Tese de Doutorado

EFICÁCIA ANTI-HIPERTENSIVA DE DIURÉTICOS TIAZÍDICOS ISOLADOS OU EM ASSOCIAÇÃO COM DIURÉTICOS POUPADORES DE POTÁSSIO EM PACIENTES COM HIPERTENSÃO ARTERIAL

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CARDIOLOGIA E CIÊNCIAS CARDIOVASCULARES

Eficácia anti-hipertensiva de diuréticos tiazídicos isolados ou em associação com diuréticos poupadores de potássio em pacientes com hipertensão arterial

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LISTA DE ABREVIATURAS

AVC = Acidente Vascular Cerebral

CTD = Clortalidona

DCV = Doença Cardiovascular

DTs = Diuréticos Tiazídicos

ECR = Ensaio Clínico Randomizado

HAS = Hipertensão Arterial Sistêmica

HCTZ = Hidroclorotiazida

MAPA = Monitorização Ambulatorial da Pressão Arterial

PA = Pressão Arterial

RESUMO

Objetivos: Investigar, resumir e comparar quantitativamente a eficácia anti-hipertensiva de diuréticos tiazídicos (DTs) isoladamente ou em combinação com poupadores de potássio em adultos com hipertensão arterial sistêmica (HAS). **Métodos:** Esta tese inclui uma metanálise em rede de ensaios clínicos randomizados e um protocolo de um ensaio clínico randomizado desenhado para comparar esses tratamentos. O desfecho primário foi pressão arterial de consultório para a metanálise e monitorização ambulatorial da pressão arterial no estudo original. **Resultados:** A metanálise foi concluída e seus resultados estão resumidos aqui. Todos os DTs (isoladamente ou em combinação com poupadores de potássio) foram mais eficazes que placebo. Em relação à redução da pressão arterial sistólica, DTs em combinação com poupadores de potássio e DTs em alta dose foram mais eficazes que DTs em baixa dose. Considerando pressão arterial diastólica, DTs em alta dose foi mais eficaz que DTs em baixa dose. Além disso, DTs em combinação com poupadores de potássio foi superior à DTs isolado, ambos em baixa dose, na redução da pressão arterial. **Conclusão:** Tanto a combinação de diuréticos poupadores de potássio quanto o uso de DTs em dose alta foram associados a aumento da eficácia anti-hipertensiva comparados a DTs em baixa dose. A qualidade dos estudos, no entanto, é baixa, sendo necessário um estudo bem desenhado comparando diuréticos tiazídicos isolados e combinados com diuréticos poupadores de potássio.

Palavras-chave: Hipertensão Arterial, Tratamento Farmacológico, Diuréticos.

ABSTRACT

Objectives: To investigate, summarize and quantitatively compare the antihypertensive efficacy of thiazide diuretics (TD) alone or in combination with potassium sparing agents in adults with hypertension. **Methods:** This thesis included a network meta-analysis of randomized controlled trials and a protocol of a randomized controlled trial prospectively designed to compare those treatments. The primary outcome was office blood pressure for the meta-analysis and Ambulatory Blood Pressure Monitoring for the original trial. **Results:** The meta-analysis was concluded and their results are summarized here. All thiazides (alone or in combination with potassium sparing) were more effective than placebo. For systolic blood pressure reduction, TD in combination with potassium sparing diuretic and high dose TD were more effective than low dose TD. Considering diastolic blood pressure, high dose TD was more effective than low dose TD. In addition, TD in combination with potassium sparing diuretic was superior to TD alone, both at low dose, to lowering blood pressure. **Conclusion:** Both the combination of potassium sparing diuretics and use of high-dose TD were associated with increased blood pressure lowering efficacy than low-dose TD. The quality of studies, however, is low, and well-designed trial comparing thiazide-like diuretics alone and combined with potassium-sparing diuretics is warranted.

Keywords: Hypertension, Drug Therapy, Diuretics.

1. INTRODUÇÃO

Pressão arterial (PA) elevada é causa dominante das doenças cardiovasculares, aliando alto risco a maior prevalência entre os fatores de risco[1]. Insuficiência cardíaca, fibrilação atrial, doença renal crônica, doenças valvares cardíacas, síndromes aórticas e demência, além de cardiopatia isquêmica e doenças cerebrovasculares (acidente vascular cerebral e demências) são predominantemente decorrentes de um desvio para a direita na distribuição da PA de toda a humanidade[2]. Ensaios clínicos seminais e metanálises com mais de cem mil participantes ofereceram a evidência cartesiana de que o risco para doenças cardiovasculares é revertido pela redução da PA em intensidade comparável ao aumento de PA identificado nos estudos de coorte[2].

Essa realidade fundamenta a prioridade de instituir-se a prevenção da elevação da PA em todos os indivíduos e instituir-se vigoroso tratamento para reduzir a PA daqueles com medidas elevadas. Abordagens não-medicamentosas devem ser implementadas em fases precoces da vida, mas têm menor efetividade para reduzir a PA em indivíduos com hipertensão arterial estabelecida[3].

Diuréticos tiazídicos (DTs) são utilizados para o tratamento da hipertensão arterial sistêmica (HAS) há mais de cinco décadas, sendo considerados os primeiros anti-hipertensivos com um perfil de segurança aceitável.[4,5] Apesar disso, a utilização desses fármacos pode estar associada a efeitos metabólicos adversos, como hipocalemia e hiperglicemia.[6,7] No entanto, os eventos adversos podem ser minimizados pela combinação de diuréticos poupadores de potássio.[8] Nesse cenário, é de fundamental importância a busca das melhores evidências para escolher a terapia de primeira linha ao optar pelos DTs, sejam sozinhos ou em combinação com poupadores de potássio.

Este documento apresenta um sumário de evidências sobre a associação entre elevação da PA e doença cardiovascular, epidemiologia, diagnóstico e tratamento. Segue-se a apresentação de efetividade de DTs e poupadores de potássio, incluindo eficácia na redução de pressão arterial. A revisão teórica delimita objetivos e hipóteses dessa tese.

Esta tese pretende contribuir com o conhecimento acerca do tratamento medicamentoso diurético com maior eficácia anti-hipertensiva e com melhor perfil de segurança, além de fornecer informações baseadas em evidências que possam ser utilizadas para aprimorar o atendimento de pacientes com HAS.

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2. REVISÃO DA LITERATURA

2.1 Hipertensão arterial sistêmica e doença cardiovascular

Nas sociedades pré-industriais, os níveis de pressão arterial (PA) apresentavam distribuições estreitas com valores médios que mudavam pouco com a idade e em torno de 115/75 mmHg, valor que provavelmente representa a PA normal (ou ideal) para humanos. No entanto, na maioria das sociedades contemporâneas, os níveis sistólicos de PA aumentam de forma constante e contínua com a idade, tanto em homens quanto em mulheres.[1] Esse achado onipresente poderia ser explicado porque a idade é um representante para a probabilidade e a duração da exposição aos inúmeros fatores ambientais que aumentam a PA gradualmente ao longo do tempo, como consumo excessivo de sódio, ingestão insuficiente de potássio na dieta, sobrepeso e obesidade, ingestão de álcool e inatividade física.[2]

Dentre os fatores de risco para doença cardiovascular (DCV), a PA elevada está associada à evidência mais forte de causação, tendo uma alta prevalência de exposição.[3] A hipertensão arterial sistêmica (HAS) é um dos fatores de risco mais significativos para morbimortalidade em todo o mundo.[4] Cerca de 7,5 milhões de mortes ou 12,8% do total de todas as mortes anuais no mundo ocorrem devido à PA elevada,[5] além de 212 milhões de anos de vida saudável perdidos (8,5% do total global) a cada ano.[6] No ano de 2010, a carga global com HAS era estimada em aproximadamente 1,4 bilhão de pessoas, e é provável que ultrapasse 1,6 bilhão até 2025.[7]

A HAS está fortemente associada a eventos cardiovasculares adversos, incluindo mortalidade por doença coronariana e acidente vascular cerebral (AVC),[2] e quantitativamente é o fator de risco modificável mais importante para DCV prematura.[8] Em uma coorte com mais de 1,25 milhão de pacientes com 30 anos ou

mais sem DCV basal, incluindo 20% em uso de tratamento anti-hipertensivo, pacientes com HAS na linha de base (definida como PA sistólica ≥140 mmHg ou PA diastólica ≥90 mmHg ou uso de tratamentos anti-hipertensivos) tiveram um risco de 63,3% ao longo da vida de desenvolver DCV em comparação com um risco de 46,1% naqueles com PA basal normal.[9] Análise recente realizada com dados de 1,3 milhão de adultos em uma população ambulatorial geral, tanto a hipertensão sistólica como a diastólica influenciaram de forma independente no risco de eventos cardiovasculares adversos, independentemente da definição de HAS (≥140/90 mmHg ou ≥130/80 mmHg).[10]

Os riscos da HAS são diretamente proporcionais aos valores pressóricos usuais dos indivíduos. Em metanálise de 61 grandes estudos de coorte, com 1 milhão de indivíduos sob risco (12,7 milhões de pessoas-ano) e uma incidência de 56.000 mortes por evento cardiovascular, evidenciou-se que o risco para eventos cardiovasculares aumenta de forma constante a partir de 75 mmHg de pressão diastólica usual e de 115 mmHg de pressão sistólica usual, dobrando a cada 10 mmHg no primeiro caso e a cada 20 mmHg no segundo.[11] Em todo o mundo, aproximadamente 54% dos AVCs e 47% das doenças isquêmicas do coração são atribuíveis à PA elevada.[12]

