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João Batista da Silveira Júnior

EFEITO DOS ANTI-HIPERTENSIVOS LISTADOS NO PROGRAMA FARMÁCIA POPULAR (SUS) NA REMODELAÇÃO ÓSSEA: uma revisão sistemática da literatura

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Dissertação apresentada ao Programa de Pós-graduação em Odontologia, da Pontifícia Universidade Católica de Minas Gerais, como requisito parcial para obtenção do título de Mestre em Odontologia - Área de Concentração: Clínicas Odontológicas – Área Temática: Ortodontia.
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Orientador: Prof. Dr. Ildeu Andrade Júnior
Coorientadora: Profa. Vânia Eloísa de Araújo Silva

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“*Caiu a chuva, transbordaram os rios, sopraram os ventos e deram contra aquela casa, e ela não caiu, porque tinha seus alicerces na rocha*.” (**Mateus 7:25)**

RESUMO

A hipertensão arterial sistêmica (HAS) é a enfermidade cardiovascular mais frequente na população e uma importante questão de saúde pública no Brasil e no mundo. No Brasil, o Programa Farmácia Popular (PFP), criado pelo Governo Federal Brasileiro para os usuários do Sistema Único de Saúde (SUS), disponibiliza anti-hipertensivos de forma gratuita à população. Entretanto, a ação dos anti-hipertensivos pode extrapolar o sistema cardiovascular e tem sido relacionada a outros nichos fisiológicos, como o tecido ósseo. O objetivo desta revisão sistemática, foi investigar os efeitos dos anti-hipertensivos disponíveis no PFP na remodelação óssea avaliando a qualidade das evidências científicas existentes em estudos em animais. Foi realizada uma busca nas bases de dados eletrônicas MEDLINE via PubMed, Web of Science™ Core Collection, Scopus® e EMBASE, sem restrição de data ou idioma. Também foi realizada uma busca manual nas referencias dos artigos elegíveis e em um periódico especializado, a revista BONE. Foram localizados estudos experimentais controlados, in vivo, correlacionando os efeitos dos anti-hipertensivos captopril, hidroclorotiazida, enalapril, losartana e propranolol com a remodelação óssea. Uma síntese narrativa foi realizada com as características e resultados dos estudos. Os dados levantados foram coletados e avaliados conforme critérios previamente estabelecidos. A análise de qualidade dos estudos incluídos foi realizada através da ferramenta Syrcle para risco de parcialidade. Vinte e dois estudos foram selecionados envolvendo os anti-hipertensivos listados no PFP. A maioria dos estudos mostraram níveis de evidência de alto risco de parcialidade. O anti-hipertensivo captopril mostrou ter efeito de regulação negativa e positiva na remodelação óssea dependendo do tipo de modelo de doença empregado. A hidroclorotiazida aumentou a concentração sérica de cálcio. O enalapril não apresentou efeitos significativos sobre a remodelação óssea. A losartana e o atenolol apresentaram um efeito osteoprodutor e reduziram a ação osteoclástica. O propanol em baixas concentrações mostrou efeitos protetivos em relação a reabsorção óssea. Embora a qualidade da evidência tenha sido considerada baixa, levantando reservas sobre a força das recomendações relevantes, os resultados desta revisão sistemática mostram que é preciso considerar as possíveis implicações relacionadas ao uso de anti-hipertensivos disponíveis no PFP e a remodelação óssea. Portanto, os estudos com baixo risco de parcialidade desta revisão, envolvendo o uso do propranolol e captopril, podem indicar uma linha terapêutica a ser observada na prática clínica relacionada aos usuários destes anti-hipertensivos.

Palavras-chave: Remodelação óssea; Anti-Hipertensivos; Técnicas de movimentação dentária; Efeitos fisiológicos de drogas.

ABSTRACT

Systemic arterial hypertension (SAH) is the most common cardiovascular disease around the world and an important public health issue as well. In Brazil, the Popular Pharmacy Program (PPP), created by the Brazilian Federal Government for users of the Unified Health System (UHS), provides antihypertensive drugs at no cost to the entire population. However, the action of antihypertensive drugs can go beyond the cardiovascular system and it has been related to other physiological niches, such as the bone tissue. The objective of this systematic review of animal research was to investigate the effects of the antihypertensive drugs available in the PFP on bone remodeling by assessing the quality of the scientific evidence of these studies. A search was performed in the electronic databases MEDLINE via PubMed, Web of Science ™ Core Collection, Scopus® and EMBASE, without restriction of date or language. A manual search was also carried out in the references of eligible articles and in the peer-reviewed medical jornal Bone. In vivo controlled experimental studies were found, correlating the effects of the antihypertensive drugs captopril, hydrochlorothiazide, enalapril, losartan and propranolol with bone remodeling. A narrative synthesis was carried out with the characteristics and results of the studies. The data were collected and evaluated according to previously established criteria. The quality analysis of the included studies was performed using the Syrcle tool for risk of bias. Twenty-two studies were selected involving the antihypertensive drugs listed in the PFP. Most studies have shown levels of evidence of high risk of bias. The antihypertensive captopril has been shown to have a negative and positive regulation effect on bone remodeling depending on the type of disease model employed. Hydrochlorothiazide increased the serum calcium concentration. Enalapril had no significant effect on bone remodeling. Losartan and atenolol had an osteoproductive effect and reduced osteoclastic action. Propanol in low concentrations showed protective effects in relation to bone resorption. Although the quality of the evidence was considered low, which raised reservations about the strength of the relevant recommendations, the results of this systematic review show that it is necessary to consider the possible implications related to the use of the antihypertensive drugs available in PFP in the bone remodeling process. Therefore, the studies with a low risk of bias in this review, involving the use of propranolol and captopril, may indicate a line of therapy to be observed in clinical practice related to users of these antihypertensives.

Keywords: Bone remodeling; Anti-hypertensive drugs; Tooth movement techniques; Physiological effects of drugs.

LISTA DE QUADROS

LISTA DE SIGLAS E ABREVIATURAS

ANG II	Angiotensina II
AT1R	Receptor de angiotensina I
ATC	Anatômica Terapêutica Química
ATR2	Receptor de angiotensina II
COL 1	Colágeno tipo I
CTXIA	Telopeptídeo C-terminal do tipo colágeno 1- Biomarcador para osteólise
ECA 1	Enzima de conversão de angiotensina 1
ECA 2	Enzima conversora de angiotensina 2
ECRS	Ensaios clínicos randomizados
IL-1 β	Interleucina – 1 beta
IL-10	Interleucina 10
IL-6	Interleucina 6
LILACS	Ciências da Saúde da América Latina e do Caribe
MASR	Mitochondrial assembly receptor (receptor de angiotensina) - Outro tipo de receptor de angiotensina, um receptor *Mas*.
MDO	Movimentação Dentária Ortodôntica
MEDLINE	Sistema de Análise e Recuperação de Literatura Médica Online
OPG	Osteoprotegerina
PFP	Programa Farmácia Popular
PGE2	Prostaglandina E2
PICO	Anagrama P: population/população; I: intervention/intervenção; C: control/controle; O: outcome/desfecho
PNAF	Política Nacional de Assistência Farmacêutica
PNM	Política Nacional de Medicamentos
PROSPERO	Registro Prospectivo Internacional de Revisões Sistemáticas

RANKL	Ligante do receptor ativador do fator nuclear kappa B
RENAME	Relação Nacional de Medicamentos Essenciais
RUNX2	Fator de transcrição 2 relacionado ao *runt*
SCOPUS	Maior banco de dados de resumos e citações da literatura revisada por pares: revistas científicas, livros e anais de congressos. É o maior banco de dados de resumos e citações da literatura com revisão por pares: revistas científicas, livros, processos de congressos e publicações do setor.
SOST	Gene responsável pela expressão da esclerotina.
SYRCLE	Centro de Revisão Sistemática para Experimentação de Animais de Laboratório
TNF	Fator de necrose tumoral

SUMÁRIO

1 INTRODUÇÃO

A hipertensão arterial sistêmica (HAS) é uma condição clínica multifatorial caracterizada pela pressão arterial continuamente elevada, acompanhada de possíveis alterações metabólicas, hormonais, hipertrofia cardíaca e/ou vascular (WHELTON *et al.*, 2018). A HAS é resultado do aumento de tônus da musculatura lisa dos vasos periféricos, o que leva ao aumento da resistência arteriolar e redução da capacidade do sistema venoso (EGAN, 2013). Ela é a enfermidade cardiovascular mais frequente em todo o mundo e uma importante questão de saúde pública no Brasil (BENJAMIN *et al.*, 2019). Idade, gênero, etnia, fatores socioeconômicos, ingestão de sal, obesidade, uso de bebidas alcoólicas e o sedentarismo estão relacionados ao risco de desenvolvimento da HAS (GEORGIOPOULOU; KALOGEROPOULOS; BUTLER, 2012; GRAUDAL; HUBECK-GRAUDAL; JURGENS, 2012). A prevalência da HAS é elevada e aumenta em faixas etárias maiores. Estima-se que 40% dos acidentes vasculares encefálicos e em torno de 25% dos infartos ocorridos em pacientes hipertensos poderiam ser prevenidos com terapia anti-hipertensiva adequada (RADOVANOVIC *et al.*, 2014).

O tratamento da HAS pode ser feito através de alterações no estilo de vida como: redução do peso corporal, restrição ao consumo de sódio, redução consumo de bebidas alcóolicas, restrição ao tabagismo e por aumento das atividades físicas. Quando as mudanças de hábitos não são suficientes para controle da pressão arterial, utiliza-se a terapia com fármacos anti-hipertensivos (GEORGIOPOULOU; KALOGEROPOULOS; BUTLER, 2012). Estes fármacos atuam sob a resistência periférica e/ou débito cardíaco (RADOVANOVIC *et al.*, 2014). A terapêutica medicamentosa foca na redução da morbidade e mortalidade do indivíduo hipertenso (BENJAMIN *et al.*, 2019).

A ação dos anti-hipertensivos pode ser: diurética; bloqueadora adrenérgica; bloqueadora de canais de cálcio; vasodilatadora direta; inibidora da ECA (enzima conversora da angiotensina) e bloqueadora dos receptores AT1 da angiotensina II (SCIARRETTA *et al.*, 2011; VERDECCHIA *et al.*, 2008).

Os anti-hipertensivos diuréticos exercem sua ação através da eliminação de líquidos e sal pela urina (ROUSH; SICA, 2016). Os bloqueadores adrenérgicos controlam a frequência de contração cardíaca (CRUICKSHANK, 2016). Já os bloqueadores de canais de cálcio causam um efeito sistêmico de vasodilatação

arterial com consequente redução da pressão arterial (TAMARGO; RUILOPE, 2016). Os vasodilatadores diretos proporcionam o relaxamento da musculatura lisa vascular agindo sobre os canais de cálcio na membrana plasmática (MCCOMB; CHAO; NG, 2016). Os Inibidores da ECA reduzem a carga cardíaca e, consequentemente, a pressão arterial, atuando principalmente nos rins, no miocárdio e no cérebro (HELMER; SLATER; SMITHGALL, 2018). E por fim, os bloqueadores dos receptores da angiotensina, que agem bloqueando os receptores AT1 da angiotensina II, reduzindo a ação deste potente vasoconstritor (SALVADOR *et al.*, 2017).

O sistema de saúde pública brasileiro, denominado Sistema Único de Saúde (SUS), possui em seu programa mecanismos de ação que envolvem o acesso gratuito a esses medicamentos, que é regulamentado através da Política Nacional de Medicamentos (PNM), da Política Nacional de Assistência Farmacêutica (PNAF), da Política de Medicamentos Genéricos e do Programa Farmácia Popular (PFP) (VIEIRA, 2010).

Para a regulamentação e controle das medicações disponibilizadas pelo SUS existe a Relação Nacional de Medicamentos Essenciais (RENAME) (NASCIMENTO *et al.*, 2017). Os medicamentos listados na RENAME são selecionados com base em prioridades nacionais de saúde, na segurança, em eficácia terapêutica comprovada, na qualidade e na disponibilidade dos produtos. Os anti-hipertensivos estão agrupados na RENAME no tópico Relação Nacional de Medicamentos por Classificação Anatômica Terapêutica Química (ATC), subitem C, Aparelho Cardiovascular (NASCIMENTO *et al.*, 2017). Um importante subgrupo desta relação contida no RENAME é a lista dos Anti-hipertensivos fornecidos pelo PFP. Este último subgrupo é composto pelos anti-hipertensivos mais consumidos pela população em geral, visto que são os medicamentos disponibilizados pelas farmácias públicas vinculadas ao SUS (BOING *et al.*, 2013; MENGUE *et al.*, 2016). O PFP disponibiliza os seguintes anti-hipertensivos: Diuréticos (Hidroclorotiazida), bloqueadores adrenérgicos (Atenolol e Propranolol), inibidores de ECA (Captopril e Enalapril) e antagonistas dos receptores de angiotensina (Losartana) (SILVA; CAETANO, 2015).

Entretanto, a ação dos anti-hipertensivos pode extrapolar o sistema cardiovascular e tem sido relacionada a outros nichos fisiológicos, como o tecido ósseo (DE OLIVEIRA *et al.*, 2014; ORSOLINI; BERTOLDI; ROSSINI, 2020). Na remodelação óssea, o controle dos osteclastos e osteblastos acontece por fatores sistêmicos ou locais. A ação de medicamentos pode interferir em vários momentos

da mediação inflamatória que conduz a remodelação óssea. Sendo assim, qualquer medicação que altere a fisiologia da remodelação óssea poderá alterar também a regeneração de fraturas, o tratamento de doenças ósseas e a movimentação dentária ortodôntica (MDO) (BOYCE; XING, 2008; ROBERTS; HUJA; ROBERTS, 2004; SODEK; MCKEE, 2000).

Estudos experimentais têm mostrado a interferência da ação dos anti-hipertensivos na remodelação óssea. Os diuréticos, especialmente os do grupo tiazida, afetam o metabolismo do cálcio reduzindo a excreção deste mineral na urina e aumentando sua reabsorção no túbulo renal distal. Isto eleva a concentração sérica de cálcio. Estudos mostram que a administração crônica dos diuréticos tiazídicos pode ser acompanhada de aumento da densidade óssea em humanos (ARRABAL-MARTÍN *et al.*, 2016). Os bloqueadores adrenérgicos Atenolol e Propranolol atuam em receptores beta-adrenérgicos, pré e pós-sinápticos, reduzindo a pressão arterial primordialmente pela diminuição de débito cardíaco e redução de tônus simpático. A administração sistêmica de β-agonistas resulta em diminuição da formação óssea em camundongos, enquanto a administração de propranolol, um β-bloqueador não seletivo, tem efeitos opostos (DE OLIVEIRA *et al.*, 2014). Além disso, outros estudos sugerem que o uso de betabloqueadores está associado a um risco reduzido de fraturas e pode superar a perda de massa óssea na pós-menopausa (SCHLIENGER *et al.*, 2004). Os inibidores da enzima conversora de angiotensina (ECA), a exemplo do captopril e o enalapril, interferem no sistema renina-angiotensina bloqueando a conversão de angiotensina I em angiotensina II (BROULÍK *et al.*, 2001). Estudos em animais revelam que a ação local do sistema renina-angiotensina pode estar envolvida em alterações esqueléticas associadas à idade, nefropatia obstrutiva e diabetes tipo 1 (ZHANG, Yan *et al.*, 2017; BABALYAN *et al.*, 2019). A relação deste sistema com o processo de cicatrização de fraturas em modelo animal de camundongo também tem sido reportada (ZHANG, Wei *et al.*, 2011). Existe também a relação dos inibidores de ECA com inibição da diferenciação dos osteoblastos in vitro (LIU *et al.*, 2011). Entre os antagonistas dos receptores de angiotensina, o PFP fornece a losartana. Este medicamento, pela ação da angiotensina II, é capaz de alterar o metabolismo ósseo através dos receptores de angiotensina localizados em osteoblastos e osteoclastos (MOURA *et al.*, 2016). A losartana também pode interferir no metabolismo ósseo através do fluxo sanguíneo capilar da medula óssea (KOKLINA *et al.*, 2015).

