Clinical Study Protocol

Study Title: The effect of simvastatin on bone density in postmenopausal women with type 2 diabetes: a double-blind, randomized, active-comparator (ezetimibe) controlled clinical trial

Short Title: Statin and bone health

Protocol Date: 10 April 2022

Version Number: 02

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Protocol Synopsis

Study Title: The effect of simvastatin on bone density in postmenopausal women with type 2 diabetes: a double-blind, randomized, active-comparator (ezetimibe) controlled clinical trial

Study Objectives:

Primary outcome

The change in total hip bone mineral density after 18 months of simvastatin compared with ezetimibe

Secondary outcomes

(1) The changes in bone mineral density over lumbar spine, femoral neck and distal radius after 18 months of simvastatin compared with ezetimibe
(2) The changes in bone turnover markers after 6 months and 18 months of simvastatin compared with ezetimibe
(3) The changes in trabecular bone score after 18 months of simvastatin compared with ezetimibe

Study Design: Prospective 18-month double-blind 1:1 randomized controlled trial

Study Methodology: This study aims to recruit 240 patients, with 120 in the treatment arm (simvastatin) and 120 in the active-comparator arm (ezetimibe), for a duration of 18 months.

Study Population:

Inclusion criteria
(1) Chinese women
(2) Aged 50 to 74 years (inclusive)
(3) BMI 15.0 to 37.0 kg/m^2 (inclusive)
(4) Type 2 diabetes with duration of 5 years or less: diagnosed based on American Diabetes Association criteria: fasting glucose ≥7.0 mmol/L, 2-hour glucose ≥11.1 mmol/L on 75-gram oral glucose tolerance test, or HbA1c ≥6.5%
(5) Postmenopausal: confirmed with the last menstrual period >12 months by the time of recruitment into the study

Exclusion criteria
(1) Entry HbA1c >8.5%;
(2) On thiazolidinedione;
(3) Baseline LDL-cholesterol >3.0 mmol/L, triglyceride >5.0 mmol/L, or known familial hypercholesterolaemia;
(4) History of hip and/or clinical vertebral fractures;

(5) Osteoporosis by BMD criteria on DXA;
(6) On anti-osteoporosis therapy within the prior 2 years;
(7) Evidence of secondary causes of osteoporosis including Cushing's syndrome, acromegaly, thyrotoxicosis, primary hyperparathyroidism, metabolic bone diseases (e.g. osteomalacia), and systemic glucocorticoid treatment;
(8) Evidence of documented ASCVD, which includes previous acute coronary syndrome, stable angina, coronary revascularization, stroke and transient ischaemic attack and peripheral arterial disease;
(9) On lipid-lowering therapy within the prior 2 years;
(10) Known contraindications to statin therapy including allergy, intolerance and significant liver function abnormality (alanine aminotransferase level >3 times upper limit of normal);
(11) Significant diabetic complication(s): pre-proliferative / proliferative diabetic retinopathy, diabetic maculopathy, overt proteinuria, estimated glomerular filtration rate (eGFR) <30 mL/min;
(12) Inability to give an informed consent

Study Assessments:

Primary Assessments: BMD measurements at baseline and 18-month
Secondary Assessments: bone turnover markers and trabecular bone scores at baseline and 18-month
Safety Assessments: Liver function test and creatine kinase measurements at baseline, 3-month, 6-month, 12-month and 18-month

Statistical Analyses

Sample size calculation

General Statistical Methodology

Sample size calculation is performed with R package (1). According to the study on the impact of lovastatin on TH BMD by Safaei et al. (2), a difference in BMD change over 18-month study period between lovastatin-treated and control groups was 0.098 g/cm2 for TH, with a pooled standard deviation of 0.13 g/cm^2. The estimated effect size of TH BMD change over the 18-month study period is 0.75 (95% CI: 0.2-1.3). Assuming the lower CI for the estimated effect size of 0.2, the study would require a sample size of 96 in each group (i.e. total sample size of 192), to achieve 90% power and a level of significance of 5%, for declaring that simvastatin is superior to the active comparator at a 0.02 g/cm2 margin of superiority. To ensure an analysis size of 96 individuals, an overall sample size of 120 individuals per treatment arm will be recruited, anticipating a drop-out rate of approximately 20%.