Recentemente, Ma et al.[13] avaliaram uma coorte com mais de 29 mil chineses com média de idade de 61 anos, buscando possíveis associações entre uma redução mais expressiva da PA com o risco de DCV. Os autores estimaram a taxa de risco para DCV através de modelos de risco proporcional de Cox. Neste estudo, foi observado uma tendência significativa para aumento no risco de DCV incidente, doença coronariana ou AVC hemorrágico à medida que os níveis pressóricos aumentavam. Quando se comparou valores de PA <120/80 mmHg, aqueles com HAS estágio 1 (130-139/80-89 mmHg) apresentaram um risco aumentado para DCV [hazard ratio de

1,29 (1,18-1,42)], doença coronariana [hazard ratio de 1,27 (1,15-1,41)] e AVC [hazard ratio de 1,36 (1,10-1,70)].[13]

2.2 Prevalência da hipertensão arterial sistêmica

A HAS é uma doença prevalente, com taxas de controle abaixo do ideal. A definição de HAS mudou nos últimos anos, e essa mudança impactou nas estatísticas, já que a sua prevalência depende da definição adotada. Em 2017, o Colégio Americano de Cardiologia / Associação Americana de Cardiologia (ACC / AHA) reduziu o limiar para a definição de HAS,[14] passando de ≥140 mmHg e/ou ≥90 mmHg para ≥130 mmHg e/ou ≥80 mmHg para PA sistólica e diastólica, respectivamente. Usando a definição mais antiga de hipertensão, estima-se que 26% da população adulta mundial (972 milhões) fosse hipertensa no ano 2000, e calcula-se que chegue a 1,56 bilhões de pessoas em 2025.[15]

Especificamente no Brasil, na metanálise de Picon et al., os 40 estudos transversais e de coorte incluídos mostraram tendência à diminuição da prevalência nas últimas três décadas.[16] Considerando o critério antigo (PA ≥140/90 mmHg), a prevalência de HAS nas décadas de 1980, 1990 e 2000 foi de 36,1% (IC95% 28,7-44,2%), 32,9% (29,9-36,0%) e 28,7% (26,2-31,4%), respectivamente.

Em estudo com 15.103 servidores públicos de seis capitais brasileiras observou prevalência de HAS em 35,8%, com predomínio entre homens (40,1% vs. 32,2%).[17] Do total de pessoas classificadas como apresentando HAS, 76,8% estavam em uso anti-hipertensivos. Já em um estudo transversal de base populacional com 918 adultos, conduzido no estado do Rio Grande do Sul de 1999-2000, tendo HAS definida como PA ≥140/90 mmHg ou uso atual de anti-hipertensivos, mostrou prevalência de HAS

de 33,7%.[18] Somente 50,8% dos indivíduos hipertensos estavam cientes do diagnóstico, e apenas 10,4% estavam com a HAS controlada.

Aplicando as diretrizes atualizadas do ACC / AHA de 2017 aos dados do *National Health and Nutrition Examination Surveys* (NHANES) de 2011 a 2014, 46% dos adultos com 20 anos ou mais de idade nos Estados Unidos tinham HAS (definida como uso de medicamentos anti-hipertensivos ou pressão sistólica ≥130/80 mmHg).[19] Com base no tamanho da população adulta, isso se traduziu em mais 31 milhões de adultos, para um total de 103 milhões de adultos nos Estados Unidos, com HAS.

A taxa de controle adequado da PA varia de acordo com a região geográfica. Em um estudo transversal que incluiu mais de um milhão de adultos em 44 países de baixa e média renda, apenas 10% dos pacientes com HAS alcançaram controle adequado da PA; as taxas variaram de 20% entre os países da América Latina e do Caribe a menos de 5% na África subsaariana.[20] Neste estudo, HAS foi definida como PA ≥140/90 mmHg ou uso relatado de medicamento para HAS.

2.3 Diagnóstico

É necessária uma técnica padronizada e apropriada para a medição da PA. Idealmente, várias etapas devem ser seguidas para alcançar a máxima precisão. A 7ª Diretriz Brasileira de Hipertensão instrui que o indivíduo deva estar em pelo menos 5 minutos de repouso, com os dois pés no chão, sem a bexiga cheia. É recomendado não praticar exercício físico, além de evitar café, álcool ou cigarros previamente à aferição. Também é importante medir a PA com o paciente sentado, com as pernas descruzadas, pés apoiados no chão e dorso recostado; o braço deve estar na altura do coração e a palma da mão virada para cima. Atenção especial deve ser dada nos pacientes diabéticos e idosos, aferindo a PA na posição de pé, após 3 minutos, onde a hipotensão postural pode ser suspeitada.[21]

De acordo com a diretriz americana (ACC / AHA) de 2017, o indivíduo adulto tem PA normal quando a PA sistólica e diastólica se encontram abaixo de 120 e 80 mmHg, respectivamente; já valores ≥130 e ≥80 mmHg para sistólica e diastólica, respectivamente, classificam o indivíduo como portador de HAS.[14] A **Tabela 1** apresenta em detalhes os critérios diagnósticos da Diretriz Americana.

Categoria	PA Sistólica		PA Diastólica
Normal	<120 mmHg	E	<80 mmHg
Elevada	120-129 mmHg	E	<80 mmHg
HAS Estágio 1	130-139 mmHg	OU	80-89 mmHg
HAS Estágio 2	≥140 mmHg	OU	≥90 mmHg

Tabela 1. Categorias da pressão arterial em adultos de acordo com a diretriz do *American College of Cardiology/American Heart Association* (2017).

2.4 Tratamento

A modificação do estilo de vida deve ser prescrita a todos os pacientes com HAS. O tratamento não-medicamentoso da HAS envolve controle ponderal, medidas nutricionais, prática de atividades físicas, cessação do tabagismo, controle de estresse, entre outros.

Fundamentalmente, os objetivos do tratamento da HAS são o controle da pressão alta e redução da morbimortalidade cardiovascular associada, usando a terapia mais adequada disponível. Porém, nem todos os pacientes necessitam de terapia farmacológica. O início da medicação anti-hipertensiva é recomendado para adultos com PA sistólica ≥140 mmHg ou PA diastólica ≥90 mmHg e aqueles com PA sistólica entre 130 e 139 mmHg ou PA diastólica entre 80 e 89 mmHg com alto risco de eventos de DCV.[14,22]

Há evidências científicas robustas que mostram benefício do tratamento medicamentoso na redução de desfechos primordiais. Em uma metanálise de 68 ensaios clínicos randomizados (ECRs) (245.885 indivíduos), o tratamento anti-hipertensivo mostrou reduções substanciais de risco em relação a eventos cardiovasculares (maiores para AVC e insuficiência cardíaca, mas também significativos para doença coronariana e mortalidade).[23]

Evidências clínicas substanciais concluíram que a magnitude de redução da PA é o principal determinante da redução do risco cardiovascular em pacientes hipertensos. Metanálise de Law et al. incluiu 147 ECRs com fármacos anti-hipertensivos e mais de 464.000 pacientes na avaliação de doença arterial coronariana e AVC.[24] Neste estudo, com exceção do efeito protetor extra dos beta-bloqueadores administrados logo após infarto agudo do miocárdio e o menor efeito adicional dos bloqueadores do canal de cálcio na prevenção do AVC, todas as classes de medicamentos anti-hipertensivo tiveram um efeito semelhante na redução de eventos de doença coronária e AVC para uma dada redução da PA, excluindo efeitos pleiotrópicos relevantes. Outra metanálise de 31 estudos com 190.606 participantes teve como objetivo quantificar as reduções de risco relativo referentes a desfechos cardiovasculares maiores obtidas com diferentes esquemas de medicamentos para reduzir a PA em adultos jovens e idosos.[25] Os resultados não mostraram diferença entre os efeitos das classes de medicamentos quanto a eventos cardiovasculares maiores. Ettehad et al., através da metanálise de dados de 123 estudos com 613.815 pacientes, mostraram reduções de risco relativas em desfechos cardiovasculares maiores proporcionais à magnitude das reduções de PA alcançadas.[26] Cada redução de 10 mmHg na PA sistólica reduziu significativamente o risco de eventos cardiovasculares maiores (risco relativo 0,80, IC95% 0,77-0,83), doença arterial coronariana (0,83,

IC95% 0,78-0,88), AVC (0,73, IC95% 0,68-0,77) e insuficiência cardíaca (0,72, IC95% 0,67-0,78), que, nas populações estudadas, levaram a uma significativa redução de 13% na mortalidade por todas as causas (0,87, IC95% 0,84-0,91).[26]

Desta forma, é necessário que para o adequado tratamento do paciente com diagnóstico de HAS, e consequente redução de morbimortalidade cardiovascular, o profissional de saúde escolha o tratamento medicamentoso cuja eficácia anti-hipertensiva seja superior às demais opções disponíveis.