Para o clínico é de fundamental importância o conhecimento de todos os fatores que podem alterar a fisiologia óssea, porque alterações na remodelação óssea podem afetar diretamente a cicatrização de fraturas, lesões ósseas e a MDO (MOURA *et al.*, 2016; LIN *et al.*, 2017). Outro fato muito relevante para se conhecer a ação de anti-hipertensivos na fisiologia óssea é a facilidade do acesso a tais medicações pela população brasileira, pois estes anti-hipertensivos são cedidos gratuitamente pelo SUS (SILVA; CAETANO, 2015).

Como o consumo crônico dos anti-hipertensivos é elevado tanto pela alta morbidade da HAS, quanto pela facilidade de acesso ao medicamento (BOING *et al.*, 2013), e uma grande parcela da população está passando por alguma intervenção médica ou odontológica que demande um fisiológico processo de remodelação óssea (GHAFARI *et al.*, 2019), cabe aos profissionais de saúde dessas áreas, a responsabilidade de buscar na literatura embasamento científico para respaldar sua atuação e suas decisões clínicas referentes aos usuários de anti-hipertensivos.

2 OBJETIVOS

2.1 Objetivo geral

Revisar sistematicamente as evidências científicas descritas pela literatura quanto aos efeitos dos anti-hipertensivos contidos no PFP (Atenolol, Captopril, Enalapril, Hidroclorotiazida, Losartana, Propranolol) sobre a remodelação óssea.

2.2 Objetivos específicos

a) Avaliar os efeitos do atenolol, captopril, hidroclorotiazida, enalapril, losartana e propranolol na remodelação óssea;
b) Resumir os resultados dos estudos selecionados e avaliar o nível de evidência dos possíveis efeitos dos anti-hipertensivos na remodelação óssea.

3 MATERIAL E MÉTODOS

3.1 Protocolo e registro

Esta pesquisa foi desenvolvida de acordo com o protocolo Prisma-P (Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols) Checklist 2015 (MOHER *et al.*, 2016).

Esta revisão sistemática foi registrada na base de dados PROSPERO da National Institute of Health Research Database (www.crd.york.ac.uk/prospero), sob o protocolo CRD42019117888.

3.2 Critérios de elegibilidade

Os critérios de elegibilidade foram baseados no Acrônimo PICO: População, Intervenção, Comparação e Desfechos (Outcomes) aplicado a esta revisão assim como a pergunta da revisão: Quais são os efeitos dos anti-hipertensivos listados no PFP sobre a remodelação óssea de animais experimentais? (Quadro 1).

Quadro 1- Pergunta estruturada para elaboração da Revisão Sistemática.

P	População	Animais
I	Intervenção	Uso de anti-hipertensivos listados no PFP (Hydrochlorothiazida, Atenolol, Propranolol, Captopril, Enalapril, Losartana).
C	Comparação	Remodelação óssea em animais que não estejam sob efeito de anti-hipertensivos.
O	Desfecho (*Outcome*)	Alterações na remodelação óssea evidenciadas por avaliações bioquímicas/biomoleculares, histológicas, morfométricas e imaginológicas.

Fonte: Elaborado pelo autor

3.2.1 Critérios de inclusão

a) Estudos realizados em animais que incluam pelo menos um grupo experimental e um grupo controle ou *sham*;
b) Administração sistêmica ou local de anti-hipertensivos disponíveis no PFP que possam interferir nos processos fisiológicos do osso.
c) Descrição da dosagem e administração dos regimes terapêuticos;
d) Descrição da técnica de mensuração das alterações na remodelação óssea.

3.2.2 Critérios de exclusão

a) Tipo de estudo: outros desenhos de estudo que não correlacionem medicações à movimentação ortodôntica, remodelação óssea e fisiologia do osso alveolar. Revisões descritivas também serão excluídas do estudo, assim como estudos “in vitro”.
b) Tipo de intervenção: testes de anti-hipertensivos que não estejam relacionadas diretamente a remodelação óssea e MDO.
c) Estudos com resultados parciais, estudos pilotos, estudos que não possuam o texto completo;

3.3 Fontes de informação

A coleta de trabalhos foi conduzida através da busca de estudos cujos registros estavam idexados nas bases de dados MEDLINE via PubMed (http://www.ncbi.nlm.nih.gov/PubMed), Web of Science™ Core Collection (http://apps.webofknowledge.com/), Scopus®, EMBASE; sem restrição de idioma ou data.

Para validação da busca eletrônica uma busca manual foi realizada nas referências de todos os estudos potencialmente elegíveis. Outra busca manual foi realizada no periódico mais frequente entre os trabalhos encontrados, relacionado ao tecido ósseo e sua fisiologia, a revista BONE (Cell Molecular Biology; Pathophysiology; Treatment) até o ano 2019. A busca por estudos na literatura cinzenta foi feita no banco de teses e dissertações do portal da Coordenação de

Aperfeiçoamento de Pessoal de Nível superior (CAPES) (http://www.capes.gov.br/servicos/banco-de-teses).

3.4 Busca

A estratégia de busca foi desenvolvida usando palavras-chave apropriadas. Várias combinações de termos foram utilizadas na pesquisa de acordo com os parâmetros de busca de cada base eletrônica de dados. Uma busca mais abrangente foi realizada contemplando a lista de anti-hipertensivos da RENAME e posteriormente foi aplicada uma restrição apenas aos fármacos de distribuição gratuita do PFP.

A estratégia de busca realizada no Pubmed está detalhada no anexo 1. A estratégia desenvolvida para o Medline via PubMed serviu como parâmetro para as buscas nos demais bancos de dados. Os estudos encontrados nos bancos de dados eletrônicos foram alocados em uma única base com o intuito de excluir duplicatas através do programa computacional EndNote (Clarivate Analytics).

3.5 Seleção de estudos

Os estudos encontrados pelas ferramentas eletrônicas de busca foram reunidos em uma única base para tabulação e exclusão dos estudos duplicados. Artigos e resumos da pesquisa foram examinados para excluir estudos irrelevantes. O processo de seleção dos artigos foi realizado por dois revisores independentes (J.B.S.J e D.S.P).

A seleção dos estudos recuperados nas buscas foi realizada em duas fases, por dois revisores independentes, que incluem a análise de títulos, resumos e textos completos. As discordâncias foram resolvidas por discussão ou envolvendo um terceiro revisor até que o consenso fosse alcançado.

Os textos completos dos estudos potencialmente elegíveis foram recuperados e examinados cuidadosamente em conformidade com os critérios de elegibilidade e de forma independente pelos dois revisores. Os desacordos foram resolvidos por um terceiro revisor (V.E.A).

3.6 Processo de coleta de dados e itens coletados

A extração de dados foi realizada por dois revisores independentes (J.B.S.J e D.S.P). Os dados foram extraídos de textos, figuras, tabelas e / ou gráficos. Os dados coletados foram: número de grupos experimentais, tipos de grupos controle, número de animais por grupo, randomização dos animais e dos experimentos. Todas as espécies, sexos, pesos, idades e todos os modelos de remodelação óssea. Agentes de medicamentos, classes e doses, tempo de administração e frequência, e suas interferências na remodelação óssea. Maior detalhamento da coleta está disponível no protocolo PROSPERO da revisão (www.crd.york.ac.uk/prospero), CRD42019117888.

3.7 Avaliação do risco de parcialidade e análises adicionais

O risco de parcialidade para estudos experimentais em animais foi mensurado pela ferramenta desenvolvida pelo grupo SYRCLE (Hooijmans *et al* 2014).

A avaliação de parcialidade ocorreu nos seguintes domínios: víes de seleção, viés de desempenho, viés de detecção, viés de atrito, viés de relatório e outros vieses. Após análise foi emitido uma classificação de parcialidade para cada tipo de viés analisado: "baixo risco" de parcialidade, "alto risco" de parcialidade ou "risco incerto" de parcialidade.

A qualidade metodológica dos estudos individuais foi avaliada de acordo com os critérios da ferramenta CAMARADES (MACLEOD *et al* 2004*)*. A avaliação foi realizada por dois revisores independentes. As discordâncias foram resolvidas por envolvendo um terceiro revisor.

3.8 Síntese de resultados

Foi realizada uma síntese narrativa das características e resultados dos estudos incluídos, estruturados em torno do tipo de anti-hipertensivo, desenho de estudo, tipo de animal utilizado, modelo de doença simulado, dosagem, tempo do experimento, métodos de avaliação e resultados dos experimentos.

4. ARTIGO CIENTÍFICO

Effect of antihypertensives on bone remodeling: a systematic review of the literature

Será submetido ao periódico **BONE Cell Molecular Biology; Pathophysiology; Treatment** (Qualis: A1).

As normas para submissão encontram-se no endereço https://ees.elsevier.com/bone/

EFFECT OF ANTIHYPERTENSIVES ON BONE REMODELING: a systematic review of the literature

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Abstract

Systemic arterial hypertension (SAH) is the most common cardiovascular disease around the world and an important public health issue as well. In Brazil, the Popular Pharmacy Program (PPP), created by the Brazilian Federal Government for users of the Unified Health System (UHS), provides antihypertensive drugs at no cost to the entire population. However, the action of antihypertensive drugs can go beyond the cardiovascular system and it has been related to other physiological niches, such as the bone tissue. The objective of this systematic review of animal research was to investigate the effects of the antihypertensive drugs available in the PFP on bone remodeling by assessing the quality of the scientific evidence of these studies. A search was performed in the electronic databases MEDLINE via PubMed, Web of Science ™ Core Collection, Scopus® and EMBASE, without restriction of date or language. A manual search was also carried out in the references of eligible articles and in the peer-reviewed medical jornal Bone. In vivo controlled experimental studies were found, correlating the effects of the antihypertensive drugs captopril, hydrochlorothiazide, enalapril, losartan and propranolol with bone remodeling. A narrative synthesis was carried out with the characteristics and results of the studies. The data were collected and evaluated according to previously established criteria. The quality analysis of the included studies was performed using the Syrcle tool for risk of bias. Twenty-two studies were selected involving the antihypertensive drugs listed in the PFP. Most studies have shown levels of evidence of high risk of bias. The antihypertensive captopril has been shown to have a negative and positive regulation effect on bone remodeling depending on the type of disease model employed. Hydrochlorothiazide increased the serum calcium concentration. Enalapril had no significant effect on bone remodeling. Losartan and atenolol had an osteoproductive effect and reduced osteoclastic action. Propanol in low concentrations showed protective effects in relation to bone resorption. Although the quality of the evidence was considered low, which raised reservations about the strength of the relevant recommendations, the results of this systematic review show that it is necessary to consider the possible implications related to the use of the antihypertensive drugs available in PFP in the bone remodeling process. Therefore, the studies with a low risk of bias in this review, involving the use of propranolol and

captopril, may indicate a line of therapy to be observed in clinical practice related to users of these antihypertensives.

Key-words: Bone remodeling; Anti-hypertensive drugs; Tooth movement techniques; Physiological effects of drugs.

INTRODUCTION

Rationale

Systemic arterial hypertension is the most common cardiovascular disease throughout the world and an important public health issue as well (1). It is estimated that 40% of strokes and 25% of infarctions in hypertensive patients could be prevented with adequate antihypertensive therapy (2-4).

The action of antihypertensive drugs can be: diuretic, adrenergic blocker, calcium channel blocker, direct vasodilator, inhibitor of ACE (angiotensin-converting enzyme) and blocker of angiotensin II AT1 receptors (5-7).

The Brazilian public health system, called Sistema Único de Saúde (SUS), has a free distribution program for antihypertensive drugs. This is a process conducted by the National Medicines Policy (PNM), the National Pharmaceutical Assistance Policy (PNAF), the Generic Medicines Policy and the Popular Pharmacy Program (PFP) (8).

For the regulation and control of medications made available by SUS, there is the National List of Essential Medicines (RENAME) (9). RENAME contains the list of antihypertensive drugs provided by PFP. These antihypertensive drugs are the most consumed by the population and are the drugs distributed at no cost by public pharmacies linked to SUS (10). PFP provides diuretic antihypertensive drugs (hydrochlorothiazide), adrenergic blockers (atenolol and propranolol), ACE inhibitors (captopril and enalapril) and angiotensin receptor antagonists (losartan) (11,12).

However, the action of antihypertensive drugs can extrapolate the cardiovascular system and can affect other physiological sites such as the bone tissue (13,14). The effects of medications can interfere with various points of inflammatory mediation within bone remodeling (15,16). Therefore, any medication that alters the physiology of bone remodeling can also alter fracture regeneration, treatment of bone diseases and orthodontic tooth movement (OTM) (17-19).

Experimental studies have shown the interference of the action of antihypertensive drugs in bone remodeling (20). Diuretics, especially those in the thiazide group, affect calcium metabolism by reducing the excretion of this mineral in the urine and increasing its reabsorption in the distal renal tubule (21). Studies show that the chronic administration of thiazide diuretics can be accompanied by increased bone density in humans (21,22). Systemic administration of β-agonists results in decreased bone formation in mice, while administration of propranolol, a non-selective β-blocker, produces opposite effects (13). The use of β-blockers is also

associated with a reduced risk of fractures and may prevent bone loss in postmenopausal women (23). Angiotensin-converting enzyme (ACE) inhibitors, such as captopril and enalapril, interfere with the renin-angiotensin system by blocking the conversion of angiotensin I to angiotensin II (24). Animal studies show that the local action of the renin-angiotensin system is involved in skeletal changes associated with age, obstructive nephropathy and type 1 diabetes (25,26). Among angiotensin receptor antagonists, PFP provides losartan. This drug, due to the action of angiotensin II, alters bone metabolism through angiotensin receptors located in osteoblasts and osteoclastos (16,27). Losartan can also interfere with bone metabolism through bone marrow capillary blood flow (25).

Knowledge of all the factors that can alter bone physiology is very important. Another very relevant fact to know the action of antihypertensive drugs in bone physiology is the great access to such medications by the Brazilian population (26,28).

Objective

The aim of this review was to systematically investigate and assess the quality of available evidence on the effects of antihypertensive drugs listed in PFP on bone remodeling.

METHODS

Protocol and registration

This review was developed according to the Prisma-P protocol (Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols) Checklist 2015 (29) and registered in the PROSPERO database of the National Institute of Health Research Database (www.crd.york.ac.uk/prospero), under the protocol CRD42019117888.

Eligibility criteria

The eligibility criteria were based on the Acronym PICO: Population, Intervention, Comparison and Outcomes applied to this review as well as the question of the review: What are the effects of antihypertensive drugs listed in the PFP on bone remodeling of experimental animals? (Chart 1).

Inclusion criteria

a) Animal studies that include at least one experimental group and a control or sham group;
b) Systemic or local administration of antihypertensive drugs available in PFP that may interfere with bone physiological processes;
c) Description of the dosage and administration of the therapeutic regimens;
d) Description of the technique for measuring changes in bone remodeling.