Timelines:

Study duration: 18 months
Timeline:
(1) First patient in: Quarter 2, 2022
(2) Last patient in: Quarter 3, 2023
(3) Last patient out: Quarter 4, 2024

(4) Estimated enrolment duration: 15 months
(5) Estimated treatment duration: 18 months
(6) Database lock planned date: Quarter 4, 2024
(7) Estimated time of completion of data analysis: Quarter 1, 2025

Schedule of Visits

	Screening (-4 wks)	V1 (Baseline, Day 0)	V2 (3 month)	V3 (6 month)	V4 (12 month)	V5 (EOS, 18 month)
Visit Type	**Clinic**	**Clinic**	**Clinic**	**Clinic**	**Clinic**	**Clinic**
Window period	**--**	**-4 weeks**	**±7days**	**±7days**	**±7days**	**±7days**
Informed Consent	**x**					
Anthropometric parameters						
Body height & weight	**X**					**X**
Body composition (BIA)		**x**				**X**
Waist & hip circumference		**x**				**x**
Blood pressure		**x**	**X**	**x**	**X**	**X**
Blood tests						
A1c, FG	**x**		**x**	**x**	**x**	**x**
Liver & Renal function test	**x**		**x**	**x**	**x**	**x**
Lipid profile	**x**		**x**	**x**	**x**	**x**
Calcium, phosphate	**x**		**x**	**x**	**x**	**x**
Creatine kinase	**x**		**x**	**x**	**x**	**x**
25OHD		**X**	**X**			
PTH		**X**				
Bone turnover markers		**X**		**X**		**x**
Biomarkers		**X**		**X**		**x**
DXA	**x**					**x**
Randomization		**X**				

	Screening (-4 wks)	V1 (Baseline, Day 0)	V2 (3 month)	V3 (6 month)	V4 (12 month)	V5 (EOS, 18 month)
Visit Type	**Clinic**	**Clinic**	**Clinic**	**Clinic**	**Clinic**	**Clinic**
Window period	**--**	**-4 weeks**	**±7days**	**±7days**	**±7days**	**±7days**
Treatment allocation		**X**				
Concomitant medications	**x**	**x**	**x**	**x**	**x**	**x**
AE / SAE		**x**	**x**	**x**	**x**	**x**
Medication compliance			**x**	**x**	**x**	**x**

Background

Bone fragility in type 2 diabetes: the global burden

Osteoporosis is characterized by poor bone strength due to reduced bone density and impaired bone quality. It is clinically silent until complications of fragility fractures occur. Globally around 200 million people are affected by osteoporosis, and 8.9 million fractures occur every year (3). Among the fragility fractures, hip and vertebral fractures are associated with significant morbidity and mortality (3). The operational definition of osteoporosis is based on measurement of bone mineral density (BMD) by dual-energy x-ray absorptiometry (DXA), which has been shown to predict fracture risks. Apart from BMD measurement, there are a number of well-recognized clinical risk factors of osteoporosis adopted in the fracture probability assessment tool (FRAX), including age, sex and body mass index (BMI) (3). Indeed, fragility fractures do not only occur in patients with osteoporosis, but also with osteopenia, a state of low bone density, which is also prevalent and associated with a significant health care burden (4). Hence, prevention and treatment of osteoporosis is important.

Type 2 diabetes is also a major global health issue with a prevalence of around 10% in Hong Kong, affecting about 450 million people worldwide (5). People with type 2 diabetes have higher fracture risks, including a 1.4-fold increase in hip fracture risk (6–8), and worse post-fracture complications (9). Paradoxically, BMD in type 2 diabetes is similar or even higher than non-diabetes (6,7). Hence, there is an excess of diabetes-specific fracture risk not captured by BMD. It is not only related to cardiometabolic risk factors in type 2 diabetes (10), but it is also contributed by bone fragility in type 2 diabetes due to defects in bone quality. Various bone structural characteristics among individuals with type 2 diabetes have been described, such as greater cortical porosity, smaller cortical area and decreased bone material strength (11). Bone material quality is maintained through bone remodelling, a process consisting of bone resorption and formation. It is shown that in type 2 diabetes, both bone resorption and bone formation are attenuated, in contrast to postmenopausal osteoporosis where the predominant pathophysiology is accelerated bone resorption (11). Trabecular bone score (TBS) is an indirect index reflecting this bone quality, which can be easily derived from DXA-based lumbar spine image. TBS has been demonstrated to capture more of the diabetes-specific fracture risk (12).

Bone fragility in type 2 diabetes, also known as ‘diabetic bone disease’, is increasingly recognized as a diabetic complication (13). With an aging population, diabetes and osteoporosis are becoming more prevalent, so is 'diabetic bone disease' (14,15).

The pleotropic effect of statin on bone

Statins, 3-hydroxy 3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, play an essential role in the management of type 2 diabetes, significantly reducing risks of cardiovascular events (16). The pleiotropic bone effects of statins have been well described, with the lipophilic statins, particularly simvastatin and atorvastatin, being the most investigated statins associated with beneficial results (17). Statins exert their anabolic effects on the bone by differentiating mesenchymal cells to osteoblasts via upregulating BMP-2 and protecting the osteoblasts from apoptosis (17). Moreover, they may reduce osteoclastogenesis by inhibiting osteoclastic differentiation, via scavenging reactive oxygen species (18). In view of the anabolic effect of statins on bone, studies have evaluated its use in type 2 diabetes, a condition

associated with reduced bone formation and resorption.

