updates on this topic.[20]-[23][24]

To our knowledge, there has been no network meta-analysis studying the dose-dependent effects of statins on osteoporosis so far. This study aims to conduct a systematic review and network meta-analysis comparing the efficacy and safety of various statins treating osteoporosis 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 network meta-analysis 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 a network meta-analysis 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

1.Type of studies

We will review the Chinese Clinical Trials Registry Platform (CHiCTR), WHO International Clinical Trials Registry Platform (ICTRP) and ClinicalTrials.gov for registered published randomized clinical trials (RCTs) and preprint servers (such as medRxiv and Research Square) for unpublished data focusing on statins used for osteoporosis treatment, without language and data restriction. RCTs focusing on antiosteoporosis 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.

2. Participants

We will search RCTs enrolling participants as follows:

(1) Adults aged at 18 years and above.

(2) Participants with a medical diagnosis of primary osteoporosis associated with age/heredity/life-styles 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 osteoporosis having comorbidities not associated with the onset of OP will be included (e.g., hyperlipidaemia).

We will also conduct exclusion criteria as follows:

(1) Paediatric and adolescent patients.

(2) Patients diagnosed with secondary osteoporosis (induced by other diseases or drugs) will be excluded.

(3) Patients with osteoporosis comorbidities associated with the onset of OP will be excluded (e.g., 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 World Health Organization (WHO) as follows: i) Individuals who experience a low-trauma hip or vertebral fracture. ii) T-score of −2.5 or lower at the lumbar spine, femur neck, or total hip by bone mineral density testing. iii) 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. iv) FRAX scores with ≥3 % (hip) or 20 % (central) 10-year fracture risk also confer an osteoporosis diagnosis.

3. 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 two 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 supplementations and lifestyle modifications, alone or in combination, will be considered. RCTs setting placebo and no pharmacotherapy intervention as control will be included as well.

4. 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 standard deviations (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 (DEXA) 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 causing by treatments will be evaluated. Bone turnover markers contain N-terminal propeptide of type I procollagen (PINP), C terminal telopeptide of type I collagen (CTX), cross-linked N-telopeptide of type I collagen (NTX), alkaline phosphatase (A.P.). Sources of 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, Cochrane Central

Register of Controlled Trials (CENTRAL), China National Knowledge Infrastructure (CNKI), Wanfang Database, SinoMed and China Science and Technology Journal Database (VIP). In the meantime, we will comprehensively search ongoing trials via the WHO International Clinical Trials Registry Platform (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 (Osteoporosis), Intervention (Statins, HMG-CoA reductase inhibitors), Outcomes (Fracture, BMD, adverse event, and bone turnover markers), and RCTs (randomized controlled trials). Synonyms of search terms were selected by the "OR" operator, whilst the "AND" operator combined terms from different categories: Participants, Interventions, Outcomes, and RCTs. The sample search strategies adapting for databases were detailed in the supplement materials. Literary works have no date or language restrictions.

Study selection

Four researchers (X-MX, Z-W, Z-GW and X-YJ) will work in pairs to complete the study selection. Two will independently review the title and abstract of each study based on the PICO 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 re-assess 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 (X-MX and X-YJ) 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 (T-ZK and D-AL) will independently judge the risk of bias in individual studies complying with the revised Cochrane risk of bias tool for randomized trials (RoB.2),[33] then will double check each other to guarantee there is no error. The assessment criteria contain domains list as "bias arising from the randomization process", "bias due to deviations from intended interventions", "bias due to missing outcome data", "bias in the measurement of the 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 judgment 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, they will be deemed "some concerns".[34] Any disagreement will be resolved through consulting the research professor (XN).

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 indicating significant heterogeneity, and P < 0.01 as a threshold exposing considerable heterogeneity.[35] Given that the expected between-study heterogeneity due to differences in treatments, we will apply a random-effects model. Furthermore, the odds ratio (OR) with 95% confidence Intervals (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 network meta-analysis in WINBUGSS software version 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 (CrIs). 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 a 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 multi-arm trials will be used. The deviance information criterion (DIC) will be used to measure the model fit to penalize model complexity. The result turns out that the lower 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 of the pairwise

comparison has no significant heterogeneity. Otherwise, the random-effect model will be selected. If the data is insufficient for the NMA, the pairwise meta-analysis will be possible, in which case the random-effect 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 represents 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 be also conducted based on different kinds of primary osteoporosis (post-menopausal vs age-related vs others).