Exclusion criteria

a) Type of study: other study designs that do not correlate medications with bone remodeling. Descriptive reviews will also be excluded from the study, as well as “in vitro” studies;
b) Type of intervention: antihypertensive tests that are not directly related to bone remodeling and OTM;
c) Studies with partial results, pilot studies, studies that do not have the full text;

Information sources

The search for studies was conducted in the MEDLINE databases via PubMed (http://www.ncbi.nlm.nih.gov/PubMed), Web of Science™ Core Collection (http://apps.webofknowledge.com/), Scopus®, EMBASE; without language restriction and without publication date limit.

A manual search was carried out in the references of all potentially relevant studies and in the peer-reviewed medical jornal BONE (Cell Molecular Biology; Pathophysiology; Treatment), year 2019. The search for studies in the gray literature was done in bank of theses and dissertations from the portal of the Coordenação de Aperfeiçoamento de Pessoal de Nível superior (CAPES), http://www.capes.gov.br/servicos/banco-de-teses.

Search

The search strategy was developed using appropriate keywords. Various combinations of terms were used in the search according to the search parameters of each electronic database. A more comprehensive search was carried out covering the list of anti-hypertensive drugs from RENAME (National List of Essential

Medicines - SUS, Brazil) and subsequently a restriction was applied only to drugs that are freely distributed in PFP. The search strategy carried out is detailed in ANNEX 1. The strategy developed for Medline via PubMed was the basis for searches in other databases. The studies found in the electronic databases were allocated on a single basis to exclude duplicates through the computer program EndNote (Clarivate Analytics).

Study selection

Research articles and abstracts were examined to exclude irrelevant studies. The article selection process was carried out by two independent reviewers (J.B.S.J and D.S.P). The full texts of the potentially eligible studies were retrieved and carefully examined in accordance with the inclusion and exclusion criteria and independently by the two authors. Disagreements were resolved by a third reviewer (V.E.A).

Data collection process

The studies found by the electronic search tools were gathered on a single basis for tabulation and exclusion of duplicate studies.

Data collection was carried out in two phases, by two independent reviewers, which included the analysis of titles, abstracts and full texts. Disagreements were resolved by discussion or involving a third reviewer until consensus was reached.

Data items

The data were extracted from the text, figures, tables and / or graphics. The questions collected were: number of experimental groups, control groups, number of animals per group, species, sex, weight, age, simulated diseases, randomization of animals, randomization of experiments, bone remodeling models, type of antihypertensive, dosages, frequency of administration and assessment methods.

Risk of bias in individual studies

The risk of bias for experimental animals studies was carried out by the system proposed by the SYRCLE’s risk of bias tool (30). After analysis, a bias classification was issued for each type of bias analyzed: "low risk" of bias, "high risk"

of bias "uncertain risk" of bias. The methodological quality of the individual studies was assessed according to the criteria of the CAMARADES's tool (31).

Synthesis of results

A narrative synthesis of the characteristics and results of the included studies was carried out, structured around the type of antihypertensive agent, type of study, study design, type of animal used, simulated disease model, dosage, time of the experiment, evaluation methods and results of experiments.

RESULTS

Study selection

Initial search identified 326 references without duplicates. After restriction to PFP drugs, 273 references resulted without duplicates. 250 articles were excluded after analyzing the titles and abstracts. The main causes of exclusion were studies not in animals and the non-use of antihypertensive drugs listed in the PFP. Among the 23 remaining works, one was excluded (32) because it did not have a full text (there was no possibility of access to the author because the evaluated abstract did not have contact details). Finally, 22 studies were included in the systematic review. Figure 1 shows the Prisma flowchart for this review.

Study characteristics

The period of publication of the articles was 29 years (1991 to 2020). The studies evaluated 1260 animals, being rats or mice. The types of induced conditions in the rats were: osteoporosis (22,25,33-39), arterial hypertension (22,24,27,40-42), OTM (13,16,43), nutritional changes (44,45), osteolysis induced by foreign body reaction (46) and diabetes mellitus (47). One study did not induce any specific condition in animals (24). The follow-up time of the experiments varied between 10 and 168 days. The methods for evaluating the results were: macroscopic morphometric analysis (42), histological analysis by optical microscopy (routine histology, immunohistochemistry, immunofluorescence) (16,22,25,27,33-36,38-41,44-48), biochemical analyzes (serological and mineral research) (24,27,33,34,36,38,40,46,47), biomolecular analyzes (ELISA method, Western-Blot and RT-PCR) (13,16,36,39,44,46,47), imaging methods (radiography, cone beam tomography, micro tomography) (24,27,35,38,39,46,47) and quantity of OTM (linear

measurements through microscopy,imaging software or cone beam computed tomography) (13,16,43). Regarding the antihypertensive drugs listed in the PFP: 11 studies (45.45%) evaluated propranolol (13,34-38,40,43-45,48), five (19.04%) losartan (16,24,25,27,41), three (13.63%) captopril (39,46,47), two (9.09%) hydrochlorothiazide (22,33), one (4.54%) enalapril (42), one (4.54%) evaluated enalapril and losartan separately (24). One (4.54%) study evaluated atenolol and propranolol separately (43). (Table 1).

Risk of bias within studies

According to the evaluation of the SYRCLE risk assessment tool in animal research, only three studies (14.0%) obtained a low risk of bias (13,47,48). These studies showed random allocation and data blinding during the stages of the experiment. However, these studies did not report whether there were changes in the experimental or control groups throughout the experiment. Seven studies (36.36%) were classified as of unclear risk (16,27,34,36,44-46). The scarcity of methodological information was the main reason for this classification. 12 studies were classified as high risk of bias (52.38%) (22,24,25,33,35,37-43). The lack of details in relation to the domains of random sequence generation, allocation blinding and evaluator blinding contributed to the classification of high risk of bias (Table 3).

Results of individual studies

Studies involving hydrochlorothiazide did not show significant effects on bone resorption markers, but in a model of osteoporosis induced by parathyroid hormone, the diuretic had a protective effect on bone tissue (22,33).

Atenolol, 0.1 mg/kg/day, presented a positive stimulus for osteoblasts, an inhibitory effect for osteoclasts and a reduction in the OTM rate on the compression side. Increased OPG expression and reduced expression of RANKL and sclerotin have also been observed (43).

Propranolol also showed an osteoblast stimulating and osteoclast inhibitor effect regardless of the model used. However, this effect was only observed in low doses of the antihypertensive (up to 0.10 - 10.0 mg/kg/day). High doses (above 10.0 - 50.0 mg/kg/day) did not show significant effects for bone resorption or for positive regulation of osteoblasts (13,34,35,38,40,43-45,48). Propranolol (0.10 mg/kg/day) also showed effects of reduction in the OTM rate in the respective model (13,43).

According to the included studies, the action of captopril (12.5; 25.0; 40.0 and 50.0 mg/kg/day) showed a negative regulatory action for osteoclast action and positive for osteoblasts in models of osteolysis and osteoporosis post-menopause (39,46). However, at a dosage of 10.0 mg/kg/day, in diabetic animals, captopril had an opposite effect on osteoregulation (47).

Enalapril has shown controversial results. One study showed an increase in bone neoformation activity (42) and another no significant difference in bone formation (24).

A study on losartan found no statistically significant difference in the antihypertensive action on osteoblastic action and found a significant increase in RANKL, osteoclast activating molecules (24). However, four studies (16,25,27,41) showed that losartan increases osteoblastic activity (increases in periostin expression, dentin matrix protein, alkaline phosphatase, collagen 1A1, semaphorin 3A3, metalloproteinase, osteoprotegerin, bone volume formed, mineralized surface, bone formation rate) and reduces osteoclastic action (reduction in the number of osteoclasts, TRAP cell count, RANK, RANKL, cathepsin K and metalloproteinase 13 RNA levels). Losartan (10.0 mg/kg/day) also had a reducing effect on the OTM rate in normal rats (16). Details of the individual results can be seen in Table 2.

Risk of bias across studies

Regarding the antihypertensive drug captopril, three studies were included (39,46,47). For the evaluation of this medication in models of diabetes (47), the risk of bias classification was low risk. For models of osteolysis induced by a foreign body (46) the risk of bias was uncertain. In postmenopausal osteoporosis models (39), the risk of bias classification was high risk.

Among the eleven articles included on propranolol (13,34-38,43-45,48), two (13,48) were classified as low risk of bias. One for the hypertension model (48) and the other for OTM (13). The classification of uncertain risk of bias included four articles (34,36,44,45), two in the osteoporosis model (34,36) and two in the nutritional model (44,45). The remaining five studies were classified as high risk of bias (35,37,38,40,43), three in osteoporosis model (35,37,38) and two in arterial hypertension (40,43).

A study related to atenolol was included (43). The study used an OTM model in hypertensive rats and was classified as having a high risk of bias.

For enalapril, two inclusions were made (24,42). Both studies were classified as high risk of bias, one for the hypertension model (42) and the other in normal rats (24).

Regarding losartan, five studies were included (16,24,25,27,41). Two articles were classified as having an uncertain risk of bias, one for the MDO model (16) and one for the hypertension model (27). The other three articles (24,25,41) were classified as high risk of bias, one in normal rats (24), one in an osteoporosis model (25) and one in hypertensive rats (41).

Finally, two inclusions were made for hydrochlorothiazide (22,33) and both (100.0%) obtained a high risk of bias classification. One study using an osteoporosis model (33) and another testing hypertensive rats and postmenopausal osteoporosis (22).

DISCUSSION

Summary of evidence

Antihypertensive drugs are widely prescribed drugs and are widely studied for their hemodynamic and antihypertensive activities. However, there is little information on the effects of this medication on bone remodeling. As well as knowledge of the action of antihypertensives on the treatment of bone diseases, healing of fractures and OTM. The objective of this work was to systematically review, in studies conducted in animals, the effects of anti-hypertensive drugs freely distributed by PFP on bone remodeling (captopril, propanol, enalapril, losartan and hydrochlorothiazide).

Hydrochlorothiazide (2.0 mg/day/animal) increased the serum calcium concentration and did not change the plasma levels of TRCP – phosphatase and creatinine in normal rats (33). This increase is due to the effect of thiazide diuretics in reducing calcium excretion. The increase in serum calcium concentrations may be related to the increase in bone density (21). These results confirm the study in models of hypertensive rats with postmenopausal osteoporosis induction. Hydrochlorothiazide (10.0 mg/kg/day for 2 weeks) prevented bone loss by reducing bone remodeling, mineral apposition, the eroded surface covered by osteoid and the frequency of activation of remodeling. However, in eight weeks of treatment there was no significant difference between the experimental and control groups (22). Even in different disease models, hydrochlorothiazide has been shown to have an osteoprotective effect. However, studies have a high risk of bias.

Atenolol 0.1 mg/kg/day (in OTM model in hypertensive rats) has been shown to have a relevant action on bone remodeling. This medication caused the inhibition of osteoclastic action by reducing the expression of RANKL (43). Another mechanism for reducing bone remodeling presented by atenolol was the reduction of sclerotin expression (SOST), facilitating the bone formation process initiated by mechanotransduction. Atenolol also increased the expression of OPG favoring the action of bone formation by osteoblasts. Through these mechanisms, atenolol showed the ability to reduce the amount of OTM in the hypertensive rat model (43). For this medication the study was classified as high risk of bias due to the absence of data such as randomization of animals, experimental processes and outcome evaluations.

Propranolol in low doses (0.1 - 10.0 mg/kg/day regardless of the animal model used) was the medication where all the studies included were unanimous in reports about changes in bone remodeling tending to greater osteoblastic action, greater bone formation, reduction of osteoclasts, greater mineral deposition, increased bone mass, increased osteocalcin, reduced RANKL expression, sclerotin (SOST), IL-6, IL-1β, IL-10, a-CTX, TNF. All studies reported that high doses of propranolol do not produce the same effects mentioned above and do not significantly alter bone remodeling (13,34-36,38,40,43-45,48). For this drug, one study (13) were rated at low risk of bias in OTM model. For this study, the strength of the evidence was relevant for animal experiments.

In this review captopril proved to be capable of altering bone remodeling. At doses of 12.0 - 40.0 mg/kg/day, the drug had the effect of increasing the expression of positive regulatory factors for osteoblasts (OPG, ACE2; ATR2, MasR) (39,46). This explains the increase in protected bone mass, trabecular and cortical bone augmentation presented in postmenopausal osteoporosis induction models. Captopril also reduced the expression of Ang II, AT1R, ACE1, TNF-α, IL-1β and RANKL, which are regulators of the action of osteoclasts. This justifies the protective effect on bone tissue observed by the study because osteoclastic activity was shown to be reduced (39,46). At doses of 12.5 and 25.0 mg/kg/day, captopril reduced the inflammatory infiltrate, the thickness and the size of the inflammatory membrane caused by osteolysis induced by a foreign body reaction (46). However, this protective effect is not seen in the diabetes induction model (47). In this case captopril (10.0 mg/kg/day) increased the excretion of calcium and phosphorus, increased carbonic anhydrase,

increased the bone surface of osteoclasts and reduced osteoblasts. This demonstrates an increased bone resorption action. Captopril also inhibited the action of osteoblasts through the negative regulation of Col I and RUNX2 (47). In animal models, captopril showed a protective effect for hypertension and induced osteolysis models. However, for the diabetes model, the effect of captopril was to induce bone resorption. In this model, one study (47) was rated at low risk of bias, which for animal studies is a relevant risk classification.

In this systematic review, the evidence found reveals that enalapril (0.4 mg/kg/day in normal rats) increased the urinary excretion of bicyclo-PGE2. Prostaglandins derived from skeletal tissue in rats produce bone resorption while endogenously produced prostaglandins modulate bone resorption (15). This finding could be related to the increase in bone resorption in rats. But the study also showed that the lipoperoxidation marker used was not significantly different between the experimental and control groups. The reported increase in PGE2 was probably mediated by kinins of non-skeletal origin and there were no statistical differences in bone mass, volume and density (24). Another study evaluated the action of enalapril (5.0 mg/kg/day in hypertensive rats) on fractures of the femur. The experimental group showed higher rates of bone regeneration compared to the control (42). However, both studies obtained a high risk of bias.

Losartan administration (2.0 mg/kg/day in normal rats) did not increase the urinary excretion of bicyclo-PGE2 and tramboxane B2. The medication did not cause significant changes in the bone and mineral density of the femur and did not cause any changes in the bone measurements of the femur (24). However, these effects were different from other studies. For losartan 30.0 mg/kg/day in hypertensive rats the report was of increased expression of OC, RANKL, VEGF and PECAM in 7, 14 and 21 days (41). These results contribute to the interpretation of an increased osteoclast action. However, the study reports an intense osteoforming activity. This same study obtained a high risk of bias classification. Losartan 6.0 mg/kg/day in rats, with induction of postmenopausal osteoporosis, showed a protective effect of blood microcirculation in the femur. The drug also had an endothelial protection effect and prevented the reduction in the thickness of the trabecular bone, decreasing the bone remodeling process (25). But this study also has a high risk of bias. For losartan 10.0 mg/kg/day, in an OTM model with normal rats, a reduction in the number of osteoclasts was observed, a reduction in the levels of RANK, RANKL, cathepsin k and

metalloproteinase 13. There was also an increase in the expression of periostin, dentin matrix protein, alkaline phosphatase, collagen 1A1, semaphorin 3A3, osteoprotegerin. These data contribute to changes in bone remodeling with reduced of OTM (16). However, the risk of bias for this study is unclear. With losartan 30.0 mg/kg/day, hypertensive rats showed an increase in bone surface mineralization, a higher rate of bone formation and mineral apposition (27). These data corroborate for the reduction of bone remodeling and are in agreement with the two previous studies, however the classification of risk of bias for this study was unclear.