3. DIURÉTICOS TIAZÍDICOS E POUPADORES DE POTÁSSIO

Os diuréticos tiazídicos (DTs) têm sido comumente utilizados como agentes farmacológicos para o tratamento da HAS há mais de cinco décadas, tornando-se o primeiro anti-hipertensivo oral com um perfil de efeito adverso aceitável.[27,28] Os membros dessa classe de medicamentos são derivados da benzotiadiazina (os chamados "diuréticos tipo tiazida", como hidroclorotiazida (HCTZ) e bendroflumetiazida). Os medicamentos com ação farmacológica semelhante no rim que não possuem estrutura química da tiazida, como indapamida, clortalidona (CTD) e metolazona, são denominados "diuréticos semelhantes à tiazida". Apesar da variação estrutural entre os diferentes componentes, o termo “diurético tiazídico” inclui todos os diuréticos que se acredita terem uma ação primária no túbulo distal.

Os DTs são amplamente utilizados no tratamento da HAS devido à eficácia demonstrada na redução da PA, perfil de segurança favorável e baixo custo. Em pacientes com HAS, foi demonstrado que os DTs são eficazes em doses baixas.[29-36]

CTD e indapamida demonstraram maior eficácia anti-hipertensiva do que a HCTZ em níveis de dose semelhantes.[36-39] A CTD é 1,5 a 2 vezes mais eficaz que a HCTZ na redução da PA na mesma dosagem.[40] A menor eficácia da HCTZ pode ser explicada por uma menor duração de ação em comparação à CTD e indapamida.[40,41]

Em um pequeno ECR com 30 pacientes, unicego, com monitorização ambulatorial de pressão arterial (MAPA), 25 mg de CTD reduziram 5 mmHg a mais da PA sistólica de 24 horas do que 50 mg de HCTZ.[37] A diferença foi ainda mais acentuada no período do sono (7,1 mmHg). DTs são tipicamente consideradas ineficazes quando a taxa de filtração glomerular diminui para menos de 30 a 40 ml/min por 1,73 m2 de área de superfície corporal.[41]

O uso de DTs pode estar associado a efeitos metabólicos adversos, como: hipocalemia, hiponatremia, hiperuricemia, hiperglicemia, hiperlipidemia e hipomagnesemia.[29,42,43] A incidência dessas complicações metabólicas aumenta com a dose.[24,29,44] Em pacientes estáveis com uma dose fixa de DTs, a perda de potássio ocorre principalmente durante as duas primeiras semanas de terapia antes que a estabilidade ocorra.[45] Pacientes hipertensos que são tratados com altas doses de diurético sem um agente poupador de potássio têm uma incidência aumentada de morte súbita cardíaca.[46] O risco de hipocalemia pode ser minimizado pela combinação de DTs com antagonistas dos receptores mineralocorticóides (por exemplo, espironolactona e eplerenona) ou bloqueadores do canal epitelial de sódio (por exemplo, amilorida e triantereno), que também podem atenuar a intolerância à glicose associada aos DTs.[47] Os antagonistas dos receptores mineralocorticóides e os bloqueadores do canal epitelial de sódio são comumente referidos como diuréticos poupadores de potássio.

Embora as propriedades anti-hipertensivas dos antagonistas dos receptores mineralocorticóides espironolactona e eplerenona tenham sido bem documentadas,[48-52] o efeito de amilorida e triantereno na redução da PA não foi tão claramente determinado. Uma revisão da Cochrane de seis pequenos estudos relatou não haver efeito significativo na PA com doses baixas de amilorida e triantereno.[53] Por outro

lado, alguns estudos sugerem que a amilorida pode ser eficaz no tratamento da hipertensão resistente[54] e pode ter um efeito anti-hipertensivo mais potente em doses mais altas.[47,55] Em ECR realizado em Porto Alegre, amilorida aumentou a eficácia anti-hipertensiva de HCTZ, e foi bem tolerada.[56] A combinação CTD/amilorida foi mais eficaz que losartana para reduzir a PA em ECR realizado no Brasil.[57] O triantereno e a amilorida são comumente administrados com HCTZ, embora outras combinações de tiazídicos e agentes poupadores de potássio estejam disponíveis.

Ainda não se sabe se diferentes diuréticos estão associados a diferentes desfechos clínicos. Tanto CTD como indapamida demonstraram redução de eventos cardiovasculares em estudos randomizados de grande porte,[58,59] enquanto não há evidências de que a HCTZ sozinha reduza eventos cardiovasculares.[60]

O primeiro trabalho a sugerir que clortalidona pudesse ser superior à HCTZ na prevenção de desfechos primordiais foi o *Multiple Risk Factor Intervention Trial* (MRFIT), um grande estudo de prevenção primária iniciado em 1973, o qual testou o efeito de um programa de intervenção multifatorial sobre mortalidade cardiovascular.[61] Em 1980, houve uma mudança no protocolo de tratamento anti-hipertensivo, que passou a recomendar CTD, não HCTZ, como tratamento inicial.[62] Os dados que levaram a essa mudança indicavam que nas clínicas em que o uso de HCTZ predominava, a tendência de mortalidade era desfavorável para o grupo intervenção comparado com cuidado usual, porém era favorável nas clínicas que utilizavam CTD. Mais recentemente, uma metanálise de 9 ECR incluindo 50946 pacientes comparou indiretamente a eficácia de HCTZ e CTD.[63] Comparada com HCTZ, CTD reduziu significativamente o risco de eventos cardiovasculares. Os resultados desta metanálise são consistentes com os dados observacionais do estudo MRFIT.[64] Entre os homens hipertensos do estudo, 2392 foram tratados com CTD e

4049 com HCTZ. Durante 6 anos de seguimento, eventos cardiovasculares foram significativamente menos comuns com CTD em comparação a HCTZ. Seguindo nesta direção, uma metanálise comparou indiretamente diuréticos "tipo tiazida" versus diuréticos "semelhantes à tiazida", avaliando sua eficácia contra placebo ou outros agentes anti-hipertensivos.[65] Comparado com diuréticos "tipo tiazida", os diuréticos "semelhantes à tiazida" reduziram significativamente o risco de eventos cardiovasculares e insuficiência cardíaca.

Por outro lado, Psaty et al.[66] conduziram uma metanálise que comparou indiretamente os desfechos de saúde de terapias diuréticas em baixa dose baseadas em clortalidona versus não-CTD, usando dados de uma metanálise em rede anterior.[31] Neste estudo, os desfechos cardiovasculares maiores para a CTD e outros DTs pareciam ser semelhantes. Estes resultados vão ao encontro de estudo observacional com 29873 pacientes idosos, que demonstrou que CTD não foi associada a menor risco de morte ou hospitalização cardiovascular comparada com HCTZ, mas foi associada com um risco aumentado de hospitalização por hipocalemia e hiponatremia.[67]

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4. JUSTIFICATIVA

Não há ECRs que compararam diretamente os diferentes DTs (isoladamente ou em combinação com diuréticos poupadores de potássio) quanto a desfechos cardiovasculares primordiais em pacientes com HAS, e comparações indiretas anteriores forneceram resultados conflitantes.

Os profissionais de saúde precisam dispor das melhores evidências para escolher a terapia de primeira linha ao optar por DTs, seja em monoterapia, seja associado a poupadores de potássio. Este cenário sustenta a pertinência de se testar comparativamente estas abordagens medicamentosas. Há forte evidência de que a magnitude da redução da PA é o principal determinante da redução de risco cardiovascular em pacientes hipertensos, o que torna a redução da PA um desfecho intermediário adequado para comparação entre os DTs.

HIPÓTESE CONCEITUAL

A associação de DT com diurético poupador de potássio é superior ao DT em monoterapia na redução da PA em pacientes com HAS.

5. OBJETIVOS

Artigo 1

Objetivo primário

Investigar, sumarizar e comparar quantitativamente a eficácia na redução da PA de DTs isoladamente ou em combinação com diuréticos poupadores de potássio em pacientes com hipertensão arterial.

Objetivos secundários

Investigar, sumarizar e comparar quantitativamente o impacto dos DTs isoladamente ou em combinação com diuréticos poupadores de potássio em relação a parâmetros laboratoriais [potássio sérico, ácido úrico, glicose plasmática em jejum, hemoglobina glicada (HbA1C) e níveis lipídicos (colesterol total, LDL-C, HDL-C e triglicerídeos), eventos cardiovasculares maiores (mortalidade por todas as causas, mortalidade cardiovascular, acidente vascular cerebral fatal e não fatal, infarto do miocárdio fatal e não fatal e hospitalização por insuficiência cardíaca) e perdas.

Artigo 2

Objetivo primário

Comparar clortalidona 25 mg associada a amilorida 20 mg versus outras combinações de tiazídicos com amilorida em relação à eficácia na redução da pressão arterial em indivíduos com hipertensão arterial.

Objetivo secundários

Comparar, em indivíduos com hipertensão arterial, clortalidona 25 mg associada a amilorida 20 mg versus outras combinações de tiazídicos com amilorida em relação à:

- Incidência de eventos adversos;
- Variação de parâmetros laboratoriais;
- Proporção de pacientes que alcançaram o controle da pressão arterial.