Statin and bone density in type 2 diabetes: work done by others

Only a few longitudinal studies have evaluated the impact of statin therapy on BMD among individuals with type 2 diabetes. A retrospective observation study of 69 patients with type 2 diabetes showed that statin-treated patients (n=36) had BMD improvement over femoral neck after a mean interval of 15 months (19). In contrast, among the 33 patients in the control group, BMD loss over lumbar spine was observed. In this retrospective study, both men and women were included, and patients were treated with different statins (lovastatin, pravastatin and simvastatin) at different dosages. Subsequently, a non-randomized trial involving 122 patients with type 2 diabetes (20), divided into treatment (n=59) and control (n=63) groups according to their baseline use of statin (pravastatin or simvastatin both at 10mg/day), showed that patients who continued statin therapy had a smaller annual decrease in distal radius BMD than those who were not on statin, over 2 years. In that study, BMD was measured only over distal radius but not over other conventional sites such as lumbar spine and hip. Moreover, most patients in the treatment group were already on statin for at least 6 months before the start of study. Nonetheless, it was noted that there was no significant difference in the baseline characteristics including the cholesterol levels, suggesting that the influence on BMD is not mediated through lowering of cholesterol levels, but possibly the direct effect on bone. A subsequent open-label study focused on 55 postmenopausal women with type 2 diabetes (2), where treatment and control group assignment was based on entry LDL-cholesterol levels. Patients with LDL-cholesterol >3.4mmol/L were treated with lovastatin and anti-diabetic treatments while those with LDL-cholesterol ≤3.4mmol/L received the usual anti-diabetic treatments without statin. Baseline BMD was comparable between the two groups. After 18 months, there was a significant improvement in BMD over femoral neck and total hip, and a non-significant improvement in BMD over lumbar spine. In that study, there was a 3.9% placebo-corrected difference in BMD gain over femoral neck, and 2.5% placebo-corrected BMD gain over total hip. It has been shown in a meta-regression of published trials of osteoporosis treatments that these BMD gains of 2-4% could potentially translate to a 20-30% reduction in hip fracture risks (21). Although all these existing studies suggest benefits of statins on BMD, several issues limited their applicability, including the non-randomized study design, lack of associated bone turnover marker measurements, and potential confounders such as vitamin D status. Hence, further clarifications of the effect of statin on BMD with a randomized trial incorporating these factors associated with BMD are necessary to support the use of statin for bone health in type 2 diabetes.

Bone health in type 2 diabetes: the potential role of statin – work done by us

In a retrospective analysis of a Chinese cohort of 5469 individuals, we demonstrated that patients with type 2 diabetes had a higher incidence of hip fractures (3.01 per 1000 person-years), compared to individuals without diabetes (1.36 per 1000 person-years) upon a median follow up of 7 years (age- and sex-adjusted p = 0.017) (8). Moreover, we have shown in a cross-sectional study of 358 Chinese postmenopausal women that those with type 2 diabetes (n=100) had higher BMD over lumbar spine (0.914 vs 0.853 g/cm^2, p<0.001) and over total hip (0.888 vs 0.857 g/cm^2, p=0.014) but lower TBS (1.262 vs 1.282, p=0.032), compared with the non-diabetes control (n=258), along with lower bone formation and resorption markers (22). Results suggest that 'diabetic bone disease' is also present among Chinese postmenopausal women with type 2 diabetes, consistent with Caucasian studies.

Our group has recently carried out a territory-wide retrospective analysis evaluating the impact of statin therapy on the risk of incident hip fractures among Chinese individuals with type 2 diabetes aged ≥60 years, using the electronic health records in Hong Kong. Individuals who had undergone diabetic complication screening between 2008 and 2012 were included (the index date) and observed for incident hip fractures during follow-up. In order to evaluate the impact of statin initiation on fracture risk, individuals with statin exposure before the index date were excluded. The cumulative duration of statin exposure was recorded for each statin user. Marginal structural Cox model (MSM) with inverse probability treatment weighting (IPTW) was used to calculate the hazard ratio (HR) of incident hip fractures for statin users compared with non-users. Adjustments were also made for a list of demographics, comorbidities and diabetic complications. In this analysis, statin use was the time-varying exposure, while LDL-cholesterol levels and the presence of cardiovascular disease during follow-up were the time-varying confounding factors. To reduce the time-window bias, in the main model, we considered only the 'statin users' whose statin was initiated within one year after the index date. We repeated the analyses after inclusion of all individuals who had statin initiated at any time after the index date. In total, 85170 individuals were included (43014 statin users; 42156 non-users). (**Table 1**) Simvastatin accounted for 95% of the statin prescriptions. During a median follow-up of 7.0 years, 3502 incident hip fractures were observed. In MSM with IPTW, statin users had a reduced risk of incident hip fractures, compared to statin non-users (adjusted hazard ratio 0.71, 95% CI 0.61-0.82, p<0.001). A greater risk reduction was observed with a longer duration of statin use. (**Table 2**) Similar results were observed when including all statin users. These protective effects were consistent across categories of age, body mass index, HbA1c, estimated glomerular filtration rate and duration of diabetes, except among men and individuals with diabetes duration ≥20 years. (**Figure 1**) Our study showed that statin use was associated with a lower incidence of hip fractures in older individuals with type 2 diabetes, particularly postmenopausal women, in a duration-dependent manner.