Limitations

The main limitation of this review is the nature and characteristics of the studies included. The studies included during the methodological process obtained the low risk of bias and moderate methodological quality as the best assessment (Table 4). Most studies were considered to be at high risk of bias because they did not describe or make it clear to the reader which random allocation techniques were used in the studies (32,49). The same is observed with regard to the description of blinding methods for handling the animals, for carrying out the tests and for determining the results (32). The heterogeneity of the study designs and tests applied in the included articles are also points of limitation as they do not allow the realization of a meta-analysis. Another limitation of the evidence is the absence of a description of the use of sample calculation, test power calculation, analysis of agreement between examiners or intra-examiner. Only one study presented a sample size calculation (16) but did not present the other analyzes listed.

A point that cannot be overlooked is that the results obtained in this systematic review refer to studies in animals and, therefore, cannot be directly extrapolated to the effects in humans. The dosage methods used for medications were for short periods of time, not long. In humans, the use of antihypertensive drugs is chronic, leading to this systematic review pointing out the need for studies that better simulate the longevity of the action of these drugs in real clinical situations (20,50).

The evidence found in this systematic review showed different behaviors for different health situations pointing to the need to know the potential actions of captopril, propranolol, enalapril, losartan and hydrochlorothiazide in each clinical situation in daily practice.

For an increasingly growing population of hypertensive patients and chronic users of antihypertensive drugs, well-designed experimental studies are extremely necessary to understand the effects of these medications on bone remodeling. A greater detail of the experimental studies favors a better quality of the works.

Based on the scientific evidence found in this systematic review, it is recommended for future research: 1) initiatives as registration bases for animal study protocols, as well as for randomized clinical studies. 2) Specific guidelines for handling and allocating animals as a way to standardize these practices and provide better conditions for comparison between experimental research on antihypertensives and bone remodeling in animals.

CONCLUSION

Among the antihypertensive drugs provided by PFP, propranolol had a lower risk of bias and demonstrated the effect of increasing osteoblastic activity in models of hypertension and OTM. The evidence for captopril was shown to be of low risk of bias for increased osteoclastic action in models of diabetes. Losartan reduces osteoclastic action and increases osteoblastic function in models of OTM, hypertension and osteoporosis, but the risk of partiality of the evidence is unclear. The evidence for enalapril and hydrochlorothiazide is at high risk for bias and non-consensual results. The strength of the evidence in animal studies is limited but provides guidance for a more cautious assessment of the effects of PFP antihypertensive drugs on bone remodeling.

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Chart 1 – Study guidelines (PICO)

P	Population	Animals.
I	Intervention	Use of antihypertensives listed in the PFP (Hydrochlorothiazide, Atenolol, Propranolol, Captopril, Enalapril, Losartana).
C	Comparison	Bone remodeling in animals not submitted to antihypertensive administration.
O	Outcome	Changes in bone remodeling evidenced by biochemical, biomolecular, histological, morphometric and imagological evaluations.

Figure 1: Flow of records of the reviewing process.

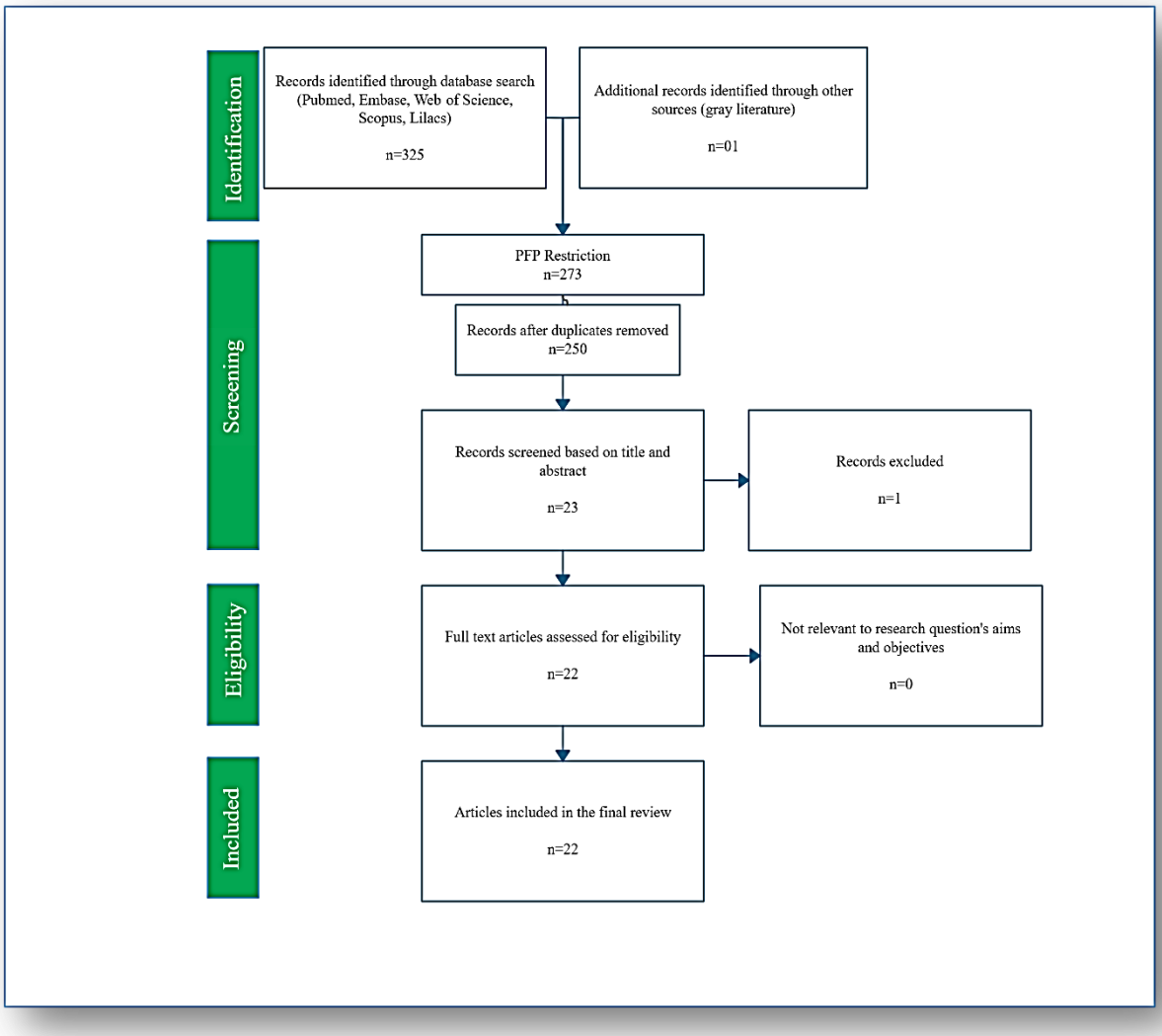

Table 1: Characteristics of included studies (part 01).

Study	**Drug**	**Design**	**N**	**Animal** (features)	**Model**	**Time**	**Control**	**Dosage** (mg/kg/day)
Abuohashisha *et al., 2017*	Captopril	Experimental Controlled	60	Wistar 220-250 g	Osteoporosis	14 weeks	01 sham 01 OVX	40.0
Al-Subaie *et al., 2016*	Propranolol	Experimental Controlled Randomized Blinded	24	Sprague-Dawley Female 10-12 weeks	Hipertension	02 weeks	01 internal	5.00
Babalyan *et al., 2019*	Enalapril	Experimental Controlled	30	Gray, Wistar SHR 9 months 210±30 g	Hipertension	28 days	01 normal Wistar 01 SHR	5.00
Bonnet *et al., 2008*	Propranolol	Experimental Controlled	75	Wistar 34 weeks Female OVX	Osteoporosis	10 weeks	01 Sham	0.10 5.00 20.0
Bonnet *et al., 2006*	Propranolol	Experimental Controlled Randomized	90	Wistar 34 weeks Female OVX Sham	Osteoporosis	10 weeks	01 sham (base line) 01 sham	0.10 5.00 20.0

Table 1: Characteristics of included studies (part 02).

Study	**Drug**	**Design**	**N**	**Animal** (features)	**Model**	**Time**	**Control**	**Dosage** (mg/kg/day)
Broulik*;* Pacovsks 1991	Hidroclorotiazide	Experimental Controlled	40	Velaz Prague H Males 32 g	Osteoporosis	10 days	01 normal	2.00
Broulík *et al., 2001*	1) Enalapril 2)Losartan	Experimental Controlled	24	Wistar Female 14 weeks 200 g	Normal	14 weeks	01 normal	0.40 2.00
Oliveira *et al., 2014*	Propranolol	Experimental Controlled Randomized Blinded	20	Wistar Male 03 months 200–250 g	OTM	10 days	1) intra-animal; 2) sham; 3) normal.	0.10 20.0
Folwarczna et al., 2011	Propranolol	Experimental Controlled	35	Wistar Male 24 weeks	Osteoporosis	4 weeks	01 normal	10.0
Gealh et al., 2014	Losartan	Experimental Controlled	48	Wistar Kyoto SHR 250-300 g	Hipertension	28 days	01 normal (Wistar); 01 normal (Wistar medicated)	30.0

Table 1: Characteristics of included studies (part 03).

Study	**Drug**	**Design**	**N**	**Animal** (features)	**Model**	**Time**	**Control**	**Dosage** (mg/kg/day)
Koklina et al., 2015	Losartan	Experimental Controlled	267	White Wistar Female OVX 250 ± 25 g	Osteoporosis	8 weeks	01 sham (non medicated)	6.00
Ma et al., 1997	Hidroclorotiazide	Experimental Controlled Blinded	96	SHR 12 weeks 220 g	Hipertension and Osteoporosis.	56 days	01 baseline; 01 sham (non medicated)	10.0
Moura et al., 2016	Losartan	Experimental Controlled Randomized	40	C57BL6/J Male 10 weeks	OTM	12 days	01 normal	10.0
Mulinari-Santos *et al., 2019*	Losartan	Experimental Controlled Randomized	32	1) SHR 16 weeks 250-300 g 2) Albino Wistar 16 weeks 250-300 g	Hipertension	67 days	01 normal 01 SHR (non medicated)	30.0
Pintos *et al., 2013*	Propranolol	Experimental Controlled Randomized	72	Wistar Males 21-23 days 46.70 g ± 1.80	Nutritional	4 weeks	01 normal	7.00

Table 1: Characteristics of included studies (part 04).

Study	**Drug**	**Design**	**N**	**Animal** (features)	**Model**	**Time**	**Control**	**Dosage** (mg/kg/day)
Sato *et al., 2010*	Propranolol	Experimental Controlled	-	1) SHR, Males 7 weeks 2) Wistar, Males 7 weeks	Hipertension	12 weeks	01 SHR (non medicated) 01 normal (Wistar)	1) 1.00; 5.00; 50.0; 100.0; 2) 0.10; 1.00; 10.0
Sliwinski *et al., 2013*	Propranolol	Experimental Controlled	46	Wistar Female 3 months OVX	Osteoporosis	4 weeks	01 sham 01 ovx (non medicated)	10.0
Tasat *et a.,l 2014*	Propranolol	Experimental Controlled Randomized	40	Wistar Male 21-23 days 44 g	Nutritional	4 weeks	01 normal	7.00
Uchibori *et al., 2020*	1) Propranolol 2) Atenolol	Experimental Controlled	24	SHR/Izm WKY/Izm Japan SLC	Hipertension	12 weeks	01 (non medicated)	1) 1.0 2) 0.1
Zhang et al., 2007	Propranolol	Experimental Controlled	43	Sprague- Dawley Female OVX 7 weeks 220 ± 5 g	Osteoporosis	24 weeks	01 sham 01 ovx (non medicated)	2.80

Table 1: Characteristics of included studies (part 05).

Study	**Drug**	**Design**	**N**	**Animal** (features)	**Model**	**Time**	**Control**	**Dosage** (mg/kg/day)
Zhang *et al., 2011*	Captopril	Experimental Controlled Randomized	32	BALB/C Female 10 weeks	Osteolysis	10 days	01 (non medicated)	12.5 25.0 50.0
Zhang *et al., 2017*	Captopril	Experimental Controlled Randomized Blinded	34	Rat (db/db) and (db/+) C57BL/6-KS	Diabetes	8 weeks	01 (non medicated)	10.0

Table 2. Tests and results of experiments (part 01).

Study	*Evaluation*	*B.R. effects*	*OTM Evaluation*	*OTM effects*
Abuohashisha *et al.*, *2017*	1) ELISA (BALP, OC, TRACP-5B, CTXE E DPD URINARY). 2) Micro CT femoral morphometry. 3) Mineral quantification of the femoral bone. 4) Westernblot for AngII, Ang1-7, ACE-1, ACE-2, AT1R, AT2R, Mas-receptor, RANKL and OPG.	1) Negative biomarking. 2) Femoral mass and microarchitecture were protected against bone loss. 3) Protection of the femoral bone. 4) Reduction of AngII), AT1R, ACE-1 and RANKL. 5) Increase in Ang1-7, AT2R, ACE-2, MasR and OPG.	-	-
Al-Subaie *et al.*, *2016*	1) MicroCT of the Tibia. 2) Histomorphometric quantification of osteoclasts.	1) BV / TV increase. 2) Tb reduction. Sp. 3) Reduction of osteoclasts, increase in collagen and mineralization.	-	-
Babalyan *et al.*, *2019*	1) Macroscopic evaluation of fractured bone tissue. 2) Histological examination of the injured bone tissue.	1) Increased bone fusion with pronounced bone spur and without angular mobility of the bone.	-	-
Bonnet *et al.*, *2008*	1) Immunohistochemistry for Osteocalcin. 2) PCR for b1AR and b2AR. 3) MicroCT for trabecular and cortical analysis of the tibia, femur and L4. 4) Histomorphometry of the right tibia. 5) Mechanical testing of the femoral bone. 6) Immunosorbent assay for Osteocalcin, cross-linked C-terminal collagen and IGF-1.	1) Immunohistochemical expression of Adrb2R in osteoblasts. 2) Propranolol (0.1 mg/kg) increases bone formation and decreases bone resorption. 3) Suggestion of partial participation of IGF-I in the measurement of b blockers. 4) Propranolol (0.1 mg/kg) reduces the number of osteoclasts, increases bone formation and mineral deposition.	-	-

Table 2. Tests and results of experiments (part 02).