ARTIGO 1

Thiazide Diuretics Alone or in Combination with a Potassium-Sparing Diuretic on Blood Pressure Lowering in Patients with Primary Hypertension:

A Systematic Review and Network Meta-Analysis

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ABSTRACT

Background: Thiazide diuretics have been used for the treatment of hypertension for more than five decades. Their use may be associated with adverse metabolic effects, which may be minimized by combining thiazides with potassium-sparing diuretics. It remains unknown whether different diuretics are associated with different clinical outcomes. We conducted a systematic review with a network meta-analysis to compare the antihypertensive efficacy of thiazides alone or in combination with a potassium-sparing diuretic in patients with primary hypertension, as well as the safety of such drugs through the measurement of drug-related adverse events. **Methods:** Network metanalysis of double-blind randomized controlled trials. We included studies comparing thiazide diuretics alone or in combination with potassium sparing agents with placebo or any other antihypertensive treatment. The primary outcome measure was office blood pressure (systolic and diastolic). **Results:** 307 randomized controlled trials were included, comprising 62,906 hypertensive individuals. All thiazides (alone or in combination with a potassium-sparing diuretic) included in this metanalysis were more effective than placebo for both systolic and diastolic blood pressure in adults with hypertension. For systolic blood pressure, high dose thiazide alone provided a greater reduction in blood pressure compared to low dose thiazide alone. In addition, thiazide in combination with potassium sparing was more effective than low dose thiazide alone in reducing diastolic blood pressure. Considering diastolic blood pressure, thiazide in combination with potassium sparing in any dose strata and high dose isolated thiazide provided a greater reduction in blood pressure compared to the low dose of thiazide alone. **Conclusion:** The combination of potassium-sparing diuretics and higher thiazide dose are associated with increased antihypertensive efficacy compared to low-dose thiazide diuretics.

INTRODUCTION

Background and Rationale

Thiazide diuretics have been used for the treatment of hypertension for more than five decades, becoming the first oral antihypertensive agents with an acceptable side-effect profile[1,2]. Agents of this class derived from benzothiadiazine are called "thiazide-type diuretics", such as hydrochlorothiazide and bendroflumethiazide. Drugs with a similar pharmacologic action on the kidney but that do not have the thiazide chemical structure (e.g., indapamide, chlorthalidone and metolazone) are termed "thiazide-like diuretics". Despite chemical structural variations, the term "thiazide diuretic" covers all diuretics that have a primary action in the distal tubule.

In patients with primary hypertension, thiazide diuretics have been demonstrated to be effective at low doses[3-9], where the steepest part of the dose-response curve is typically seen[10]. Chlorthalidone and indapamide, both thiazide-like diuretics, have been shown to provide greater antihypertensive efficacy than hydrochlorothiazide, a thiazide-type diuretic, at similar dose levels[11-15]. Chlorthalidone is 1.5 to 2 times as effective as hydrochlorothiazide to lowering blood pressure at the same dose[12]. The lower efficacy of hydrochlorothiazide may be explained by a shorter duration of action compared to chlorthalidone and indapamide [2,13,16].

The use of thiazide diuretics may be associated with adverse metabolic effects, especially hypokalemia and hyperglycemia, but also hyponatremia, hyperuricemia, hyperlipidemia and hypomagnesemia[3,17,18]. The incidence of these metabolic effects occurs in a dose-response manner[3,10,19]. The risk of hypokalemia may be minimized by combining thiazides with potassium-sparing diuretics - mineralocorticoid receptor antagonists (e.g., spironolactone and eplerenone) or blockers of the epithelial sodium channel (e.g., amiloride

and triamterene), which may also mitigate the impaired glucose tolerance associated with thiazides[20]. High doses of thiazides were associated with risk for sudden death, a risk that was not present in patients using an association with a potassium-sparing diuretic[21]. It should be acknowledged, however, that potassium-sparing diuretics may also have some side effects, such as hyperkalemia, and spironolactone have been associated with gynecomastia[22].

Although the antihypertensive properties of spironolactone and eplerenone have been well documented[23-27], the blood pressure-lowering effect of amiloride and triamterene has not been as clearly determined. A previous systematic review reported no significant effects on blood pressure at low doses of amiloride and triamterene[28]. In contrast, some studies suggest that amiloride may be effective in resistant hypertension[29], and may have stronger antihypertensive effect at higher doses in non-resistant hypertension[21, 30].

It remains unknown whether different diuretics are associated with different clinical outcomes. Both chlorthalidone and indapamide have been shown to reduce cardiovascular events in landmark randomized trials[31, 32], whereas there is no evidence that hydrochlorothiazide alone reduces cardiovascular events[33]. There are no randomized controlled trials that directly compared different thiazides (alone or in combination with potassium-sparing diuretics) on hard cardiovascular outcomes in hypertensive patients, and previous indirect comparisons by meta-analysis and evidence from observational studies provided conflicting results[34-38]. Given the plethora of drug types among thiazides, no between-drugs comparison has been conducted at the level of a primary study - randomized controlled trial - (and it is also unfeasible), whereas decision-makers may need the best evidence to choose the first line therapy when opting by thiazides. Since substantial clinical evidence concluded that the amount of blood pressure reduction is the major determinant of reduction in cardiovascular risk in hypertensive patients[10, 39-41], the blood pressure lowering effect among diuretics becomes an appropriate surrogate outcome. For this purpose, a

network meta-analysis of randomized controlled trials seems to be justifiable since it allows comparisons of drugs not included in the same randomized controlled trial, and may also provide a probability of success among the tested treatments.

This said, we conducted a systematic review with a network meta-analysis through a mixed-treatment comparison model, in which direct and indirect evidence were incorporated and merged whenever possible, to compare the efficacy of thiazides alone or in combination with a potassium-sparing diuretic in patients with primary hypertension, as well as the safety of such drugs through the measurement of drug-related adverse events.

Objectives

Primary objective

To investigate, summarize and compare quantitatively the blood pressure lowering efficacy of thiazide diuretics alone or in combination with potassium-sparing diuretics among themselves in patients with primary hypertension.

Thiazide diuretics alone were grouped into the category called "Treatment T" and thiazide diuretics in combination with potassium sparing agents were grouped into the category called "Treatment TP". Additionally, the treatments were classified according to the mean daily dose. The doses of each thiazide diuretic were categorized as proportions of the manufacturer's recommended starting dose. In the case where a range of starting doses is recommended by the manufacturer, the lowest dose was considered to be the starting dose (1x). Both treatment groups (T and TP) were categorized in two strata, according to the mean daily dose of the thiazide component: low dose (< 2x start dose) and high dose (≥ 2x start dose). An exception to this rule was applied to hydrochlorothiazide. Although hydrochlorothiazide has the same recommended starting dose as chlorthalidone

(12.5mg/day), the available literature suggests that chlorthalidone is 1.5 to 2 times as effective as hydrochlorothiazide to lowering blood pressure at the same dose. For this reason, the initial dose of hydrochlorothiazide was considered as 25mg/day. The dose classification of the drugs analyzed in our study is presented in Table 1.

Secondary objectives

To investigate, summarize and compare quantitatively the impact of the thiazide diuretics alone or in combination with a potassium-sparing diuretic in relation to laboratory parameters [serum potassium, uric acid, fasting plasma glucose, glycated hemoglobin (HbA1C), total cholesterol, LDL-C, HDL-C and triglycerides], major adverse cardiovascular events - MACE (all-cause mortality, cardiovascular mortality, fatal and non-fatal stroke, fatal and non-fatal myocardial infarction and hospitalization because of heart failure) and withdrawals. MACE were considered as a composite outcome and also individually, whenever reported.

Drug name	Adult Dosing HTN (mg/day)	Low dose (< 2x start dose; mg/day)	High dose (≥ 2x start dose; mg/day)
bendroflumethiazide	2,5	< 5	≥ 5
butizide	2,5-7,5	< 5	≥ 5
chlorothiazide	500-2000	< 1000	≥ 1000
chlorthalidone	12,5-100	< 25	≥ 25
cyclopenthiazide	0,25-0,5	< 0,5	≥ 0,5
hydrochlorothiazide	25-50	< 50	≥ 50
hydroflumethiazide	25-50	< 50	≥ 50
indapamide IR	2,5	< 5	≥ 5
indapamide SR	1,5	< 3	≥ 3
mefruside	25-50	< 50	≥ 50
methyclothiazide	2,5-5	< 5	≥ 5
metolazone (Mykrox)	0,5-1	< 1	≥ 1
metolazone (Zaroxolyn)	2,5-5	< 5	≥ 5
xipamide	20	< 40	≥ 40
altizide+spironolactone	7,5/12,5-15/25	< 15/25	≥ 15/25
bemetizide+triamterene	10/20-25/50	< 20/40	≥ 20/40

Table 1: Drug classification according to mean daily dose (low / high dose).

IR: immediate release; SR: slow release.

METHODS

Protocol and registration

The protocol of this network meta-analysis was written guided by Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols Statement (PRISMA-P) and the PRISMA Explanation and Elaboration article for guidance. A copy of the protocol is publicly deposited in the following repository: Open Science Framework (https://osf.io/tezf8; DOI 10.17605/OSF.IO/TEZF8), and can be found at **Appendix 1**.

This systematic review and network meta-analysis is prospectively registered at the PROSPERO database (CRD42018118492).

Eligibility criteria

Participants

Participants were adults (18 years old or more) regardless of sex and race, diagnosed with primary hypertension (as stated by the authors). To minimize a possible carryover effect, only studies in which participants were at least 2 weeks without active antihypertensive treatment prior to randomization were included. In previously treated patients, this could be achieved with drug withdrawal or placebo run-in. In previously untreated patients, no placebo period was required. All trials targeting blood pressure in patients with hypertension were included even if blood pressure was not the primary outcome (e.g., a randomized controlled trial targeting blood pressure with antihypertensive agents in type 2 diabetes, in which the common clinical outcome is glycated hemoglobin - HbA1c, e.g., the ACCORD trial [42]).