Rationale

In view of the favourable results in this territory-wide analysis particularly in postmenopausal women with type 2 diabetes, we will initiate a double-blind randomized controlled trial to study the effect of statin on BMD among postmenopausal women with type 2 diabetes. In the two prospective studies of effect of statin on BMD in type 2 diabetes (2,20), low-intensity statin was employed – pravastatin 10mg/day, simvastatin 10mg/day, or lovastatin 20mg/day. In our territory-wide analysis mentioned above, simvastatin accounted for 95% of the statin prescription. Hence, simvastatin is chosen as the statin in this study. To address the potential

ethical issue of leaving hypercholesterolaemia in patients with type 2 diabetes untreated, the active comparator arm will be treated with ezetimibe, which does not have known effect on bone. Simvastatin 10mg/day can lower LDL-cholesterol by 20-30% (23), whereas ezetimibe 10mg/day is associated with 20% of LDL-cholesterol reduction (16). The subjects of interest in our proposed study are patients with recent diagnosis of type 2 diabetes without established atherosclerotic cardiovascular diseases (ASCVD) or significant diabetic complications, because patients with type 2 diabetes with long duration of diabetes, diabetic complications, or established ASCVD require more intensive lipid-lowering therapy according to 2019 European Society of Cardiology (ESC) guideline (16). As the target LDL-cholesterol is <2.6 mmol/L for uncomplicated type 2 diabetes, entry LDL-cholesterol levels ≤3.0 mmol/L will ensure the target LDL-cholesterol be met for patients in either arm of the trial.

Study Objectives

Hypothesis

We hypothesize that treatment with simvastatin can improve BMD among postmenopausal women with type 2 diabetes after 18 months.

Primary outcome

The change in TH BMD after 18 months of simvastatin compared with ezetimibe

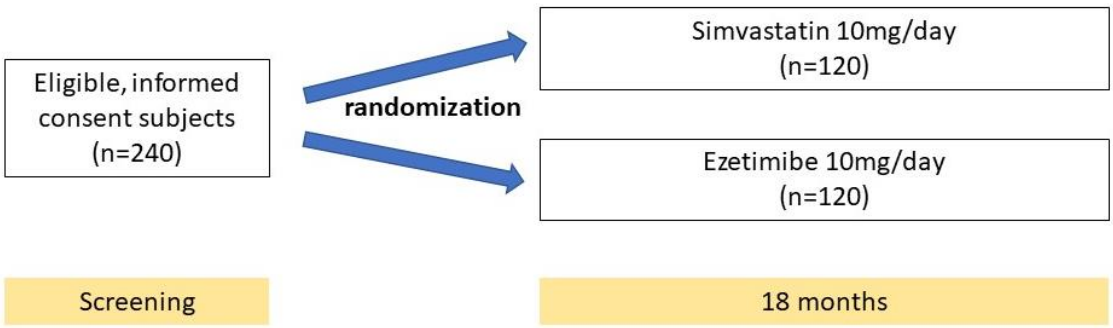
Secondary outcomes

(1) The changes in BMD over LS, FN and distal radius after 18 months of simvastatin compared with ezetimibe
(2) The changes in bone turnover markers after 6 months and 18 months of simvastatin compared with ezetimibe
(3) The changes in TBS after 18 months of simvastatin compared with ezetimibe

Study Design

Overview of the study design

This will be an 18-month double-blind randomized controlled trial to evaluate the effect of simvastatin on BMD among post-menopausal women with type 2 diabetes, compared to ezetimibe (the active comparator).



Duration of the study

The planned duration of the study is 18 months. The first patient will be recruited in Quarter 2 of 2022 and the last patient will be recruited in Quarter 2 of 2023.

Study Population

Subjects who meet all the inclusion criteria and do not meet any of the exclusion criteria are eligible to enrol in the study.