Study	*Evaluation*	*B.R. effects*	*OTM Evaluation*	*OTM effects*
Bonnet *et al., 2006*	1) Measurements of bone mineral content (BMC), area and density (BMD). 2) Scanning electron microscopy for analysis of the bone cortex. 3) MicroCT of the Tibia. 4) Histomorphometric quantification of osteoclastic activity. 5) MicroCT for analysis of bone	1) Propranolol 0.1 mg prevented trabecular and cortical bone loss. 2) Propranolol 1.0 mg avoids the effects of ovariectomy on bone architecture. 3) Propranolol 20.0 mg did not produce the same protective effect.	-	-
Broulik *et al., 1991*	1) Blood analysis for plasma Tr-ACP, calcium, phosphate and creatinine.	1) HTZ increased plasma calcium. 2) HTZ alone had no plasma effect on Tr-ACP phosphatase and creatinine concentration.	-	-
Broulík *et al., 2001*	1) Blood biochemical analysis. 2) Malondialdehyde (MDA) and HPLC spectrophotometer. 3) Urinary examination for detection of eicosanoids. 4) X-ray for morphometric measurements. 5) Quantification of bone calcium and phosphorus.	1) Enalapril and Losartana showed no increase in the urinary excretion of 6-keto PGF1α and thromboxane B2. 2) Enalapril showed an increase in the excretion of bicycles-PGE2. 3) Enalapril or losartan did not increase blood MDA.	-	-
Oliveira *et al., 2014*	1) ELISA for IL-1β and IL-6 levels. 2) Westernblot for anti-RANKL, anti-ICAM-1 and a-tubulin.	1) Propranolol 0.1 mg/kg reduced expression of IL-1β and IL-6. 2) Propranolol 0.1 mg/kg reduced the expression of RANKL. 3) Propranolol 20.0 mg/kg did not alter the expression of RANkL.	1) Traction with nickel-titanium spring (0.5N force), in the first molar and upper incisors. 2) Cone beam computed tomography for linear measurement in the anteroposterior direction between the distal surface of the first molar and the mesial surface of the second molar.	1) Propranolol 0.1mg/kg reduced the OTM. 2) Propranolol 20.0 mg/kg did not reduce OTM.

Table 2. Tests and results of experiments (part 03).

Study	*Evaluation*	*B.R. effects*	*OTM Evaluation*	*OTM effects*
Folwarczna *et al., 2011*	1) Mechanical properties of the tibia and femur. 2) Study of bone mineralization of the femur, tibia and vertebra L4. 3) Bone histomorphometry. 4) Serum levels of osteocalcin. 5) Enzyme immunoassay for TRACP 5b.	1) Propranolol 10.0 mg/kg decreased the bone mass/body mass ratio and the diameter of the femur. 2) Propranolol decreased the width of the trabeculae and the epiphyseal cartilage. 3) Propranolol reduced the serum concentration of osteocalcin.	-	-
Gealh *et al., 2014*	1) Histomorphometric and immunohistochemistry evaluation for anti-OPG, anti-RANK, anti-RANKL, anti-OC, anti-TRAP, anti-VEGF, and anti-PECAM.	1) Losartan 30.0 mg/kg/day increased RANKL expression at 7, 14 and 21 days of treatment. 2) Losartan 30.0 mg/kg/day increased the expression of OC, VEGF and PECAM.	-	-
Koklina *et al., 2015*	1) Doppler laser analysis of the microcirculation in the proximal metaphysis of the femur. 2) Calculation of the endothelial dysfunction coefficient based on the doppler laser. 3) Histomorphological study of the proximal metaphysis of the femur.	1) Losartan 30.0 mg/kg/day prevents the reduction of regional blood flow in the femur. 2) Losartan has an endothelial protective action. 3) Losartan prevented the reduction in the mean thickness of the trabecular bone.	-	-
Ma *et al., 1997*	1) Medullary and cortical histomorphometry of the number and thickness of the trabecular area, percentage of erosion, osteoid, mineral apposition rate, formation rates (BFR) (tissue volume (TV), BFR / TV; bone volume (BV), BFR / BV; referring to the bone surface (BS), BFR / BS).	1) HCTZ 2 weeks prevented trabecular bone loss associated with decreased bone turnover (BFR / BV), reduced levels of mineral apposition of the reabsorbed surface covered by osteoid and reduced the frequency of activation. 2) HCTZ 8 weeks: not significant.	-	-

Table 2. Tests and results of experiments (part 04).

Study	*Evaluation*	*B.R. effects*	*OTM Evaluation*	*OTM effects*
Moura *et al., 2016*	1) Histological analysis for osteoclast count. 2) Analysis by RT-PCR for RANK, RANKL, osteoprotegerin, cathepsin K, metalloproteinase, periostin, dentin matrix protein, alkaline phosphatase, collagen 1A1, semaphorin 3A3 and metalloproteinase 2 molecules.	1) Losartan: reduction of osteoclasts. 2) Losartan: reduction of TRAP positive cells during OTM. 3) Losartan: reduction of RANK, RANKL, cathepsin K and metalloproteinase 13 RNAs in compression areas. 4) Losartan: increased expression of periostin, dentin matrix protein, alkaline phosphatase, collagen 1A1, semaphorin 3A3, metalloproteinase, osteoprotegerin on the compression and tension sides.	1) Orthodontic traction with nickel-titanium spring (0.25x 0.76 mm / 35.0g of force), in the first molar and upper incisors. 2) Measurement of microscopic images by Software Image J. 3) Measure the distance between the cementum-enamel junction first and second molars in the right hemimaxyl.	1) After 12 days the amount of OTM decreased in animals treated with Losartan.
Mulinari-Santos *et al., 2019*	1) Histological analysis by laser microscopy for calcein fluorochrome and alizarin fluorochrome method.	1) Losartan increased bone volume. 2) Losartan increased the mineralized surface. 3) Losartan increased the active mineralization surface. 4) Losartan increased the rate of bone formation. 5) Losartan increased the rate of mineral apposition.	-	-

Table 2. Tests and results of experiments (part 05).

Study	*Evaluation*	*B.R. effects*	*OTM Evaluation*	*OTM effects*
Pintos *et al., 2013*	1) Evaluation of biomechanical properties of the femoral diaphysis. 2) Evaluation of mechanical efficiency of bones. 3) Evaluation of longitudinal growth of the tibia. 4) ELISA for type I collagen carboxylic end-telopeptide (α-CTX). 5) Determination of the endocrine-metabolic condition. 6) Calcemia by atomic absorption spectrophotometry. 7) Phosphatemia was determined by calorimetry.	1) Propranolol increased the structural properties of the entire bone. 2) Propranolol 7.0 mg/kg/day increased the total bone area of the tibial cross section. 3) Propranolol reduced serum α-CTX.	-	-
Sato, T. et al 2010	1) MicroCT to evaluate trabecular microarchitecture of the L2 tibia and vertebra. 2) L6 vertebra compression test. 3) Histomorphometric analyzes. 4) Blood analysis to test osteocalcin concentration and TRAP activity form 5b (TRAP 5b).	1) Propranolol 1.0 and 5.0 mg/kg increased the bone mass of the L2 vertebra, but at 50.0 and 100.0 mg/kg it did not increase bone mass. 2) Propranolol 0.1; 1.0; 5.0 and 10.0 mg/kg increased the number of bone trabeculae. 3) Propranolol 1.0 mg/kg increases bone formation. 6) Plasma osteocalcin increased with 0.1% propranolol; 1.0 and 10.0 mg/kg. 7) The TRAP 5b level decreased with PRO doses of 0.1 and 1.0 mg/kg.	-	-

Table 2. Tests and results of experiments (part 06).

Study	*Evaluation*	*B.R. effects*	*OTM Evaluation*	*OTM effects*
Sliwinski, L. *et al* 2013	1) Histomorphometric analysis of the femoral and tibial bone. 2) Study of the biomechanical properties of bone: compression test, flexion test, maximum load and rupture load.	1) Propranolol increased the width of the trabeculae of the femoral metaphysis in ovariectomized rats. 2) Propranolol increased the endosteal growth flow in ovariectomized rats. 3) Propranolol improved bone stiffness.	-	-
Tasat *et al.,* 2014	1) Histomorphometric analysis of the femoral and tibial bone. 2) Bone mechanical proporties: compression test, flexibility test, maximum loading and breaking load. 3) Blood analysis of fragments: Type I collagen telopeptide C (CTX-I; osteocalcin, TNF and IL-10.	1) Propranolol did not alter serum levels of osteocalcin. 2) Propranolol decreased the expression of IL-6 bone resorption markers; TNF; IL-10 ($p < 0.01$).	-	-
Uchibori, *S. et al* 2020	1) Evaluation of bone volume by tomography. 2) Immunohistochemical evaluation for SOST, RANKL and OPG. 3) Histomorphometry. 4) TRAP markers for osteoclasts. 5) Measure of bone apposition rate.	1) Increase in VB/TV ratio. 2) Increase in Tb.N and Tb.Th. 3) Reduction of Tb.Sp. 4) Reduction on the compression side of the Oc.N/BS and Oc.S/BS ratios. 5) Reduction of the space between the two lines of calcein on the compression side. 6) Increase of MAR and BFR on the compression side. 7) Increased OPG expression.	1) Closed nickel-titanium spring with a force of 50.0g and activation of 4.0 mm connecting the first upper molar and the upper central incisors. 2) OTM measured by micro-CT.	1) Atenolol 0.1 mg/kg and Propranolol 1.0 mg/kg reduced the amount of OTM. 2) Atenolol and Propranolol reduced the expression of RANKL and SOST on the compression side. 4) Atenolol and propranolol increased the expression of OPG on the compression side.

Table 2. Tests and results of experiments (part 07).

Study	*Evaluation*	*B.R. effects*	*OTM Evaluation*	*OTM effects*
Zhang *et al., 2007*	1) Dual energy X-ray absorptiometry (DEXA). 2) Histomorphometry of the cortical, medullary area, bone surface. 3) Measurement of serum osteocalcin (OC).	1) Propranolol preserved tibial and femoral bone density. 2) Propranolol prevented the loss of bone volume.	-	-
Zhang *et al., 2011*	1) Histological analysis of the thickness of the inflammatory bag membrane. 2) RT - PCR analysis for TNF-α mRNA, interleukin-1β and nuclear factor receptor activator linking κB (RANKL).	1) Captopril reduced inflammation. 2) Captopril reduced the thickness of the inflammatory bag membrane. 3) Captopril reduced the levels of TNF-α, IL-1β and RANKL (P <0.05).	-	-
Zhang *et al., 2017*	1) Biological serological and urine analysis by standard method or ELISA. 2) Histological measurements in the proximal tibial metaphysis. 3) Trabecular bone mass and bone quality were analyzed MicroCT. 4) RT-PCR and immunoblot applied for analysis of mRNA and protein expression..	1) Captopril reduced albuminuria and glomerulosclerosis. 2) Increased urinary excretion of calcium and phosphorus. 3) Reduction of bone mineral density and deterioration of the tibial trabecular bone. 4) Increase in the bone surface covered by osteoclasts, reduced the coverage by osteoblasts and reduced the expression of type 1 collagen and runt-related transcription factor 2 (markers of osteoblastic functions), increased the expression of carbonic anhydrase II (marker for resorption bone). 5) Increased osteoclastic activity and decreased osteoblastic activity. 6) Increased VDR expression and decreased CaBP-28k.	-	-

Table 3. Summary of risk of bias assessment (HOOIJMANS et al.[30]) (part 01).

Studies	Signaling questions										
	1	2	3	4	5	6	7	8	9	10	summary
ABUOHASHISHA *et al*., 2017	High	Low	High	High	High	Unclear	High	Low	Low	Unclear	High
AL-SUBAIE *et al*., 2016	Low	Low	Low	Low	Low	Unclear	Unclear	Low	Unclear	Unclear	Low
BABALYAN *et al*., 2019	High	Low	High	High	Unclear	Unclear	High	High	Low	Unclear	High
BONNET *et al*., 2008	Unclear	Low	High	Low	High	Unclear	High	Low	Low	Unclear	Unclear
BONNET *et al*., 2006	Unclear	Low	Low	Low	Unclear	Unclear	High	Low	Low	Unclear	Unclear
BROULIK; PACOVSKS 1991	High	Low	High	Unclear	High	Unclear	High	Low	Low	Unclear	High
BROULÍK *et al*., 2001	High	Low	High	High	High	Unclear	High	Low	Low	Unclear	High
OLIVEIRA *et al*., 2014	Low	Low	Low	Low	Low	Low	Unclear	Low	Low	Unclear	Low
FOLWARCZNA *et al*., 2011	High	Low	High	High	High	Unclear	High	High	High	Unclear	High
GEALH *et al*., 2014	High	Low	High	Low	High	Unclear	High	High	High	Unclear	High
KOKLINA *et al*., 2015	High	Low	High	High	High	Unclear	High	Low	Unclear	Unclear	High
MA *et al*., 1997	High	Low	High	Unclear	Low	Unclear	High	Low	Unclear	Unclear	High
MOURA *et al*., 2016	Unclear	Low	Unclear	Unclear	High	Low	High	Low	Low	Unclear	Unclear
MULINARI-SANTOS *et al*., 2019	Unclear	Low	Low	Low	High	Unclear	High	Low	Low	Unclear	Unclear
PINTOS *et al*., 2013	Unclear	Low	Low	Low	Unclear	Unclear	High	Low	Low	Unclear	Unclear
SATO *et al*.,2010	High	Low	High	Low	High	Unclear	High	Low	Unclear	Unclear	High
SLIWIŃSKI *et al*., 2013	High	Low	High	High	High	Unclear	High	Low	Low	Unclear	High
TASAT *et al*., 2014	Unclear	Unclear	Low	Low	Unclear	Unclear	High	Low	Low	Unclear	Unclear
UCHIBORI *et al*., 2020	High	Unclear	High	High	High	High	High	Low	Unclear	Unclear	High
ZHANG *et al*., 2007	High	Low	High	Low	High	Unclear	High	Low	Low	Unclear	High
ZHANG *et al*., 2011	Unclear	Low	Low	High	Unclear	Unclear	High	Low	Low	Unclear	Unclear
ZHANG *et al*., 2017	Low	Low	Low	Low	High	Low	High	Low	Low	Unclear	Low

TABLE 3. SYRCLE tool bias evaluation (HOOIJMANS *et al*. 2014) (part 2).
1) Was the allocation sequence adequately generated and applied ?; 2) Were the groups similar at baseline or were they adjusted for confounders in the analysis ?; 3) Was the allocation adequately concealed ?; 4) Were the animals randomly housed during the experiment ?; 5) Were the caregivers and/or investigators blinded from knowledge which intervention each animal received during the experiment ?; 6) Were animals selected at random for outcome assessment ?; 7) Was the outcome assessor blinded ?; 8) Were incomplete outcome data adequately addressed ?; 9) Are reports of the study free of selective outcome reporting ?; 10) Was the study apparently free of other problems that could result in high risk of bias ?
Classification of bias: high risk; unclear risk; low risk

Table 4. Individual assessment of methodological quality of studies.

Studies	Signaling questions												
	1	2	3	4	5	6	7	8	9	10	Score	Results	Escale (0-7)
Abuohashisha et al., *2017*	X						X		X		3	4.4	Moderate
Al-Subaie et al., *2016*	X	X	X	X			X		X		6		
Babalyan et al., *2019*	X						X		X		3		
Bonnet et al., *2008*	X	X	X				X		X		5		
Bonnet et al., *2006*	X	X					X		X		4		
Broulik; Pacovsks 1991	X	X					X		X		4		
Broulík et al., *2001*	X								X		2		
Oliveira et al., *2014*	X	X	X	X	X		X		X		7		
Folwarczna et al., *2011*	X	X					X		X		4		
Gealh et al., *2014*	X	X					X		X		4		
Koklina et al., *2015*	X	X					X		X		4		
Ma et al., *1993*	X	X		X	X		X		X		6		
Moura et al., *2016*	X		X				X	X	X		4		
Mulinari-Santos et al., *2019*	X	X	X				X		X		5		
Pintos et al., *2013*	X	X	X				X		X		5		
Sato et al., *2010*	X	X					X		X		4		
Sliwiñski et al., *2013*	X						X		X		3		
Uchibori et al., *2020*	X	X					X		X		4		
Tasat et al., *2014*	X	X	X				X		X		5		
Zhang et al., *2007*	X	X					X		X		4		
Zhang et al., *2011*	X		X				X		X		4		
Zhang et al., *2017*	X	X	X	X	X		X		X		7		

Signaling questions: (1) peer reviewed publication; (2) control of temperature; (3) random allocation to treatment or control; (4) blinded induction of ischemia; (5) blinded assessment of outcome; (6) use of anesthetic without significant intrinsic neuroprotective activity; (7) animal model (aged, diabetic, or hypertensive); (8) sample size calculation; (9) compliance with animal welfare regulations; and (10) statement of potential conflict of interests. Also see supplementary material.