Trials with patients with the following conditions were excluded: heart failure with reduced ejection fraction (≤ 40%); heart failure with preserved ejection fraction and New York Heart Association (NYHA) functional class II–IV; chronic renal disease requiring dialysis; or a documented serum creatinine level more than 1.5 times the normal range, as thiazide diuretics are considered to be less effective in patients with impaired kidney function [43]. Also, patients taking medications that were not the interventions of our interest, but affect blood pressure, were excluded (e.g., doxazosin for benign prostatic hyperplasia, which also has an antihypertensive effect).

Interventions

The eligible interventions were antihypertensive agents from the class of diuretics (classification above mentioned), as follows:

a) Thiazide diuretics alone, specifically: hydrochlorothiazide, chlorothiazide, butizide, bendroflumethiazide, hydroflumethiazide, trichlormethiazide, methyclothiazide, polythiazide, cyclothiazide, cyclopenthiazide, chlorthalidone, metolazone, quinethazone, fenquizone, clorexolone, clopamide, indapamide, diapamide, isodapamide, mefruside, xipamide, bemetizide, benzthiazide and chlorazanil;

b) Thiazide diuretics in combination with a potassium-sparing diuretic, specifically: spironolactone, eplerenone, amiloride and triamterene.

Comparators

By the nature of this study, the eligible interventions were compared among themselves. Besides, in order to expand the geometry, treatments out of interest but connected with the ones of interest and add potentially indirect comparisons for our network were included as common comparators. The ones considered were placebo or any other antihypertensive drug, alone or in combination, regardless of the pharmacological class, including angiotensin-converting enzyme inhibitors (ACEi), angiotensin receptor blockers (ARB), beta-blockers (BB), calcium channel blockers (CCB), renin inhibitors, centrally-acting drugs and diuretics other than the interventions of interest (eg, loop diuretics). Note: as potassium chloride may have antihypertensive effect, thiazides with potassium supplementation were not be considered an eligible intervention, but this combination could also be eligible as a comparator.

Outcomes

Primary outcome

Office systolic and diastolic blood pressure measured as continuous outcome. If blood pressure measurements were available at more than one time during the 24-hour period, we used only the trough measurement. Trough blood pressure is defined as the blood pressure measurement taken before the next dosing schedule. If timing of measurement was not reported, blood pressure was assumed to have been taken at trough. When blood pressure measurement data were available in more than one position, sitting blood pressure was the first preference, followed by standing and supine position. If blood pressure measurements were available more than once within the accepted follow-up window, the last measurement was used. Studies in which blood pressure measurements were not taken under resting condition were excluded.

Secondary outcomes

Efficacy outcomes

Ambulatory blood pressure monitoring (ABPM). We qualitatively synthesized data about daytime, nighttime and 24h blood pressure (systolic and diastolic).

Major adverse cardiovascular events - MACE (all-cause mortality, cardiovascular mortality, fatal and non-fatal stroke, fatal and non-fatal myocardial infarction and hospitalization because of heart failure). We synthesized MACEs as a composite outcome and also individually whenever reported.

Note: when studies with both office and ambulatory blood pressure measurements were available, they were considered eligible, and data from all methods were analyzed. In studies in which blood pressure was measured by only one method, we collected data from that method. If several measurements were available within the acceptable window, the last measurement was used.

Safety (harms) outcomes

Change from baseline in serum potassium, uric acid, fasting plasma glucose, glycated hemoglobin (HbA1C), and lipid levels (total cholesterol, LDL-C, HDL-C and triglycerides) were analyzed quantitatively. Number of withdrawals and MACE among the eligible treatments were analyzed qualitatively. If several measurements were available within the acceptable window, the last measurement was used.

Study designs

We included only double-blind randomized controlled trials as our unit of analysis. Studies were considered suitable for inclusion if the following criteria were met: randomized controlled trials with parallel or crossover design, double-blind, controlled by placebo or active treatment. We limited trials for those beginning with 3 weeks of follow up last to 52 weeks, because trials designed with longer follow-up often target primordial cardiovascular outcomes (e.g., cardiovascular mortality) and thus blood pressure measurement could be at higher risk to be inaccurate due to a lesser relevance given in those designs.

Intensification studies in which the antihypertensive drugs of interest were used for this purpose were excluded; thus, only studies with treatment-naive patients at the time of randomization were included.

Studies with step up therapy in non-responders (i.e., addition of another antihypertensive drug as second-line therapy in patients not meeting a target goal blood pressure level) were included, as long as pre-step up blood pressure measurements were provided.

Crossover studies were included entirely if there was a clear history of at least 2 weeks of washout among the treatments tested. If not, only the first period of the study was included, as long as pre-crossover data were provided. Factorial designs were considered whenever interaction between treatments were absent. We included studies that measured office blood pressure or ABPM at baseline and at one or more time points between 3 and 52 weeks after initiation of treatment.

We excluded the following designs: open-label randomized controlled trials, non-randomized controlled trials, observational studies, case report or case series studies, open-label studies, studies with thiazides in combination with drug classes other than potassium-

sparing diuretics, and studies in patients with secondary causes of hypertension. Quasi-experimental studies (such as those that allocate using alternate days of the week or that do not have a comparator group) were also excluded. Studies with double dummy technique were included.

No restriction was imposed for the language of publication, date of publication, publication status or sample size. Whenever possible, any report (e.g., conference abstracts) in which partial data was sufficient to be analyzed (quantitatively or qualitatively) were included - for sufficient data, we considered the sample size for each group; the point-estimate within or between-groups; its related dispersion, precision or type 1 error variable.

Information sources

Electronic searches

For an extensive and comprehensive survey of the literature, we searched six electronic bibliographic databases from database inception to the data of the search (PubMed/MEDLINE, Cochrane Library, Embase, Web of Science, Scopus, Lilacs), a registration database (ClinicalTrials.gov) for potential results in unpublished studies and Educational Resources Information Center (ERIC [ProQuest]) for results in non-indexed journals or other forms of reporting (thesis, clinical report, conference summary, monograph, etc.). The main electronic search strategy was designed for MEDLINE and was adapted as appropriate for each of the databases. Literature search strategies were developed using MeSH terms and their synonyms, and boolean operators (where possible) to improve searches. Keywords and terms of MeSH included: "hydrochlorothiazide", "chlorothiazide", "bendroflumethiazide", "hydroflumethiazide", "trichlormethiazide", "methyclothiazide", "polythiazide", "cyclopenthiazide", "chlorthalidone", "metolazone", "clopamide",

"indapamide", "mefruside", "xipamide", "bemetizide", "benzthiazide", "chlorazanil", "spironolactone", “eplerenone”, "amiloride", "triamterene", "thiazide diuretics", “inhibitor of the epithelial sodium channel”, “potassium sparing diuretic” and "hypertension". In addition, we checked the reference lists of included studies or relevant reviews identified to the data through the survey so as to ensure that no eligible studies were missed out. Bibliographic research was not limited by languages. For articles not published in English, Spanish or Portuguese, we used Google Translator. Results from the search and retrieved references were imported and managed in Clarivate Analytics Endnote X9® (2018) reference management software. Comprehensive search strategies for all the bases that were consulted are included in **Appendix 2**.

Note (limitation): clinical study reports from regulatory agencies and pharmaceuticals industry were excluded by feasibility. The evidence shows barriers, time frames and predictors (e.g., the sharing only for recognized institutions such as the Cochrane Collaboration - authority fallacy) that points out for our inability to handle it [44]. Therefore, we acknowledge it as a limitation of our search strategy and also from our study since its inception.

Study records

After the queries, each electronic database was exported to a reference manager software (EndNote X9) and duplicates were removed. Other sources were inserted manually in the reference manager and checked again for duplicates. Then, titles and abstracts were stored at the reference manager till the beginning of the eligibility process. At the time of the screening process, one author split the library with the titles and abstracts accordingly to

the number of reviewers. Potentially eligible titles and abstracts and the excluded ones were stored in specific folders. Physical report was scanned for future purposes or independent researchers checking and deposited in the Google Drive® with specific folders for inclusion and exclusion with reasons. A final list of included and excluded articles in each step was recorded. If a trial was suspected to have unpublished outcomes of blood pressure efficacy, authors were contacted to seek for any potential unpublished outcome.

Data were extracted and stored in a piloted spreadsheet for data synthesis. For the assessment of the risk of bias of included studies, we used the Cochrane Collaboration spreadsheet settled for the Risk of Bias 1.0 tool and final decisions were stored at the RoB 1.0 spreadsheet. All of the materials used in this NMA-SR will be shared thereafter in a public repository, after the publication of the manuscript.

Screening Process

The screening for eligible randomized controlled trials were conducted in a two-step manner. First, reports were checked on the level of titles and abstracts. For this purpose, the liberal accelerated approach was undertook[45], in which one author flagged the potentially eligible reports and the excluded ones, and a second author reviewed records excluded by the first reviewer. Disagreements were solved by consensus. On the level of the titles and abstracts, the reports were stored in only two folders after the final decision - only for potentially eligible reports and a second one for excluded reported.