Inclusion criteria

(1) Chinese women
(2) Aged 50 to 74 years (inclusive)
(3) Type 2 diabetes with duration of 5 years or less: diagnosed based on American Diabetes Association criteria: fasting glucose ≥7.0 mmol/L, 2-hour glucose ≥11.1 mmol/L on 75-gram oral glucose tolerance test, or HbA1c ≥6.5%
(4) Postmenopausal: confirmed with the last menstrual period >12 months by the time of recruitment into the study

Exclusion criteria
(1) Entry HbA1c >8.5%;
(2) On thiazolidinedione;
(3) Baseline LDL-cholesterol >3.0 mmol/L, triglyceride >5.0 mmol/L, or known familial hypercholesterolaemia;
(4) History of hip and/or clinical vertebral fractures;
(5) Osteoporosis by BMD criteria on DXA;
(6) On anti-osteoporosis therapy within the prior 2 years;
(7) Evidence of secondary causes of osteoporosis including Cushing's syndrome, acromegaly, thyrotoxicosis, primary hyperparathyroidism, metabolic bone diseases (e.g. osteomalacia), and systemic glucocorticoid treatment;
(8) Evidence of documented ASCVD, which includes previous acute coronary syndrome, stable angina, coronary revascularization, stroke and transient ischaemic attack and peripheral arterial disease;
(9) On lipid-lowering therapy within the prior 2 years;
(10) Known contraindications to statin therapy including allergy, intolerance and significant liver function abnormality (alanine aminotransferase level >3 times upper limit of normal);
(11) Significant diabetic complication(s): pre-proliferative / proliferative diabetic retinopathy, diabetic maculopathy, overt proteinuria, estimated glomerular filtration rate (eGFR) <30 mL/min;
(12) Inability to give an informed consent

Interventions

Eligible participants will be randomly allocated 1:1 to 18 months of simvastatin 10mg/day or ezetimibe 10mg/day.

Simvastatin

Simvastatin is one of the hydroxymethylglutaryl (HMA) CoA reductase inhibitors. Lipid lowering with simvastatin has been shown to be beneficial for primary and secondary prevention of coronary heart disease in patients with dyslipidaemia.
Common side effects include muscle-related (around 5%) and abnormal liver function (0.5 – 3.0%). The muscle-related side effects are usually mild. These include myalgias, myopathy, myositis, and muscle injury. Severe myonecrosis leading to clinical rhabdomyolysis is rare, affecting 0.1% of patients (24). Most of the events of abnormal liver function are mild. Severe liver derangement only occurs in 0.1% (25).

Ezetimibe

Ezetimibe is a cholesterol absorption inhibitor that impairs dietary and biliary cholesterol absorption at the brush border of the intestine. It is effective in lowering LDL-cholesterol (26). Ezetimibe is well-tolerated (26).

Study Assessments

All participants will undergo clinical and biochemical assessments at baseline of the trial as detailed below. Participants will be seen by an endocrinologist at baseline and subsequent follow-up visits at 3, 6, 12 and 18 months respectively. The assessment schedule is summarized in Table 3.

Clinical and biochemical assessments

Participants will attend a clinical assessment session at baseline after an overnight fast for at least 8 hours. Demographic data and medical history will be obtained using a standardized questionnaire. Personal and family history of fragility fractures (spine, hip, humerus, wrist and ankle) will be recorded. Important clinical risk factors of osteoporosis will be evaluated, including smoking, drinking, family history of fragility fractures, parental history of hip fractures, prior use and duration of hormonal replacement therapy, and levels of physical activity. The levels of physical activity will be assessed through the International Physical Activity Questionnaire (IPAQ). Daily calcium intake will be assessed using a semi-quantitative questionnaire (27). Body weight, body height and blood pressure (BP) will be measured. Hypertension is defined as BP ≥140/90 mmHg or the use of antihypertensive medications.

Fasting blood will be drawn for plasma glucose, HbA1c, insulin, lipid profile, albumin, calcium, phosphate and creatinine levels. eGFR was calculated by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation. Serum 25-hydroxyvitamin D (25OHD) levels will be measured with enzyme immunoassays (Immunodiagnostic Systems) with a sensitivity of 17.0 nmol/L, and intra- and inter-assay coefficients of variation (CV) of 1.9-3.7% and 3.7-11.6% respectively. Patients with 25OHD levels <50 nmol/L will be given additional cholecalciferol 1000 units/day for 8 weeks followed by reassessment of 25OHD to ensure repletion (28).

Blood will be stored in aliquots at −70°C for assays of biomarkers. Bone turnover markers will be measured. Serum carboxy-terminal cross-linked telopeptide of type 1 collagen (CTX) levels will be measured with enzyme immunoassays (Immunodiagnostic Systems), while serum level of amino-terminal propeptides of type 1 collagen (P1NP) will be measured with Elecsys® total P1NP, an electrochemiluminescence immunoassay (Roche Diagnostics). The assay for CTX has a sensitivity of 0.02 ng/mL, an intra-assay precision of 1.7-3.0%, and an inter-assay precision of 2.5-10.9%. The assay of P1NP has a sensitivity of 5 ng/mL, intra-assay precision of 1.0-1.7%, and inter-assay precision of 2.0-4.4%.