Annex 1: Search strategy

Search Plataform	Search strategy November 2019	Recovered Studies
MEDLINE (PUBMED)	Search (((Bone Remodeling[MeSH Terms] OR Bone Remodeling[Text Word] OR Remodeling, Bone[Text Word] OR Bone Turnover[Text Word] OR Bone Turnovers[Text Word] OR Turnover, Bone[Text Word] OR Turnovers, Bone[Text Word])) AND ((((Spirolactone[MeSH Terms] OR Spirolactone[Text Word] OR Veroshpiron[Text Word] OR Verospirone[Text Word] OR Spiractin[Text Word] OR Spirobeta[Text Word] OR Spirogamma[Text Word] OR Spirolang[Text Word] OR Spirono-Isis[Text Word] OR Spirono Isis[Text Word] OR Spironone[Text Word] OR Spirospare[Text Word] OR Aldactone[Text Word] OR Verospiron[Text Word] OR Aldactone A[Text Word] OR Aquareduct[Text Word] OR Duraspiron[Text Word] OR Espironolactona Alter[Text Word] OR Espironolactona Mundogen[Text Word] OR Flumach[Text Word] OR Frumikal[Text Word] Jenaspiron OR Novo-Spiroton[Text Word] OR Novo Spiroton[Text Word] OR NovoSpiroton[Text Word] OR Practon[Text Word] OR SC-9420[Text Word] OR SC 9420[Text Word] OR SC9420[Text Word] OR Spiro L.U.T.[Text Word] OR Spiro Von Ct[Text Word] OR Ct, Spiro Von[Text Word] OR Von Ct, Spiro[Text Word])) OR ((Amlodipine[MeSH Terms] OR Amlodipine[Text Word] OR Amlodipine Besylate[Text Word] OR Amlodis[Text Word] OR Astudal[Text Word] OR Norvasc[Text Word] OR Istin[Text Word] OR Amlor[Text Word] OR Amlodipine Maleate[Text Word] OR Amlodipine Besylate, Olmesartan Medoxomil Drug Combination[MeSH Terms] OR Amlodipine Besylate, Olmesartan Medoxomil Drug Combination[Text Word] OR Amlodipine Besylate-Olmesartan Medoxomil Drug Combination[Text Word] OR Amlodipine Besylate Olmesartan Medoxomil Drug Combination[Text Word] OR Amlodipine Besylate-Olmesartan Medoxomil[Text Word] OR	120

Amlodipine Besylate Olmesartan Medoxomil[Text Word] OR Besylate-Olmesartan Medoxomil, Amlodipine[Text Word] OR Medoxomil, Amlodipine Besylate-Olmesartan[Text Word] OR Amlodipine Besylate, Olmesartan Medoxomil[Text Word] OR Azor[Text Word] OR Amlodipine, Valsartan Drug Combination[MeSH Terms] OR Amlodipine, Valsartan Drug Combination[Text Word] OR Amlodipine - Valsartan[Text Word] OR Valsartan, Amlodipine[Text Word] OR Valsartan, Amlodipine-[Text Word] OR Amlodipine-Valsartan[Text Word] OR Amlodipine Valsartan[Text Word] OR Amlodipine-Valsartan Drug Combination[Text Word] OR Amlodipine Valsartan Drug Combination[Text Word] OR Combination, Amlodipine-Valsartan Drug[Text Word] OR Drug Combination, Amlodipine-Valsartan[Text Word] OR Exforge[Text Word] OR Atenolol[MeSH Terms] OR Atenolol[Text Word] OR atenolol, chlortalidone drug combinations[MeSH Terms] OR atenolol, chlortalidone drug combinations[Text Word] OR atenolol - chlortalidone[Text Word] OR Igroseles[Text Word] OR Tenoretic[Text Word] OR Tenormine[Text Word] OR Tenormin[Text Word] OR ICI-66082[Text Word] OR ICI 66082[Text Word] OR ICI66082[Text Word] OR Captopril[MeSH Terms] OR Captopril[Text Word] OR Lopirin[Text Word] OR SQ-14,534[Text Word] OR SQ 14,534[Text Word] OR SQ14,534[Text Word] OR SQ-14534[Text Word] OR SQ 14534[Text Word] OR SQ14534[Text Word] OR Capoten[Text Word] OR SQ-14,225[Text Word] OR SQ 14,225[Text Word] OR SQ14,225[Text Word] OR SQ-14225[Text Word] OR SQ 14225[Text Word] OR SQ14225[Text Word] OR captopril, hydrochlorothiazide drug combination[MeSH Terms] OR captopril, hydrochlorothiazide drug combination[Text Word] OR captopril - hydrochlorothiazide[Text Word] OR Capozide[Text Word] OR Carvedilol[MeSH Terms] OR Carvedilol[Text Word] OR OPC-1085[Text Word] OR OPC 1085[Text Word] OR OPC1085[Text Word] OR Carteolol Hydrochloride[Text Word]

OR Hydrochloride, Carteolol[Text Word] OR Carteolol Monohydrochloride[Text Word] OR Monohydrochloride, Carteolol[Text Word] OR Enalapril[MeSH Terms] OR Enalapril[Text Word] OR MK-421[Text Word] OR MK 421[Text Word] OR MK421[Text Word] OR Renitec[Text Word] OR Renitek[Text Word] OR Enalapril Maleate[Text Word] OR Maleate, Enalapril[Text Word] OR Hydralazine[MeSH Terms] OR Hydralazine[Text Word] OR Hydrallazin[Text Word] OR Hydrazinophthalazine[Text Word] OR Apressin[Text Word] OR Nepresol[Text Word] OR Hydralazine mono-Hydrochloride[Text Word] OR Hydralazine mono Hydrochloride[Text Word] OR mono-Hydrochloride, Hydralazine[Text Word] OR Apressoline[Text Word] OR Apresoline[Text Word] OR Hydralazine Hydrochloride[Text Word] OR Hydrochloride, Hydralazine[Text Word] OR Hydrochlorothiazide[MeSH Terms] OR Hydrochlorothiazide[Text Word] OR HCTZ[Text Word] OR Dichlothiazide[Text Word] OR Dihydrochlorothiazide[Text Word] OR HydroDIURIL[Text Word] OR Oretic[Text Word] OR Sectrazide[Text Word] OR Esidrix[Text Word] OR Esidrex[Text Word] OR Hypothiazide[Text Word] OR Losartan[MeSH Terms] OR Losartan[Text Word] OR DuP-753[Text Word] OR DuP 753[Text Word] OR DuP753[Text Word] OR MK-954[Text Word] OR MK 954[Text Word] OR MK954[Text Word] OR Cozaar[Text Word] OR Losartan Potassium[Text Word] OR Potassium, Losartan[Text Word] OR Losartan Monopotassium Salt[Text Word] OR Monopotassium Salt, Losartan[Text Word] OR Salt, Losartan Monopotassium[Text Word] OR losartan carboxylic acid[MeSH Terms] OR losartan carboxylic acid[Text Word] OR EXP3174[Text Word] OR EXP-3174[Text Word] OR E-3174[Text Word] OR EXP 3174[Text Word] OR Methyldopa[MeSH Terms] OR Methyldopa[Text Word] OR alpha-Methyldopa[Text Word] OR alpha Methyldopa[Text Word] OR alpha-Methyl-L-Dopa[Text Word] OR alpha Methyl L Dopa[Text Word] OR Alphamethyldopa[Text Word] OR

Meldopa[Text Word] OR Methyldopate[Text Word] OR Dopegyt[Text Word] OR Dopergit[Text Word] OR Dopegit[Text Word] OR Sembrina[Text Word] OR Apo-Methyldopa[Text Word] OR Apo Methyldopa[Text Word] OR Dopamet[Text Word] OR Aldomet[Text Word] OR Hydopa[Text Word] OR Nu-Medopa[Text Word] OR Nu Medopa[Text Word] OR Metoprolol[MeSH Terms] OR Metoprolol[Text Word] OR Toprol[Text Word] OR Betaloc[Text Word] OR Betaloc-Astra[Text Word] OR Betaloc Astra[Text Word] OR Betalok[Text Word] OR CGP-2175[Text Word] OR CGP 2175[Text Word] OR CGP2175[Text Word] OR H 93-26[Text Word] OR H 93 26[Text Word] OR H 9326[Text Word] OR Metoprolol Tartrate[Text Word] OR Seloken[Text Word] OR Spesicor[Text Word] OR Spesikor[Text Word] OR Metoprolol Succinate[Text Word] OR Metoprolol CR-XL[Text Word] OR Metoprolol CR XL[Text Word] OR Toprol-XL[Text Word] OR Toprol XL[Text Word] OR Beloc-Duriles[Text Word] OR Beloc Duriles[Text Word] OR Lopressor[Text Word] OR Mibefradil[MeSH Terms] OR Mibefradil[Text Word] OR Ro 40-5967[Text Word] OR Ro 40 5967[Text Word] OR Ro 405967[Text Word] OR Mibefradil Dihydrochloride[Text Word] OR Posicor[Text Word] OR Nitroprusside[MeSH Terms] OR Nitroprusside[Text Word] OR Cyanonitrosylferrate[Text Word] OR Nitroferricyanide[Text Word] OR Nipruton[Text Word] OR Nitriate[Text Word] OR Nitropress[Text Word] OR Nitroprusside, Disodium Salt, Dihydrate[Text Word] OR Nipride[Text Word] OR Naniprus[Text Word] OR Nitroprussiat Fides[Text Word] OR Sodium Nitroprusside[Text Word] OR Nitroprusside, Sodium[Text Word] OR Nitroprusside, Disodium Salt[Text Word] OR Disodium Salt Nitroprusside[Text Word] OR Ketostix[Text Word] OR Propranolol[MeSH Terms] OR Propranolol[Text Word] OR Propanolol[Text Word] OR Inderal[Text Word] OR Avlocardyl[Text Word] OR AY-20694[Text Word] OR AY 20694[Text Word] OR AY20694[Text Word] OR Rexigen[Text Word] OR

	Dexpropranolol[Text Word] OR Dociton[Text Word] OR Obsidan[Text Word] OR Obzidan[Text Word] OR Propranolol Hydrochloride[Text Word] OR Hydrochloride, Propranolol[Text Word] OR Anaprilin[Text Word] OR Anapriline[Text Word] OR Betadren[Text Word]))) Sort by: Best Match	
Web of Science	ts=(Bone Remodeling OR Bone Turnover*) index=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Allotted time=All years ts=(Antihypertensive Agents OR Antihypertensive Agents OR Agents, Antihyperten-sive OR Antihypertensives OR Anti-Hypertensives OR Anti Hypertensives OR Antihypertensive Drugs OR Drugs, Antihypertensive OR Anti-Hypertensive Agents OR Agents, Anti-Hypertensive OR Anti Hypertensive Agents OR Anti-Hypertensive Drugs OR Anti Hypertensive Drugs OR Drugs, Anti-Hypertensive OR Amlodipine OR Amlodipine Besylate, Olmesartan Medoxomil Drug Combination OR amlodipine OR Amlodipine, Valsartan Drug Combination OR Atenolol OR atenolol, chlortalidone drug combinations OR Captopril OR captopril, hydrochlorothiazide drug combination OR Carvedilol OR Enalapril OR Hydrochlorothiazide OR hydrochlorothiazide, lisinopril drug combination OR Losartan OR losartan carboxylic acid OR Methyldopa OR Nitroprusside OR Propranolol) Índices=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Tempo estipulado=Todos os anos 2 AND #1 Índices=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Allotted time=All years	113
Scopus	#1 TITLE-ABS-KEY ("Bone Remodeling" OR "Remodeling, Bone" OR "Bone Turnover" OR "Bone Turnovers" OR "Turnover, Bone" OR "Turnovers, Bone")	54

	#2 TITLE-ABS-KEY ("Antihypertensive Agents" OR "Agents, Antihypertensive" OR "Antihypertensives" OR "Anti-Hypertensives" OR "Anti Hypertensives" OR "Antihypertensive Drugs" OR "Drugs, Antihypertensive" OR "Anti-Hypertensive Agents" OR "Agents, Anti-Hypertensive" OR "Anti Hypertensive Agents" OR "Anti-Hypertensive Drugs" OR "Anti Hypertensive Drugs" OR "Drugs, Anti-Hypertensive") #3 #1 AND #2	
EMBASE	#1 ('bone remodeling'/exp OR 'bone reconstruction' OR 'bone remodeling' OR 'bone remodelling' OR 'bone repair' OR 'osteoplasty') #2 ('antihypertensive agent'/exp OR 'anti hypertensic agent' OR 'anti hypertensive' OR 'anti hypertensive agent' OR 'anti hypertensive drug' OR 'antihypertension agent' OR 'antihypertensive' OR 'antihypertensive agent' OR 'antihypertensive agents' OR 'antihypertensive drug' OR 'antihypertensives' OR 'antihypertonic agent' OR 'hypotensiva' OR 'hypotensive' OR 'hypotensive agent' OR 'hypotensive drug' OR 'spironolactone'/exp OR '17 hydroxy 7 mercapto 3 oxo 17alpha pregn 4 ene 21 carboxylic acid gamma lactone 7 acetate' OR '3 (3 oxo 7alpha acetylthio 17beta hydroxy 4 androsten 17alpha yl) propionic acid gamma lactone' OR '7alpha acetylthio 3 oxo 4 androsten 17 spiro 2` tetrahydrofuran 5` one' OR 'abbolactone' OR 'acelat' OR 'adultmin' OR 'alaton' OR 'alatone' OR 'aldace' OR 'aldactone' OR 'aldactone 50' OR 'aldactone a' OR 'aldactone diurapid' OR 'aldopur' OR 'aldospirone' OR 'almatol' OR 'aquareduct' OR 'berlactone' OR 'beta aldopur' OR 'carospir' OR 'crl 635' OR 'crl635' OR 'diram' OR 'duraspiron' OR 'dyta urese' OR 'dytaurese' OR 'flumach' OR 'hypazon' OR 'idrolattone' OR 'merabis' OR 'novospiroton' OR 'osiren' OR 'osyrol' OR 'osyrol 50 100' OR 'pirolacton' OR 'pondactone' OR 'practon' OR 'prilactone' OR 'resacton' OR 'sas 1060' OR 'sas1060' OR 'sc 9420' OR 'sc9420' OR 'spiractin' OR	38