We will use the network and network graphs packages in Stata (version 14.0) to produce the graphs.[44] The result will be figured by ggplot2 3.3.5 packages in R (version 4.1.0).[45] Network meta-analyses of the primary outcomes were duplicated using the geMTC 1.0-1 package in R (version 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 (SoF).[49] Four steps are as below: 1) List direct and indirect comparisons of effect estimates and confidence intervals, respectively. 2) Rate the quality of each comparison effect estimate. 3) Determine and present the quality of evidence-based 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 network meta-analysis will only publish anonymous data and will not recruit new patients. We have already consulted physicians specialized 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 osteoporosis and researchers in similar areas.

DISCUSSION

The incidence of diseases including osteoporosis (O.P.), hyperlipidaemia and coronary artery disease (CAD) increases dramatically with age. Lipid metabolism in bone cells has long been appreciated among various metabolic pathways. The "lipid hypothesis of osteoporosis" suggested that lipid oxidation was a contributing factor to osteoporosis.[50] Bone marrow mesenchymal cells (BMSCs) can selectively differentiate into osteoblasts or adipocytes. Once the lipid oxidation occurs, its products subsequently stimulate peroxisome proliferator-activated receptors gamma (PPARγ), 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-approved drugs for hypercholesterolemia [53],[54] and have been proved to increase BMD and reduce the risk of fracture.[55]-[56][57] Previous clinical trials[13]-[16], [19] and pairwise meta-analyses [20]-[23][24] have also certified that. The positive outcome might be that statins could promote osteogenic activity through activating and improving the expression of bone morphogenetic protein-2 (BMP-2) and osteocalcin[18] by suppressing farnesylation and geranylgeranylation of Rho/Ras small G proteins in osteoblasts.[58] Statins could additionally increase osteoprotegerin (OPG) that antagonizing RANKL [58] 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 high-dosage statin use 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-dosage 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 statins 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 osteoporosis 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 statins therapies. This search strategy will contain all available treatment arms, including a variety of generations and dosage. In the final, we will use tools (The 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 osteoporosis patients. The results of this study might help patients and therapists choose the best treatment to improve bone health and provide convincing evidence for guidelines.

Contributorship Statement

X-N and Z-GW supervised and designed the study, and will carry out the statistical analyses. X-MX and X-YJ drafted and revised the protocol, designed and conducted the search strategies. X-MX, Z-W, Z-GW, and X-YJ assisted with the study design and data extraction, and will carry out most of the data collection. T-ZK, D-AL and Z-QC will assist with the data collection and provided input on the working of the manuscript. X-MX and X-YJ contributed equally to this study.

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Competing interests None declared.

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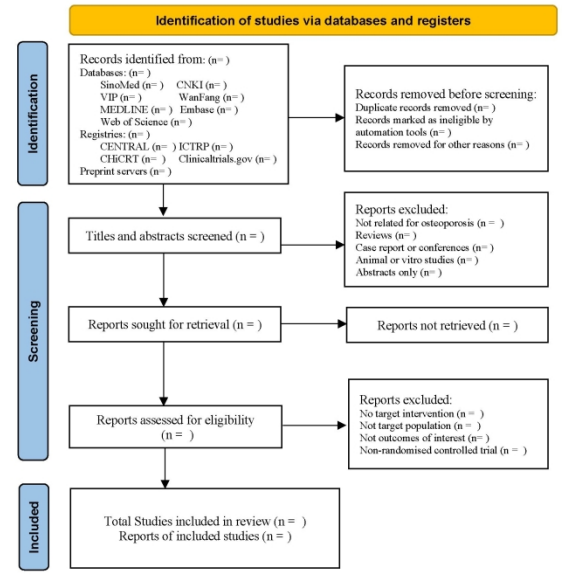

SinoMed: Chinese BioMedical Literature Database; CNKI: China National Knowledge Infrastructure; VIP: China Science and Technology Journal Database; Wang Fang: Wang Fang database; CENTRAL: Cochrane Central Register of Controlled Trials; CHiCRT: Chinese Clinical Trials Registry Platform;ICTRP: WHO International Clinical Trials Registry Platform.