After the first step, the remaining potentially eligibility records were checked by their full-texts in duplicate by pairs of independent reviewers. Disagreements were solved by consensus or by a third reviewer decision. On this level, reports were flagged as eligible or ineligible with their respective reasons. In case of any physical report to be checked, they

were separated in the same manner as digital records after final decision, but they were checked for eligibility directly by the full-text assessment.

Data collection process

Data extraction was done in duplicate, with independent reviewers through a piloted data extraction form. The piloting of the form was done by two reviewers with the first 3 eligible records and amendments were made accordingly to the process. Disagreements were solved by consensus or by the opinion of a third reviewer. Reasons for amendments and versions of the data extraction form were recorded.

Data extraction

For the purpose of our NMA study, we extracted the variables described below. For quantitative outcomes the target data to be extracted was the mean change from baseline with standard deviation or standard error or confidence interval or p-value. Also, we extracted mean and standard deviation at baseline and at follow-up. For dichotomous outcomes, we collected the number of events and the sample size for each treatment arm.

Study Characteristics: first author, year of publication and acronym. Study characteristics: Publication type, Study design (parallel, crossover, factorial), Washout period (wk), Study period (wk), Number of patients randomized (n), Industry sponsorship, Country, Language of publication, BP measurement (peak, trough), BP position (sitting, standing, supine). Patient baseline characteristics: Age (y), Gender (male/female, %), Race (white, black, other), BMI (kg/m2). Interventions and comparators: Name of the thiazide, Initial daily dose of thiazide, mean daily dose of thiazide at the end of the study, Name of

the thiazide association (with potassium-sparing diuretic), Initial daily dose of the thiazide association, mean daily dose of the thiazide association, Name of the comparator, Initial daily dose of the comparator, Mean daily dose of the comparator.

Primary outcomes: office Systolic and Diastolic blood pressure.

Secondary outcomes: metabolic variables (Serum potassium, Serum total cholesterol, Serum HDL-C, Serum LDL-C, Serum triglycerides, Fasting plasma glucose and Glycated hemoglobin (HbA1C). Ambulatory blood pressure (Daytime systolic blood pressure, Nighttime systolic blood pressure, Daytime diastolic blood pressure, Nighttime diastolic blood pressure, 24h systolic blood pressure and 24h diastolic blood pressure). MACE: All-cause mortality, Cardiovascular mortality, Fatal stroke, Non-fatal stroke, Fatal myocardial infarction, Non-fatal myocardial infarction and Hospitalization because of heart failure. Also, number of withdrawals.

Serum potassium will be presented and synthesized in mEq/L. Fasting plasma glucose, lipid profile and uric acid will be presented and synthesized in mg/dL. Glycated hemoglobin will be presented in percentage. Whenever necessary, transformations will be carried on.

Missing values

Imputations were carried out in that matter to be conservative and to not unfavor data synthesis.

Data synthesis

Main Analyses

The results were quantitatively summarized using differences between change from baseline for quantitative outcomes and relative Risk for dichotomous outcomes. Traditional metanalysis were carried out for each pair of comparison. Since heterogeneity was expected random effects models were used. Heterogeneity was measured using the I^2 statistics. To estimate between study heterogeneity the DerSimonian & Lard model was used. For continuous outcomes the effect size was estimated using the inverse of variance method and to dichotomous outcomes, the Mantel-Hanzeal method. The funnel plot visual inspection was used to assess asymmetry of results whenever 10 or more studies were available.

To compare all the thiazides classes (Treatment T low dose, Treatment T high dose, Treatment TP low dose, Treatment TP high dose) and placebo quantitatively, we ran a multiple treatment comparison (MTC) network metanalysis combining all available direct and indirect evidence from pairs of treatments. This was made through the generalized Bayesian linear model proposed by Lu and Ades (2004). For this, non-informative priori was used and study's effect sizes were considerate to formulate the likelihood. The posteriori was then generated to estimate parameters by the Monte-Carlo simulation nested to the Markov-Chain model. We checked autocorrelation, traceplots, gelman plots and DIC values. Analysis of inconsistency was also made using the split node method before moving forward to MTC estimates. Results will be presented as mean or relative risk with credible intervals through a league table. Also, a frame with the geometry of comparisons will be also provided. The classes of treatment will also be ranked using the surface under the cumulative ranking curve (SUCRA) method.

Adverse events will be only summarized qualitatively. All the statistical analyses were carried on using the R software (v. 3.5.2) using the packages "meta", "metafor" and "rjags" that nest the WinBUGS software to the R Package.

Transitivity and risk of bias between studies (overall meta-analysis)

We are considering the analyses for assumptions of transitivity and its accountability for any observed heterogeneity for such characteristics like age or baseline blood pressure levels by the method used at Cipriani et al 2018[46]. Not pre-planned variables will be provided in updated versions of this article before the data analysis, due to any potential characteristics observed during the eligibility and will be displayed in an updated version of this protocol with a rationale. Any other variable not previously tracked that would be needed to explore after data analysis will be reported in the final paper as a deviation from the protocol, with a rationale. We are also intending the check for the risk of bias between studies (e.g., "overall bias of the meta-analysis" or "confidence of the evidence of the meta-analysis) by the CINeMA tool[47]. However, none of the authors have conducted this approach before and this analysis could be deferred still at the level of the study conduction, if considered as infeasible due to technical constraints.

Risk of bias within individual studies

We assessed the risk of bias of the primary studies with the Risk of Bias for Interventions tool v. 1.0 from the Cochrane Collaboration. For the purpose of the assessment, we followed the proposed algorithm and the supporting material of the tool. We evaluated the following items: randomization; allocation concealment; blinding; incomplete outcome data reporting; selective reporting and other biases (e.g. industry sponsorship).

Support

Sponsor

There was no financial sponsorship for this study. However, the PREVER Group provided logistical and human resources necessary for this research project. This study was conducted by an academic institution and a research group that had no relationship with any pharmaceutical industry.

Role of the sponsor

The sponsor acted on the planning, conducting, reporting, data-sharing and post-publication issues of this study.

Compliance with the reproducibility standards

This network meta-analysis and systematic review (NMA-SR) is in accordance with the compliance of the reproducibility standards. We intend to publish the results in an open-access journal, indexed in the Directory of Open Access Journals, with the copyrights transferred to the authors. Also, all materials, search strategies, raw and treated data, statistical code and outputs will be publicly shared without restrictions to access the data neither expiration date. The repository was not chosen yet and will be provided in the final report of this study.

RESULTS

Study selection

The initial search identified 20,815 titles and abstracts, of which 4,636 were excluded as duplicates. Fourteen additional potentially eligible studies were identified in the reference lists of other studies. Thus, we screened the remaining 20,829 titles and abstracts for eligibility. Of these, more 15,288 studies were excluded. Thus, 905 potentially eligible studies were read in full, of which 591 were excluded. In total, 307 studies [**Appendix 3**] were included in the review. A flow diagram of study search and selection is shown in **Figure 1**.

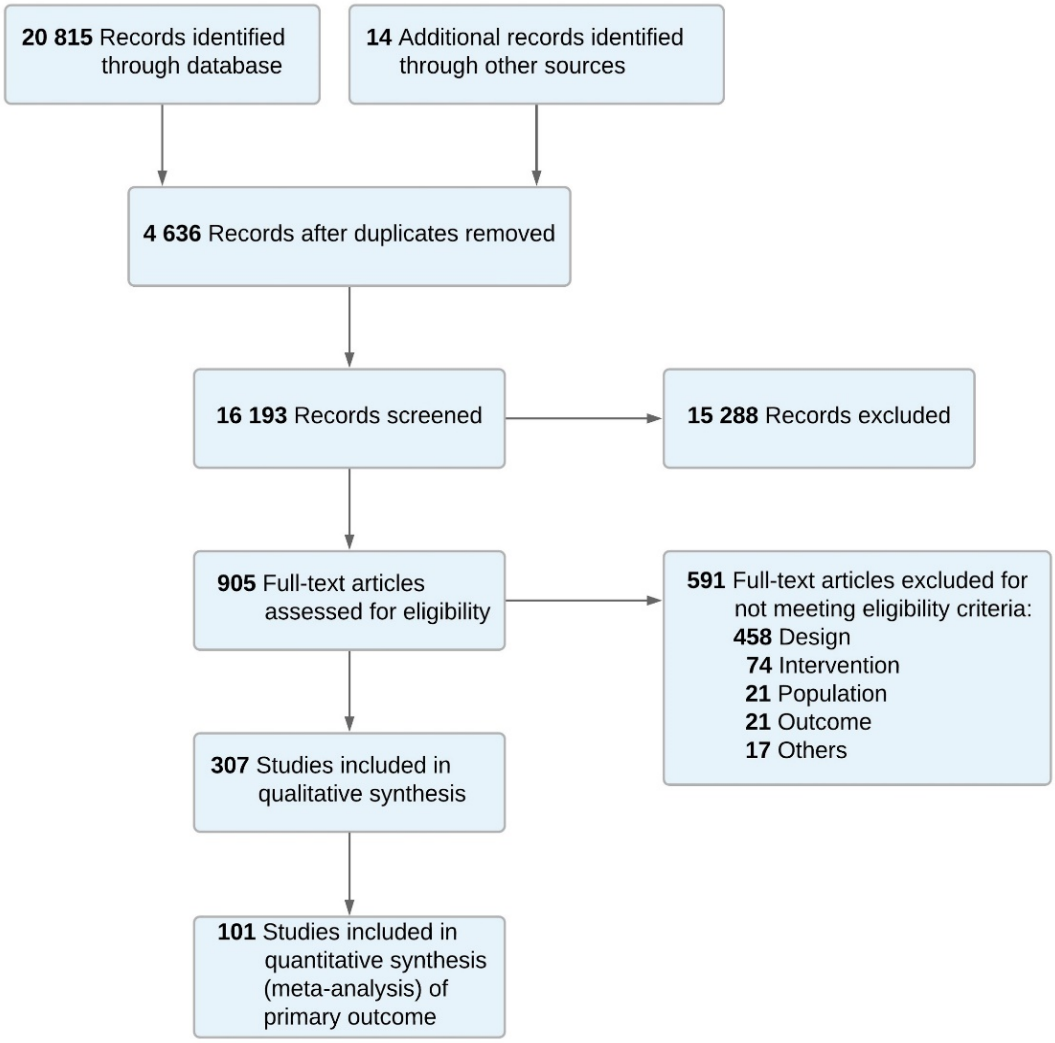

Figure 1: Flow diagram of study search and selection.