'spiridon' OR 'spirix' OR 'spiro ct' OR 'spiroctan' OR 'spiroctan m' OR 'spirohexal' OR 'spirolacton' OR 'spirolactone' OR 'spirolang' OR 'spiron' OR 'spirone' OR 'spironex' OR 'spirono-isis' OR 'spironol' OR 'spironolacton' OR 'spironolactone' OR 'spironolakton' OR 'spironone' OR 'spirothiobarbiturate 03620' OR 'spirotone' OR 'supra puren' OR 'suprapuren' OR 'uractone' OR 'verospiron' OR 'verospirone' OR 'xenalon' OR 'xenalon lactabs' OR 'youlactone' OR 'amlodipine'/exp OR '2 (2 aminoethoxymethyl) 4 (2 chlorophenyl) 1, 4 dihydro 6 methyl 3, 5 pyridinedicarboxylic acid 3 ethyl 5 methyl ester' OR '2 (2 aminoethoxymethyl) 4 (2 chlorophenyl) 1, 4 dihydro 6 methylpyridine 3, 5 dicarboxylic acid 3 ethyl 5 methyl ester' OR '2 (2 aminoethoxymethyl) 4 (2 chlorophenyl) 3 ethoxycarbonyl 1, 4 dihydro 5 methoxycarbonyl 6 methylpyridine' OR '2 [(2 aminoethoxy) methyl] 4 (2 chlorophenyl) 3 ethoxycarbonyl 5 methoxycarbonyl 6 methyl 1, 4 dihydropyridine' OR 'amdip' OR 'amloc' OR 'amlodipin' OR 'amlodipina' OR 'amlodipine' OR 'amlopin' OR 'amlor' OR 'astudal' OR 'cardilopin' OR 'istin' OR 'levamlodipine' OR 'levamlodipine malate' OR 'uk 48340' OR 'uk48340' OR 'amlodipine plus olmesartan'/exp OR 'alea' OR 'amelior' OR 'amlodipine besilate plus olmesartan medoxomil' OR 'amlodipine besylate plus olmesartan medoxomil' OR 'amlodipine besylate, olmesartan medoxomil drug combination' OR 'amlodipine plus olmesartan' OR 'amlodipine plus olmesartan medoxomil' OR 'axeler' OR 'azor' OR 'balzak (drug)' OR 'belfor' OR 'bivis' OR 'capenon' OR 'duactan' OR 'elestar' OR 'folgan' OR 'forzaten' OR 'giant (drug)' OR 'inovum' OR 'konverge' OR 'olectan' OR 'olmesartan medoxomil plus amlodipine' OR 'olmesartan medoxomil plus amlodipine besilate' OR 'olmesartan medoxomil plus amlodipine besylate' OR 'olmesartan plus amlodipine' OR 'sanoral' OR 'sevikar' OR 'sintonyn' OR 'vocado' OR 'zolnor' OR 'amlodipine plus valsartan'/exp OR 'amlodipine besilate plus valsartan' OR 'amlodipine besilate-

valsartan' OR 'amlodipine besilate/valsartan' OR 'amlodipine besylate plus valsartan' OR 'amlodipine besylate-valsartan' OR 'amlodipine besylate/valsartan' OR 'amlodipine plus valsartan' OR 'amlodipine valsartan' OR 'amlodipine, valsartan drug combination' OR 'amlodipine-valsartan' OR 'amlodipine/valsartan' OR 'copalia' OR 'dafiro' OR 'exforge' OR 'imprida' OR 'valsartan plus amlodipine' OR 'valsartan plus amlodipine besilate' OR 'valsartan plus amlodipine besylate' OR 'valsartan-amlodipine' OR 'valsartan-amlodipine besilate' OR 'valsartan-amlodipine besylate' OR 'valsartan/amlodipine' OR 'valsartan/amlodipine besilate' OR 'valsartan/amlodipine besylate' OR 'atenolol'/exp OR '1 (4 carbamoylmethylphenoxy) 3 isopropylamino 2 propanol' OR '2 [4 [2 hydroxy 3 (isopropylamino) propoxy] phenyl] acetamide' OR '4 (2 hydroxy 3 isopropylaminopropoxy) phenylacetamide' OR 'ablok' OR 'adoll' OR 'alonet' OR 'altol' OR 'anolene' OR 'anolpin' OR 'anselol' OR 'apo-atenolol' OR 'arandin' OR 'asten' OR 'atarox' OR 'atcardil' OR 'atecard' OR 'atehexal' OR 'atelol' OR 'atenblock' OR 'atendol' OR 'atenet' OR 'ateni' OR 'atenil' OR 'ateno' OR 'atenogamma' OR 'atenol' OR 'atenolol' OR 'atereal' OR 'aterol' OR 'atestad' OR 'atinol' OR 'atolmin' OR 'b-vasc' OR 'betablok' OR 'betacar' OR 'betarol' OR 'betatop ge' OR 'beten' OR 'bloket' OR 'blokium' OR 'blotex' OR 'cardioten' OR 'catenol' OR 'coratol' OR 'corotenol' OR 'durabeta' OR 'esatenolol' OR 'evitocor' OR 'farnormin' OR 'felo-bits' OR 'hypernol' OR 'hypoten' OR 'ici 66, 082' OR 'ici 66082' OR 'internolol' OR 'lo-ten' OR 'loten' OR 'lotenal' OR 'martenol' OR 'mirobect' OR 'myocord' OR 'neotenol' OR 'nolol' OR 'normalol' OR 'normaten' OR 'normiten' OR 'nortelol' OR 'noten' OR 'oraday' OR 'ormidol' OR 'paesumex' OR 'plenacor' OR 'preloc' OR 'premorine' OR 'prenolol' OR 'prenormine' OR 'ranlol' OR 'rozamin' OR 'serten' OR 'stermin' OR 'temoret' OR 'tenblok' OR 'tenidon' OR 'tenoblock' OR 'tenocor' OR 'tenol' OR 'tenolin' OR 'tenolol' OR 'tenopress' OR 'tenoprin' OR 'tenormin' OR 'tenormin mite' OR 'tenormine' OR 'tenostat' OR 'tensig' OR

'tensinor' OR 'ternolol' OR 'therabloc' OR 'tn 891' OR 'tn891' OR 'tredol' OR 'vascoten' OR 'velorin' OR 'vericordin' OR 'wesipin' OR 'atenolol plus chlortalidone'/exp OR 'ablok plus' OR 'atecard-d' OR 'ateclero' OR 'ateclor' OR 'atemine' OR 'atenigron' OR 'ateno-basan' OR 'atenoblok - co' OR 'atenolol and chlorthalidone' OR 'atenolol plus chlortalidone' OR 'atenolol plus chlorthalidone' OR 'atenoric' OR 'atensil-d' OR 'ateron' OR 'blokium diu' OR 'blokium-diu' OR 'blokiuret' OR 'chlortalidone plus atenolol' OR 'chlorthalidone plus atenolol' OR 'co tenidone' OR 'co-tenidone' OR 'corinol' OR 'cotenidone' OR 'diube' OR 'poten' OR 'prenoretic' OR 'teneretic' OR 'tenolone' OR 'tenorectic' OR 'tenoret' OR 'tenoret 50' OR 'tenoretic' OR 'tenoretic 100' OR 'tenoretic 50' OR 'tenoretic co' OR 'tenoretic ge' OR 'tenoretic mite' OR 'tenoric' OR 'teridon' OR 'captopril'/exp OR '(2 methyl 3 thiopropionyl) proline' OR '1 (3 mercapto 2 methylpropionyl) 2 pyrrolidinecarboxylic acid' OR '1 (3 mercapto 2 methylpropionyl) proline' OR '3 mercapto 2 methylpropanoyl proline' OR '3 mercapto 2 methylpropanoylproline' OR '3 mercapto 2 methylpropionylproline' OR 'ace-bloc' OR 'acenorm' OR 'acepress' OR 'acepril' OR 'aceprilex' OR 'aceril' OR 'aceten' OR 'adocor' OR 'alopresin' OR 'altran' OR 'apuzin' OR 'asisten' OR 'capace' OR 'capocard' OR 'caposan' OR 'capoten' OR 'capotena' OR 'capotril' OR 'capril' OR 'captace' OR 'captensin' OR 'capti' OR 'captoflux' OR 'captohexal (captopril)' OR 'captolane' OR 'captomax' OR 'capton' OR 'captopren' OR 'captopril' OR 'captoprilan' OR 'captoril' OR 'captral' OR 'cardiopril' OR 'cardipril' OR 'catona' OR 'catoplin' OR 'catopril' OR 'cesplon' OR 'cryopril' OR 'debax' OR 'dexacap' OR 'dextro (3 mercapto 2 methylpropanoyl) proline' OR 'dextro 2 methyl 3 mercaptopropanoyl levo proline' OR 'dextro captopril' OR 'ecapres' OR 'ecaten' OR 'epicordin' OR 'epsitron' OR 'farcopril' OR 'farmoten' OR 'hiperil' OR 'hypopress' OR 'hypotensor' OR 'insucar' OR 'iopril' OR 'isopresol' OR 'katopil' OR 'ketanine' OR 'keyerpril' OR 'lapril' OR 'levo

captopril' OR 'locap' OR 'lopirin' OR 'lopril' OR 'medepres' OR 'midrat' OR 'minitent' OR 'nolectin' OR 'oltens ge' OR 'petacilon' OR 'praten' OR 'primace' OR 'proline, 1 (3 mercapto 2 methylpropionyl)' OR 'proline, 3 mercapto 2 methylpropanoyl' OR 'rilcapton' OR 'ropril' OR 'smarten (drug)' OR 'sq 14225' OR 'tenofax' OR 'tensicap' OR 'tensiomen' OR 'tensiomin' OR 'tensobon' OR 'tensoprel' OR 'tensoril' OR 'tenzib' OR 'topace' OR 'toprilem' OR 'typril-ace' OR 'vasosta' OR 'zapto' OR 'zorkaptil' OR 'captopril plus hydrochlorothiazide'/exp OR 'acediur (captopril plus hydrochlorothiazide)' OR 'aceplus' OR 'aceplus mite' OR 'acezide' OR 'adcomp' OR 'capozid' OR 'capozide' OR 'capozide 25/15' OR 'capozide 25/25' OR 'capozide 50/15' OR 'capozide 50/25' OR 'capozide forte' OR 'captea' OR 'captohexal (captopril plus hydrochlorothiazide)' OR 'captopril and hydrochlorothiazide' OR 'captopril plus hydrochlorothiazide' OR 'captoprilan-d' OR 'cesplon plus' OR 'co zidocapt' OR 'co-zidocapt' OR 'cozidocapt' OR 'ecadiu' OR 'ecazide' OR 'hydrochlorothiazide plus captopril' OR 'jutacor comp' OR 'lopiretic' OR 'return (captopril plus hydrochlorothiazide)' OR 'uresan' OR 'zapto-co' OR 'carvedilol'/exp OR '1 (4 carbazolyloxy) 3 [2 (2 methoxyphenoxy) ethylamino] 2 propanol' OR '1 (carbazol 4 yloxy) 3 [2 (2 methoxyphenoxy) ethylamino] 2 propanol' OR 'bm 14190' OR 'bm14190' OR 'cardiol (carvedilol)' OR 'cardivas' OR 'carvedilol' OR 'carvedilol phosphate' OR 'carvedlol' OR 'carvipress' OR 'carvrol' OR 'coreg' OR 'coreg cr' OR 'dilatrend' OR 'dilbloc' OR 'dimitone' OR 'dq 2466' OR 'dq2466' OR 'eucardic' OR 'kredex' OR 'querto' OR 'skf 105517' OR 'skf105517' OR 'v-bloc' OR 'enalapril'/exp OR '1 [n (1 carboxy 3 phenylpropyl) alanyl] proline 1` ethyl ester' OR 'enalapril' OR 'n (1 carbethoxy 3 phenylpropyl) alanylproline' OR 'n (1 ethoxycarbonyl 3 phenylpropyl) alanylproline' OR 'hydralazine'/exp OR '1 hydrazinophthalazine' OR 'alazine' OR 'alphapress' OR 'apdormin' OR 'apresolin' OR 'apresolina' OR 'apresoline' OR

'apresoline hydrochloride' OR 'apressin' OR 'aprezin' OR 'ba 5968' OR 'ba5968' OR 'c 5968' OR 'c5968' OR 'ciba 5968' OR 'ciba5968' OR 'clorana' OR 'deselazin' OR 'dralzine' OR 'hidral' OR 'hydralacin' OR 'hydralazin' OR 'hydralazine' OR 'hydralazine chloride' OR 'hydralazine dehydrochloride' OR 'hydralazine dihydrochloride' OR 'hydralazine hydrochloride' OR 'hydralizine' OR 'hydrallazine' OR 'hydrallazine hydrochloride' OR 'hydrapres' OR 'hydrazaline' OR 'hydrazinophtalazine' OR 'hydrazinophtalizine' OR 'hydrazinophthalazine' OR 'hydrolazine' OR 'hydrolazine intoxication' OR 'hypatol' OR 'hyperphen' OR 'hypoftalin' OR 'hypophthalin' OR 'idralazina' OR 'lopress' OR 'nonpolin' OR 'novo-hylazin' OR 'phthalazine, hydrazino' OR 'plethorit c' OR 'praeparat 5968' OR 'resporidin' OR 'slow apresolin' OR 'slow apresoline' OR 'slow-apresoline' OR 'solesorin' OR 'tetrasoline' OR 'travinon' OR 'hydrochlorothiazide'/exp OR '6 chloro 3, 4 dihydro 2h 1, 2, 4 benzothiadiazine 7 sulfonamide 1, 1 dioxide' OR '6 chloro 3, 4 dihydro 7 sulfamoyl 1, 2, 4 benzothiadiazine 1, 1 dioxide' OR '6 chloro 3, 4 dihydro 7 sulfamoyl 2h 1, 2, 4 benzothiadiazine 1, 1 dioxide' OR '6 chloro 3, 4 dihydroxy 7 sulfamoyl 2 h 1, 2, 4 benzothiadiazine' OR 'apo-hydro' OR 'aquarius' OR 'aquazide h' OR 'behyd ra' OR 'bisalunil' OR 'bpzide' OR 'bremil' OR 'chloro 3, 4 dihydro 7 sulfamoyl 2h' OR 'chlorosulthiadil' OR 'chlorsulfonamidodihydrobenzothiadiazine dioxide' OR 'cidrex' OR 'clothia' OR 'dehydratin neo' OR 'di-ertride' OR 'di-eudrin' OR 'diaqua' OR 'dichlorosal' OR 'dichlothiazide' OR 'dichlotride' OR 'dichlotride k' OR 'dichlozid' OR 'diclotride' OR 'didralin' OR 'dihydrochlorothiazide' OR 'dihydrodiuril' OR 'direma' OR 'disalunil' OR 'disaluril' OR 'disothiazide' OR 'dithiazide' OR 'diu melusin' OR 'diu-melusin' OR 'diumelusin' OR 'diurace' OR 'diuret-p' OR 'diurex' OR 'esidrex' OR 'esidrex k' OR 'esidrex k forte' OR 'esidrix' OR 'fluvin' OR 'h.c.t.' OR 'hidrenox' OR 'hidril' OR 'hidroronol' OR 'hidrosaluretil' OR 'hudorex' OR 'hychlozide' OR 'hydrex-semi' OR 'hydril' OR 'hydro aquil' OR 'hydro chlorothiazide' OR