Bone health assessment: BMD and TBS measurements, FRAX and TBS-adjusted FRAX

BMD at the lumbar spine (LS), femoral neck (FN), total hip (TH) and distal radius will be

measured with a dual-energy x-ray absorptiometry (DXA) machine (Hologic QDR 4500, Waltham, MA, USA). The *in vivo* precision values for the BMD at the LS, FN and TH are 0.8, 0.9 and 0.7%, respectively. All BMD measurements will be performed by an operator who has received training by the equipment manufacturers and has accreditation by the International Society for Clinical Densitometry (ISCD). TBS will be measured with TBS iNsight™ version 3.0.2.0, using the lumbar spine DXA image.

The Hong Kong version of FRAX will be used to calculate the 10-year probability of fractures with the online tool. For each participant, four 10-year probability scores will be generated: (i) major osteoporosis fracture (MOF) with BMD, (ii) MOF with BMD, adjusted for TBS; (iii) hip fracture with BMD, and (iv) hip fracture with BMD, adjusted for TBS.

Follow-up visits

During each follow-up visits, participants will have fasting blood tests checked for liver and renal function tests, creatine kinase, calcium and phosphate, fasting glucose, HbA1c and lipid profile.

Glycaemic control will be managed according to the standard of care. During follow-up visits, tolerance to lipid-lowering therapy will be assessed. Persistent elevation of liver enzymes (alanine aminotransferase and aspartate aminotransferase) to >3 times the upper limit of normal, increase in CK with clinical signs and symptoms of muscle involvement, or drug intolerance will be excluded from the trial.

During follow-up visits, participants may have changes in clinical conditions and thus be indicated for anti-osteoporosis therapy, or higher-intensity statin. Those who develop incident hip or vertebral fractures, or osteoporosis, and thus require anti-osteoporosis therapy, will be excluded from the trial. Those who develop incident ASCVD, and thus require higher intensity statin, will also be excluded from the trial.

At the end of the study (18-month visit), both P1NP and CTX will be reassessed, and 3-site DXA will be repeated.

Study Procedures and Assessments

Screening Procedures

Patients will be recruited from medical out-patient clinics, mainly from the primary health care clinics, in the Hong Kong West Cluster of the Hong Kong Hospital Authority. Consecutive participants who fulfil the inclusion and exclusion criteria are invited to participate in this randomized controlled trial after obtaining informed consent.

Treatment Plan

Eligible participants will be randomly allocated 1:1 to 18 months of simvastatin 10mg/day or ezetimibe 10mg/day. The computer-generated sequence will be supplied by the study statistician, independent of the investigators. To facilitate double-blinding, placebo tablets with the same shapes as simvastatin 10mg and ezetimibe 10mg, respectively, are produced by Europharm Laboratories Co. Ltd. During the entire 18-month study period, participants in the

simvastatin arm will take one simvastatin 10mg-tablet and one placebo tablet with the shape of ezetimibe 10mg each day. On the other hand, participants in the ezetimibe arm will take one ezetimibe 10mg-tablet and one placebo tablet with the shape of simvastatin 10mg each day. All participants will also receive supplements of elemental calcium 400 mg/day and cholecalciferol 1000 units/day during the entire 18-month study period.

The treatment plan includes regular medical monitoring, regular blood tests, and clinical follow-up visits.

Withdrawal from study

Patients are informed orally and in writing that they are free to withdraw their participation in the study without bias or prejudice. A patient who decides to stop all therapeutic interventions will be followed by the clinical team for the usual medical care. The date of withdrawal and reason for discontinuation, if known, will be recorded in the medical record.
We will make every effort to re-contact the patient, to identify the reason why he/she failed to attend the visit and to determine his/her health status, including at least his/her vital status. Attempts to contact such patients will be documented in the patient's record (e.g. times and dates of attempted telephone contact, receipt for sending a registered letter). Patients who did not complete the study visits and for whom no endpoint data are available will be considered as lost to follow-up. The statistical analysis plan will specify how these patients will be analyzed. Patients who have been withdrawn from the registry cannot be re-included.

Protocol Deviations

Protocol deviations are defined as any instance in which the patient or clinical team does not perform scheduled activities/tasks such as missed visits and missed tests and evaluations. Protocols deviations will be reported on the patient's chart.

Statistical Analyses

All statistical analyses will be performed with using R package or IBM® SPSS® version 26. Data will be presented as mean±SD, 95% confidence interval (CI), median with 25^{th}–75^{th} percentile, and number with percentage as appropriate.

All analyses described in this section will be performed based on intention-to-treat analysis and repeated for the per-protocol analysis. Data not normally distributed will be logarithmically transformed before analysis. Between-group comparisons are done with t-test or Mann-Whitney U test for continuous data, and chi-square or Fisher exact test for categorical variables. Two-sided p-value <0.05 will be considered statistically significant.

Baseline demographics and anthropometric parameters (age, BMI), laboratory parameters (HbA1c, LDL-cholesterol, serum creatinine), bone health assessment (BMD, TBS, bone turnover markers, FRAX score), clinical risk factors of osteoporosis, family history of fragility

fractures (partly reflecting involvement of genetics in bone health), and concomitant medications (various classes of anti-hypertensives and anti-diabetic agents) will be compared between simvastatin and ezetimibe arms.