Study characteristics

Overall, 307 double-blind RCTs (comprising 62,906 patients) done between 1964 and 2016 were included in the analysis. The mean study sample size was 205 participants (range 9 to 2,776). The mean age was 55.2 years; 28,119 (44.7%) of the sample population were women. The mean duration of follow-up was 10.6 weeks (range 3 to 52 weeks). One hundred twenty seven (41.4%) of 307 studies randomly assigned participants to three or more groups.

292 (95.1%) articles were published in English, 5 (1.6%) in Italian, 4 (1.3%) in German, 4 (1.3%) in French, 1 (0.3%) in Spanish and 1 (0.3%) in Chinese. 249 (81.1%) studies had parallel design, 42 (13.7%) had crossover design and 16 (5.2%) had factorial design. The primary outcome analysis was based on the 101 studies (comprising 14,595 patients) that compared our eligible interventions (thiazide alone or in combination with a potassium-sparing diuretic) with at least one arm of another eligible intervention (direct comparison) or placebo.

Intervention characteristics

The evidence network for the main analyses comprised 101 RCTs and 15 different eligible interventions. The most common active treatment arm was hydrochlorothiazide (65 studies), followed by chlorthalidone (21 studies), indapamide (20 studies), hydrochlorothiazide+amiloride (8 studies), bendroflumethiazide (6 studies), hydrochlorothiazide+triamterene (6 studies), metolazone (5 studies), cyclopenthiazide (4 studies), chlorthalidone+triamterene (3 studies), hydrochlorothiazide+spironolactone (2 studies), bemetizide+triamterene (1 study), butizide (1 study), butizide+spironolactone (1 study), chlorothiazide (1 study) and xipamide (1 study). Placebo was used as a comparator in 67 studies. Among potassium-sparing diuretics, epithelial sodium channel blockers were the drugs most frequently combined with thiazides: triamterene (10 studies) and amiloride (8 studies). Only 3 studies in included mineralocorticoid receptor antagonists (spironolactone) in association with thiazides, and none assessed eplerenone.

According to the classification of the primary analysis, the most frequent treatment arm was low dose thiazide alone (n = 77), followed by high dose thiazide alone (n = 47),

high dose thiazide plus potassium-sparing diuretic (n = 13) and low dose thiazide plus potassium-sparing diuretic (n = 8).

Figure 2 shows the network of eligible comparisons for office blood pressure. 68 (67%) of 101 studies had at least one placebo-controlled arm. **Appendix 4** provides detailed results of pairwise meta-analyses.

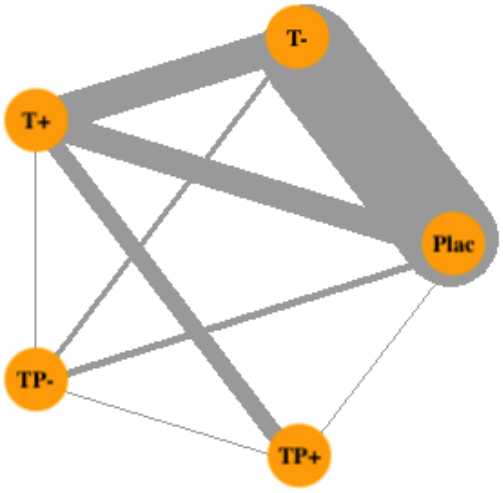

Figure 2a: Network meta-analysis of eligible comparisons for office systolic blood pressure.

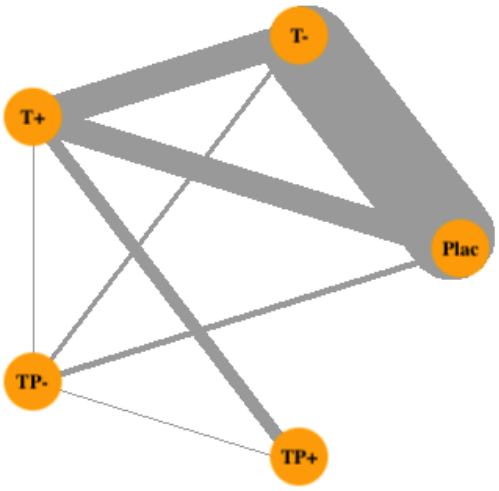

Figure 2b: Network meta-analysis of eligible comparisons for office diastolic blood pressure.

Width of the lines is proportional to the number of trials comparing every pair of treatments. TP+: high dose thiazide plus potassium-sparing diuretic; TP-: low dose thiazide plus potassium-sparing diuretic; T+: high dose thiazide alone; T-: low dose thiazide alone.

Primary outcomes

Figure 3 shows the network meta-analysis' results for the primary outcomes (office systolic and diastolic blood pressure). In terms of systolic blood pressure, all treatment groups were more effective than placebo, with mean differences (MD) ranging between -7.24 mmHg (95% credible interval [CrI] -8.11 to –6.39) for T- and -14.84 mmHg (-19.16 to -10.54) for TP+. Regarding active treatment comparisons, TP (both high and low dose) and T+ were more effective in reducing blood pressure when compared to T-, with MD ranging between -4.24 mmHg (95% CrI -8.38 to –0.007) for TP- and -7.61 mmHg (-11.9 to -3.30) for TP+.

In terms of diastolic blood pressure lowering efficacy, all treatment groups were more effective than placebo, with MD ranging between -3.42 mmHg (95% CrI -3.97 to –2.89) for T- and -6.54 mmHg (-8.55 to -4.54) for TP-. Regarding active treatment comparisons, both TP- and T+ were more effective in reducing blood pressure when compared to T- (MD -3.12 mmHg; CrI -5.19 to -1.05 and MD -2.17 mmHg; CrI -3.25 to -1.1, respectively).

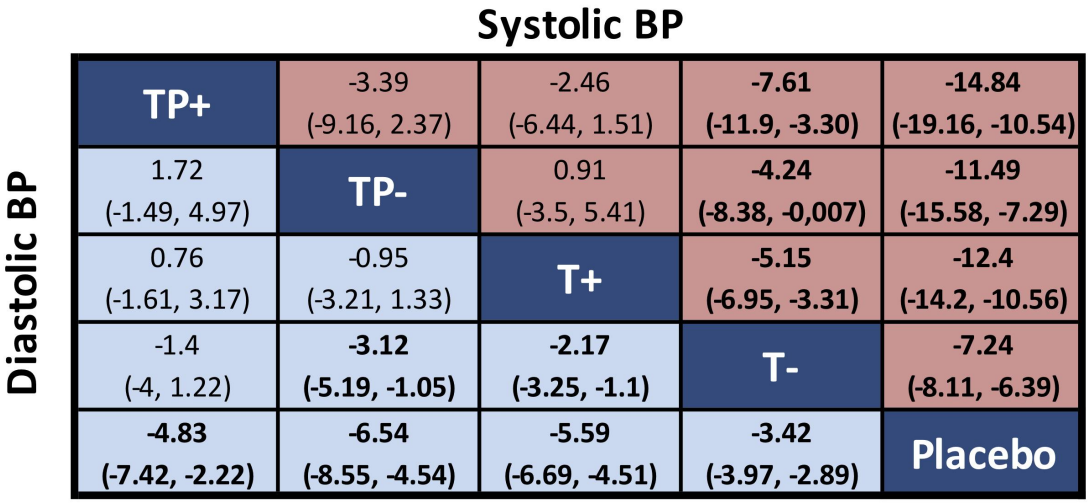

Figure 3: Network meta-analysis by classes of drugs. The figure shows the average difference of reductions (mmHg) after treatment (and its 95% credibility) of systolic blood pressure (SBP; δ-SBP, above the diagonal identified by treatment group) and diastolic blood pressure (DBP; δ-DBP, below the diagonal identified by treatment group). For SBP (above the diagonal) a negative value identifies a reduction of blood pressure (BP) in favor of the row-defining treatment; a positive value identifies a reduction of BP in favor of the column-defining treatment. For DBP (below the diagonal) a negative value identifies a reduction of BP in favor of the column-defining treatment; a positive value identifies a reduction of BP in favor of the row-defining treatment. In bold the statistically significant values (differences are considered as statistically significant when the 0 is not included in the 95% credibility interval).