'hydro diuril' OR 'hydro saluric' OR 'hydro saluric k' OR 'hydro t' OR 'hydro tonuron' OR 'hydro z 50' OR 'hydro-d' OR 'hydroaquil' OR 'hydrochlor' OR 'hydrochloro thiazide' OR 'hydrochlorothiamide' OR 'hydrochlorothiazid' OR 'hydrochlorothiazide' OR 'hydrochlorothiazide intensol' OR 'hydrochlorothiazine' OR 'hydrochlorthiazide' OR 'hydrochlorzide' OR 'hydrochlothiazide' OR 'hydrodiuril' OR 'hydromal' OR 'hydroronol' OR 'hydrosaluric' OR 'hydrosaluric k' OR 'hydrothide' OR 'hydrozide' OR 'hydrozide 50' OR 'hypothiazid' OR 'hypothiazide' OR 'ivaugan' OR 'maschitt' OR 'microzide' OR 'mictrin' OR 'nefrix' OR 'neo codema' OR 'neo flumen' OR 'neoflumen' OR 'newtolide' OR 'niagar' OR 'oretic' OR 'pantemon' OR 'ridaq' OR 'tandiur' OR 'thiadril' OR 'thiaretic' OR 'thiuretic' OR 'urodiazin' OR 'urodiazine' OR 'urozide' OR 'vetidrex' OR 'losartan'/exp OR '2 butyl 4 chloro 5 hydroxymethyl 1 [[2` (1h tetrazol 5 yl) biphenyl 4 yl] methyl] imidazole' OR 'entrizen' OR 'ex 89' OR 'ex89' OR 'lavestra' OR 'lorista' OR 'losartan' OR 'losartan potassium'/exp OR '2 butyl 4 chloro 5 hydroxymethyl 1 [ [2` (1h tetrazol 5 yl) 4 biphenylyl] methyl] imidazole potassium' OR 'acetensa' OR 'angiobloq' OR 'angioten' OR 'arbartan' OR 'avastar' OR 'azarten' OR 'convertal' OR 'cormac' OR 'cosaar' OR 'cozaar' OR 'cozaarex' OR 'dup 753' OR 'dup753' OR 'insaar' OR 'lifezar' OR 'loortan' OR 'lortaan' OR 'lorzaar' OR 'losacar' OR 'losacor' OR 'losanox' OR 'losaprex' OR 'losarix' OR 'losartan kalium' OR 'losartan potassium' OR 'losartankalium' OR 'losatrix' OR 'lozaprex' OR 'mk 954' OR 'mk954' OR 'neo-lotan' OR 'neolotan' OR 'ocsaar' OR 'satoren' OR 'tensartan' OR 'tozaar' OR 'methyldopa'/exp OR '2 methyl 3 (3, 4 dihydroxyphenyl) alanine' OR '3 (3, 4 dihydroxyphenyl) 2 methylalanine' OR '3 hydroxy alpha methyl l tyrosine' OR '3, 4 dihydroxy alpha methylphenylalanine' OR 'aldomet' OR 'aldomet m' OR 'aldomet-forte' OR 'aldomet-m' OR 'aldometil' OR 'aldomin' OR 'aldomine' OR 'alfamatil dopa' OR 'alpha methyl 3, 4 dihydroxyphenylalanine' OR 'alpha methyl dopa' OR 'alpha methyldopa' OR 'alphadopa' OR 'alphamethyldopa'

OR 'amd' OR 'amodopa' OR 'apo-methyldopa' OR 'becanta' OR 'densul' OR 'dextro alpha methyldopa' OR 'dextro methyldopa' OR 'dextrolevo alpha methyldopa' OR 'dl alpha methyldopa' OR 'dopagyt' OR 'dopamet' OR 'dopasian' OR 'dopatens' OR 'dopegit' OR 'dopegite' OR 'dopegyt' OR 'emdopa' OR 'equibar' OR 'grospisk' OR 'h.g. metil dopa' OR 'hy-po-tone' OR 'hydopa' OR 'hyperpax' OR 'hyperpaxa' OR 'hypolag' OR 'l 2 amino 2 methyl 3 (3, 4 dihydroxyphenyl) propionic acid' OR 'l 2 amino 3 (3, 4 dihydroxyphenyl) 2 methylpropionic acid' OR 'l 3 (3, 4 dihydroxyphenyl) 2 methylalanine' OR 'l alpha methyl 3, 4 dihydroxyphenylalanine' OR 'l alpha methyl dopa' OR 'l alpha methyldopa' OR 'l methyldopa' OR 'levo alpha methyldopa' OR 'levo methyldopa' OR 'medomet' OR 'medopa' OR 'medopal' OR 'medopren' OR 'meldopa' OR 'methoplain' OR 'methyl dopa' OR 'methyldihydroxyphenylalanine' OR 'methyldopa' OR 'metpata' OR 'mk 351' OR 'mulfasin' OR 'muscle methyldopa' OR 'novomedopa' OR 'nudopa' OR 'pharmet' OR 'polinal' OR 'presilan' OR 'presinol' OR 'presinol 500' OR 'presolisin' OR 'sedometil' OR 'sembrina' OR 'siamdopa' OR 'sinepress' OR 'taquinil' OR 'tensodopa' OR 'tildopan' OR 'metoprolol'/exp OR '1 isopropylamino 3 [4 (2 methoxyethyl) phenoxy] 2 propanol' OR 'beloc duriles' OR 'belok zok' OR 'betaloc' OR 'h 93-26' OR 'metoprolol' OR 'metoprolol durules' OR 'metoprolol oros' OR 'metropolol' OR 'mibefradil'/exp OR '2 [2 [[3 (2 benzimidazolyl) propyl] methylamino] ethyl] 6 fluoro 1, 2, 3, 4 tetrahydro 1 isopropyl 2 naphthol methoxyacetate' OR 'cerate 50' OR 'mibefradil' OR 'mibefradil dihydrochloride' OR 'mibefradil hydrochloride' OR 'posicor' OR 'ro 40 5967' OR 'ro 40-5967' OR 'ro 405967' OR 'ro40 5967' OR 'ro40-5967' OR 'ro405967' OR 'nitroprusside sodium'/exp OR 'mr7s1' OR 'naniprus' OR 'nipride' OR 'nipride rtu' OR 'nipride rtu in sodium chloride 0.9%' OR 'nipruss' OR 'nipruton' OR 'nitan' OR 'nitrocyanoferrate sodium' OR 'nitroferricyanide' OR 'nitropress' OR 'nitroprusiato de sodio-ecar' OR 'nitroprussiat' OR

'nitroprussiate sodium' OR 'nitroprusside' OR 'nitroprusside sodium' OR 'nitroprusside, sodium' OR 'nitrosylpentacyanoferrate sodium' OR 'sodium nitroferricyanide' OR 'sodium nitroprussiate' OR 'sodium nitroprusside' OR 'propranolol'/exp OR '1 (2 hydroxy 3 isopropylaminopropoxy) naphthalene' OR '1 (isopropylamino) 3 (1 naphthyloxy) 2 propanol' OR '1 isopropylamino 3 (1 naphthoxy) 2 propanol' OR '1 isopropylamino 3 (1 naphthyloxy) propan 2 ol' OR 'acifol' OR 'adrexan' OR 'alperol' OR 'anaprilin' OR 'anapriline' OR 'anaprilinium' OR 'anapryline' OR 'angilol' OR 'angilol la' OR 'apo-propranolol' OR 'apsolol' OR 'arcablock' OR 'arcablock retard' OR 'artensol' OR 'authus' OR 'avlocardyl' OR 'avlocardyl retard' OR 'ay 64043' OR 'ay64043' OR 'becardin' OR 'bedranol' OR 'beprane' OR 'bercolol' OR 'berkolol' OR 'beta neg' OR 'beta tablinen' OR 'beta tablinen retard' OR 'beta timelets' OR 'beta-timelets' OR 'betabloc' OR 'betadipresan' OR 'betaneg' OR 'betaprol' OR 'betares' OR 'betaryl' OR 'blocard' OR 'blocaryl' OR 'cardinol' OR 'cardinol la' OR 'ciplar' OR 'corbeta' OR 'deralin' OR 'dextrolevo propranolol' OR 'dibudinate' OR 'dideral' OR 'dl propanolol hydrochloride' OR 'dl propranolol' OR 'dociton' OR 'dociton retard' OR 'docitone' OR 'durabeton' OR 'duranol' OR 'efektolol' OR 'efektolol retard' OR 'elbrol' OR 'emforal' OR 'farmadral' OR 'farprolol' OR 'frekven' OR 'frina' OR 'hemangeol' OR 'hemangiol' OR 'hopranolol' OR 'ici 45520' OR 'ikopal' OR 'impral' OR 'inderal' OR 'inderal la' OR 'inderal retard' OR 'inderalici' OR 'inderex' OR 'indicardin' OR 'indobloc' OR 'innopran' OR 'innopran xl' OR 'inpanol' OR 'ipran' OR 'l propranolol' OR 'lederpronol' OR 'levo propranolol' OR 'levopropranolol' OR 'napriline' OR 'noloten' OR 'nsc 91523' OR 'obsidan' OR 'obsin' OR 'obzidan' OR 'oposim' OR 'phanerol' OR 'prandol' OR 'prano puren' OR 'pranopuren' OR 'prestoral' OR 'prolol' OR 'prolol plus' OR 'pronovan' OR 'propabloc' OR 'propal' OR 'propalong' OR 'propanolol hydrochloride' OR 'propayerst' OR 'propercuten' OR 'prophylux' OR 'propra ratiopharm' OR

	'propral' OR 'propranolol' OR 'propranolol hydrochloride' OR 'propranolol hydrochloride intensol' OR 'propranolol isomer' OR 'propranur' OR 'proprasylyt' OR 'proprasylyte' OR 'reducor' OR 'sagittol' OR 'slow deralin' OR 'stapranolol' OR 'sumial' OR 'tenomal' OR 'tensiflex' OR 'waucoton') #3 #1 and #2 AND [embase]/lim NOT ([embase]/lim AND [medline]/lim)

5 CONSIDERAÇÕES FINAIS

A principal força desta revisão sistemática consiste na utilização de uma metodologia com diretrizes bem estabelecidas. Um protocolo metodológico foi avaliado por pares e registrado em uma base de dados apropriada e de acesso aberto. Isto torna o processo metodológico mais transparente, possibilitando a consulta de detalhes que possam garantir a reprodutibilidade do trabalho. A estratégia de busca eletrônica empregada foi exaustiva, abrangente e bastante sensível. Não houve restrição de idioma, data ou *status* da publicação. Foram feitos esforços para reduzir ao máximo os possíveis vieses metodológicos. A triagem, verificação, elegibilidade dos estudos, a coleta de informações, a avaliação de risco de parcialidade e a avaliação de qualidade da evidência foram realizados em duplicata e qualquer divergência conceitual foi resolvida por meio de discussão entre os examinadores. As divergências foram resolvidas e pela avaliação de um terceiro pesquisador para alcançar o consenso final.

Considerando os anti-hipertensivos de acesso livre e gratuito pelo PFP, esta revisão sistemática mostrou que:

a) A hidroclorotiazida mostrou ter efeito osteoprotetor reduzindo a reabsorção óssea em modelos de hipertensão e osteoporose, mas com uma evidência de alto risco de parcialidade;
b) O atenolol reduz a ação osteoclástica e aumenta a função osteoblástica em modelos de MDO com uma evidência com alto risco de parcialidade;
c) As evidências mostraram, com baixo risco de parcialidade, que o propranolol em baixas doses foi capaz de alterar a remodelação óssea reduzindo a ação osteoclástica em modelos de MDO, mas para modelos de hipertensão e osteoporose o risco de parcialidade é no máximo incerto;
d) A evidência para o captopril mostrou ser de risco baixo de parcialidade para o aumento da ação osteoclástica em modelos de diabetes, mas de alto risco para baixa atividade osteoclástica em modelos de osteólise e hipertensão;

e) As evidências para enalapril mostraram aumento a taxa de regeneração óssea para modelo de hipertensão e não apresentou alterações em modelo de normalidade, mas considerando um alto risco de parcialidade;
f) A losartana reduz a ação osteoclástica e aumenta a função osteoblástica em modelos de MDO, hipertensão e osteoporose, mas não mostrou alterações em modelos de normalidade, mas o risco de parcialidade da evidência é no máximo de incerto.

A força da evidência em estudos animais é limitada mas proporciona um direcionamento ao profissional para uma avaliação mais cautelosa em sua prática clínica relacionada aos usuários de hidroclorotiazida, atenolol, propranolol, captopril, enalapril e losartana.

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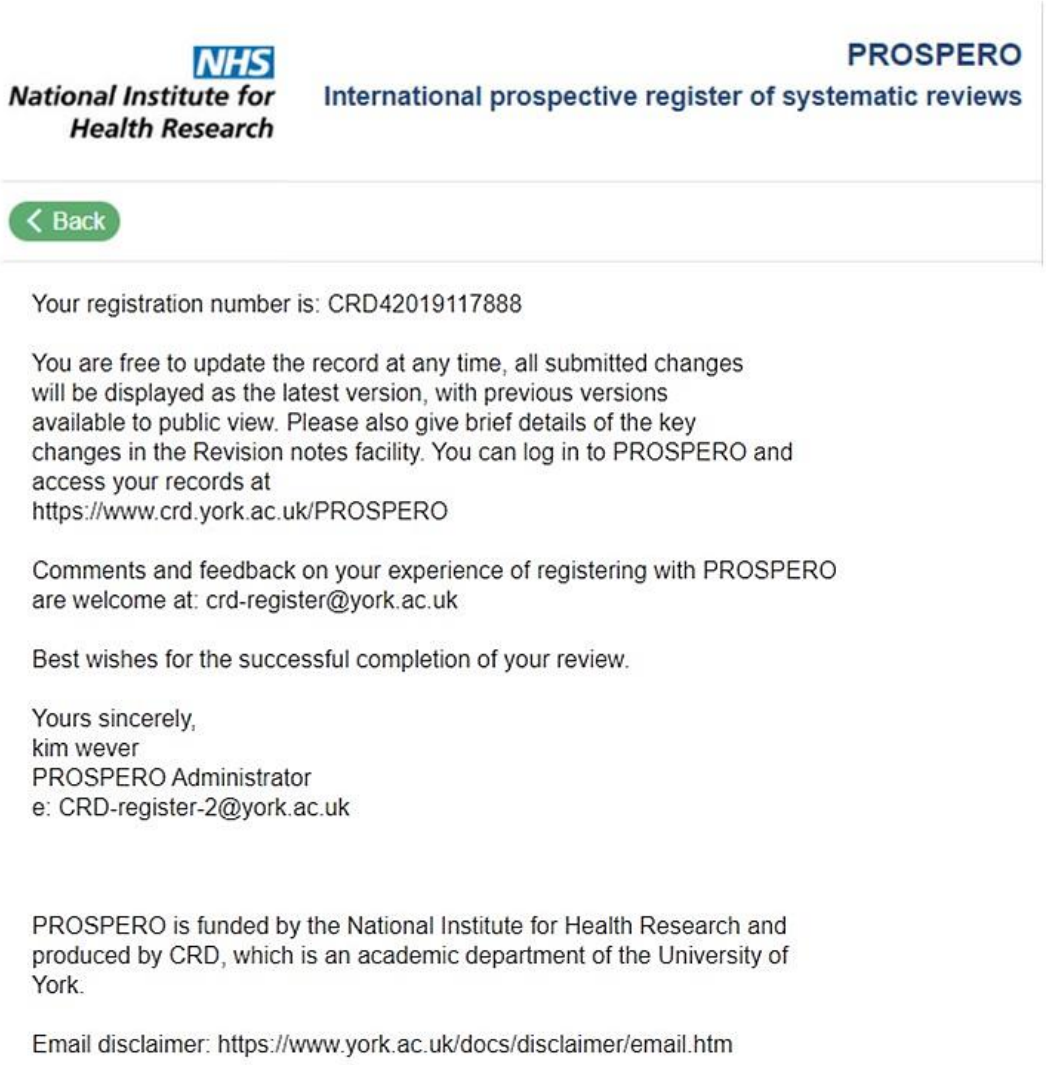
ANEXO A – Protocolo PROSPERO



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