If applicable, adjustments for covariates may be employed in Analysis of Covariance (ANCOVA). Any adjustments will be pre-specified in the description of the analysis.

BMD change over the 18-month period will be calculated for each participant. The BMD change over LS, FN, TH and distal radius from baseline will be the dependent variable in the ANCOVA model. The treatment comparison will be derived by testing the contrast (difference in least squares mean) between the two arms. TBS change over the 18-month period will be calculated. The TBS change from baseline will be the dependent variable in the ANCOVA model. The treatment comparison will be derived by testing the contrast between the two arms. P1NP and CTX will be analysed based on the ratio of the 6-month/end-of-study value relative to baseline using natural logarithm ($\log_e$) transformation. The transformation of $\log_e$ ratio of end-of-study vs. baseline value will be used to normalize the distribution of the biochemical marker parameters. Each biochemical marker will be analysed using the ANCOVA approach. The relative treatment effect defined as the exponential of the least square mean difference in $\log_e$ ratio between two treatment groups will be presented along with its 95% CI.

Sample size calculation

Sample size calculation is performed with R package (1). According to the study on the impact of lovastatin on TH BMD by Safaei *et al.* (2), a difference in BMD change over 18-month study period between lovastatin-treated and control groups was 0.098 g/cm^2 for TH, with a pooled standard deviation of 0.13 g/cm^2. The estimated effect size of TH BMD change over the 18-month study period is 0.75 (95% CI: 0.2-1.3). Assuming the lower CI for the estimated effect size of 0.2, the study would require a sample size of 96 in each group (i.e. total sample size of 192), to achieve 90% power and a level of significance of 5%, for declaring that simvastatin is superior to the active comparator at a 0.02 g/cm^2 margin of superiority. To ensure an analysis size of 96 individuals, an overall sample size of 120 individuals per treatment arm will be recruited, anticipating a drop-out rate of approximately 20%.

Adverse events and serious adverse events

The principal investigator will monitor and record all clinical and laboratory evidence of adverse events (AEs) occurred in any subject as defined in this section throughout the study. Each adverse event must be assessed and recorded for its severity grade, its causality with the study medications, its duration of persistence and the potential to constitute a serious adverse event (SAE) as defined in section. All adverse events will be followed by the principal investigator to a satisfactory conclusion.

Definition of an Adverse Event

An adverse event is any untoward medical occurrence, all episodes of abnormal findings, subjective and objective symptoms of disease, intercurrent illness and accidents in a subject during the study, which does not necessarily have a causal relationship with any study medication.
Such an event can therefore be any unfavourable or unintended sign (including an abnormal laboratory finding), symptom, reaction or disease (new or exacerbated) that is associated in time with participation in the study or the use of the study medications, whether or not the event is related to the study or the study medications, or is expected.

Adverse Event Severity

Each adverse event should be graded for severity as defined below:
Mild: The adverse event is transient and easily tolerated by the subject.
Moderate: The adverse event causes the subject discomfort and interrupts the subject's usual activities.
Severe: The adverse event causes considerable interference with the subject's usual activities and may be incapacitating or life threatening.

Adverse Event Causality

Each adverse event should be assessed for its causality with the study medications as defined below.
Not related: A causal relationship between the study medications and the AE is not a reasonable possibility.
Related: A causal relationship between the study medications and the AE is a reasonable possibility. The investigator must further qualify the degree of certainty as "possible" or "probable."
An adverse event classified as "related" to a study medication is referred to as an adverse drug reaction (ADR).

Definition of a Serious Adverse Event

A serious adverse event (SAE) is defined as any of the following untoward medical occurrence:
Results in Death: An event, which results in the death of a subject.
Life-Threatening: An event that, in the opinion of the principal investigator, would have resulted in immediate fatality if medical intervention had not been taken. This does not include an event that would have been fatal if it had occurred in a more severe form.
In-patient Hospitalization: An event that results in an admission to the hospital for any length of time. This does not include an emergency room visit or admission to an out subject facility.
Prolongation of Hospitalization: An event, which occurs while the study subject, is hospitalized and prolongs the subject's hospital stay.
Congenital Anomaly: An anomaly detected at or after birth or any anomaly that results in foetal loss.
Persistent or Significant Disability /Incapacity: An event, which results in a condition that substantially, interferes with the activities of daily living of a study subject. Disability is not intended to include experiences of relatively minor medical significance such as headache, nausea, vomiting, diarrhoea, influenza, and accidental trauma (e.g., sprained ankle).