Figure 1 PRISMA 2020 flow diagram for literature selection

SinoMed: Chinese BioMedical Literature Database; CNKI: China National Knowledge Infrastructure; VIP: China Science and Technology Journal Database; Wang Fang: Wang Fang database; CENTRAL: Cochrane Central Register of Controlled Trials; CHiCRT: Chinese Clinical Trials Registry Platform;ICTRP: WHO International Clinical Trials Registry Platform.
Figure 1 PRISMA 2020 flow diagram for literature selection

210x297mm (300 x 300 DPI)

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

PRISMA-P 2015 Checklist

This checklist has been adapted for use with protocol submissions to *Systematic Reviews* from Table 3 in Moher D et al: Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Systematic Reviews* 2015 **4**:1

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
ADMINISTRATIVE INFORMATION					
Title					
Identification	1a	Identify the report as a protocol of a systematic review	☒	☐	Page 1, Line 1 to Line 2
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	☐	☒	
Registration	2	If registered, provide the name of the registry (e.g., PROSPERO) and registration number in the Abstract	☒	☐	Page 2, Line 28
Authors					
Contact	3a	Provide name, institutional affiliation, and e-mail address of all protocol authors; provide physical mailing address of corresponding author	☒	☐	Page 1, Line 3 to Line 10
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	☒	☐	Page 16, Line 6 to Line 13
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	☐	☒	
Support					
Sources	5a	Indicate sources of financial or other support for the review	☒	☐	Page 16, Line 15 to Line 19
Sponsor	5b	Provide name for the review funder and/or sponsor	☒	☐	Page 16, Line 7
Role of sponsor/funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	☒	☐	Page 16, Line 6 to Line 13
INTRODUCTION					
Rationale	6	Describe the rationale for the review in the context of what is already known	☒	☐	Page 4, Line 1 to Page 5, Line 16
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	☒	☐	Page 9, Line 24 to Line 25
METHODS					

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
Eligibility criteria	8	Specify the study characteristics (e.g., PICO, study design, setting, time frame) and report characteristics (e.g., years considered, language, publication status) to be used as criteria for eligibility for the review	☒	☐	Page 6, Line 4 to Line 11; Page 10, Line 7 to Line 13
Information sources	9	Describe all intended information sources (e.g., electronic databases, contact with study authors, trial registers, or other grey literature sources) with planned dates of coverage	☒	☐	Page 6, Line 19 to Line 23; Page 9, Line 1 to Line 12
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	☒	☐	Page 9, Line 13 to Line 20; Supplementary 1 and 2
STUDY RECORDS					
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	☒	☐	Page 11, Line 2 to Line 22
Selection process	11b	State the process that will be used for selecting studies (e.g., two independent reviewers) through each phase of the review (i.e., screening, eligibility, and inclusion in meta-analysis)	☒	☐	Page 9, Line 22 to Page 10, Line 2
Data collection process	11c	Describe planned method of extracting data from reports (e.g., piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	☒	☐	Page 10, Line 5 to Line 14
Data items	12	List and define all variables for which data will be sought (e.g., PICO items, funding sources), any pre-planned data assumptions and simplifications	☒	☐	Page 9, Line 13 to Line 20
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	☒	☐	Page 8, Line 7 to Line 25
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	☒	☐	Page 10, Line 16 to Line 28
DATA					
Synthesis	15a	Describe criteria under which study data will be quantitatively synthesized	☒	☐	Page 11, Line 3 to Line 4; Line 13 to Line 14
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data, and methods of combining data from studies, including any planned exploration of consistency (e.g., I^2, Kendall's tau)	☒	☐	Page 11, Line 3 to Line 22
	15c	Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-regression)	☒	☐	Page 12, Line 17 to Line 21
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	☒	☐	Page 12, Line 5 to

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Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
					Line 6; Line 14 to Line 16
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective reporting within studies)	☒	☐	Page 13, Line 1 to Line 4
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (e.g., GRADE)	☒	☐	Page 13, Line 7 to Line 19