Reporting of Adverse Events and Serious Adverse Events

Adverse events and serious adverse events need to be reported to the institutional review board overseeing this study (i.e. The University of Hong Kong / Hospital Authority Hong Kong West Cluster Institutional Review Board, HKU/HA HKW IRB) and the local regulatory agency (i.e. the Hong Kong Department of Health, DOH) according to their respective requirements. The following table summarized the reporting requirements and timeframes:

Reporting to DOH	Reporting to HKU/HA HKW IRB
Serious & Unexpected ADRs: ● Fatal or life threatening: Within 7 calendar days* ● Non-fatal or non-life threatening: Within 15 calendar days* Non-Serious or Expected ADRs: ● Summary ADR report on completion of study	All SAEs: ● Fatal or life threatening: Within 7 calendar days* ● Non-fatal or non-life threatening: Within 15 calendar days*

* Remark: All the timeframes are from the time of first awareness of the events by the principal investigator and/or his study team.

Data quality assurance

This is an investigator-initiated study. The principal investigator and the study team will be responsible for ensuring that the study is conducted in compliance with this protocol and the study data collected are verified against the relevant source documents.

Ethics and Administrative Procedures

Institutional Review Board (IRB)

The ICH-GCP requires that all clinical studies be overseen by institutional review boards established and operated according to the ICH-GCP.
The HKU/HA HKW IRB will be responsible for ethical oversight of this study. This protocol, any subsequent protocol amendment, the informed consent form and any other form of study information to be provided to the subjects must be submitted for review and approved by the HKU/HA HKW IRB before they can be used in the study.
In addition, the principal investigator should report to the HKU/HA HKW IRB any significant event according to its requirements, including (but not limited to) the following:
1) Any deviation from or change to the protocol to eliminate immediate hazards to any subject;

2) Any change to the study that increases the risk to the subjects and/or affects significantly the conduct of the study;

3) Any serious adverse event or new information that may affect adversely the safety of the subjects or the conduct of the study.

Ethical Conduct of the Study

The principal investigator must assure that this study will be conducted in accordance with the protocol, the ICH-GCP, ethical principles that have their origin in the Declaration of Helsinki, the requirements of the HKU/HA HKW IRB and all applicable local regulations.

Subject Information and Informed Consent

Subjects' participation in the study is voluntary. Informed consent should be given freely and obtained from every subject prior to study participation.
Subject information and informed consent form (ICF) must be written in a language fully comprehensible to the prospective subjects. The ICF shall be reviewed and approved by the IRB and regulatory body before conducting any consent process.
The principal investigator and/or his/her delegate will explain the ICF point by point to each

subject (or his/her legally authorized representatives, if applicable) and answer all questions raised by the subject regarding the study. Prior to the performance of any study-related screening procedure on the subject, the ICF must be reviewed, signed and dated by the subject (or his/her legally authorized representatives, if applicable) and confirmed by the person who administered the informed consent process.
If a subject is illiterate, an impartial witness should be present during the entire informed consent process. Afterward, both the subject and the impartial witness should sign and date the ICF along with the person who administered the informed consent process.
A copy of the ICF must be given to the subject (or his/her legally authorized representatives, if applicable). The original fully-endorsed ICF will be kept in the investigator's study binder.

Clinical Trial Insurance

HKU is maintaining a no-fault master clinical trial insurance coverage for investigator-initiated clinical studies conducted under HKU. Coverage under that master insurance policy will be arranged through the Clinical Trials Centre of HKU. The study will not be initiated until the insurance coverage is confirmed.

Regulatory Affairs

This study will be carried out in compliance with the applicable local regulations. The principal investigator will be responsible for submitting an application for and obtaining a Certificate for Clinical Trial through the Hong Kong Department of Health before the initiation of the study.

Confidentiality of Subjects' Personal Data

Subjects' privacy is protected under the Personal Data (Privacy) Ordinance (Chapter 486 of the laws of Hong Kong).
Permission for direct access to a subject's data will be sought in writing by the principal investigator and/or his study team from the subject as part of the informed consent process. This gives permission to the principal investigator, his study team and other authorized bodies to collect, review, process, analyze, verify, store and reproduce the subjects' personal data for the purposes of the study. Any party (e.g. local regulatory authority, IRB members and relevant HKU personnel) with direct access to the subject data must take all reasonable precautions within the constraints of the applicable regulatory requirements to maintain the confidentiality of the subjects' identities and personal information.

Retention of Study Records

All study documentation pertaining to the study must be archived by the principal investigator in a secure place after completion or termination of the study until retention is deemed unnecessary.

Publication

All data, results, information, reports, analyzes, opinions and documents generated from the study shall be the sole and exclusive property of the principal investigator and The University of Hong Kong. The principal investigator should have the right to publish or disclose the results and data generated from this study provided that the privacy of the subjects are properly protected.

Completion or Termination of Study

Upon completion of the study, the principal investigator is responsible to provide a summary of the study's outcome in the format of final report to the HKU/HA HKW IRB and the DOH following study closure.
If the study is prematurely terminated, the principal investigator will inform the HKU/HA HKW IRB and the DOH of the termination and the reason(s) for the action.

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