The network meta-analysis results with representation of the direct and indirect evidence component are shown in **Figures 4a** and **4b**.

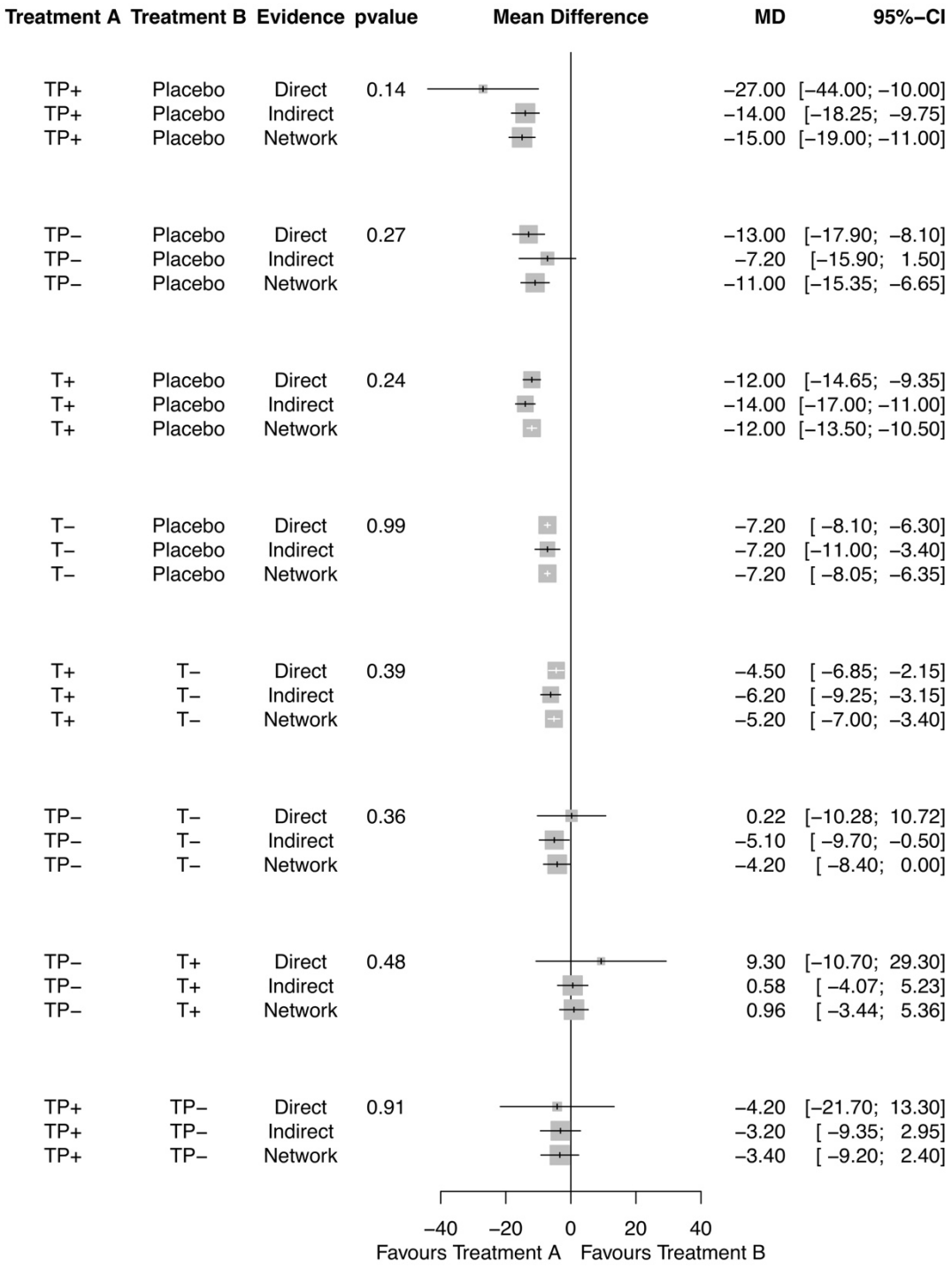

Figure 4a: network meta-analysis results with representation of the direct and indirect evidence component for systolic blood pressure. P-value for test of inconsistency.

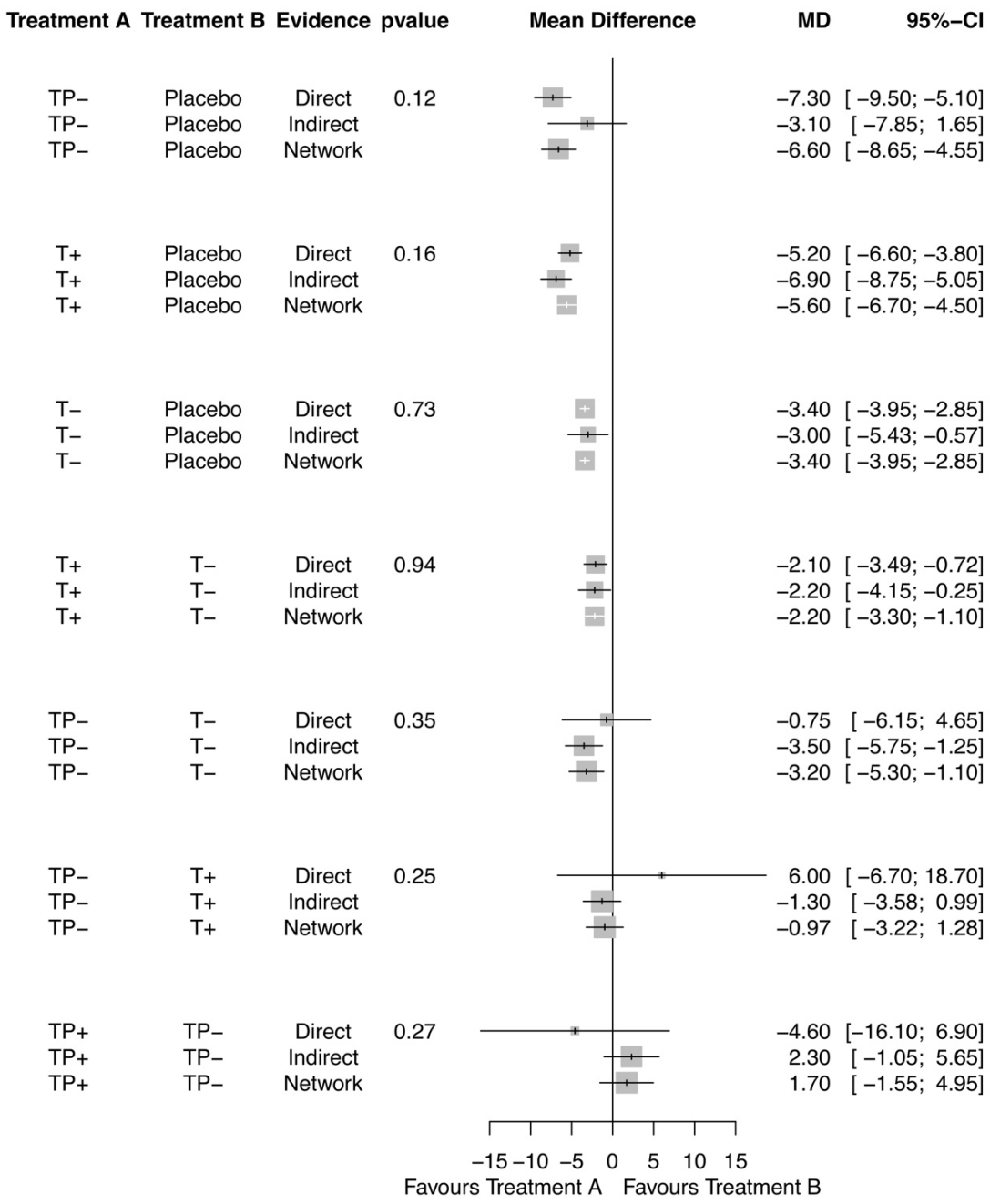

Figure 4b: network meta-analysis results with representation of the direct and indirect evidence component for diastolic blood pressure. P-value for test of inconsistency.

The ranking of treatments based on cumulative probability plots and SUCRAs is shown in **Figure 5**. The rank probability diagram shows that TP+ has the highest likelihood of being ranked first in systolic blood pressure reduction, followed by T+, TP- and T-. In relation to

diastolic blood pressure, the SUCRA rankings shows that TP- is most likely to result in the greatest blood pressure reduction, while T- appears less appealing among the active treatments.

		Diastolic							Systolic			
RANK 5	RANK 4	RANK 3	RANK 2	RANK 1	SUCRA	Treatment	SUCRA	RANK 1	RANK 2	RANK 3	RANK 4	RANK 5
0.0000	0.1464	0.5516	0.1939	0.1077	0.5353	TP+	0.9524	0.8595	0.1294	0.0508	0.0002	0.0000
0.0000	0.0016	0.0876	0.1701	0.7404	0.9123	TP-	0.5810	0.1055	0.2536	0.6173	0.0236	0.0000
0.0000	0.0000	0.2129	0.6353	0.1517	0.7347	T+	0.7126	0.0750	0.6169	0.3080	0.0000	0.0000
0.0000	0.8516	0.1477	0.0005	0.0000	0.2877	T-	0.2540	0.0000	0.0000	0.0237	0.9762	0.0000
0.9998	0.0002	0.0000	0.0000	0.0000	0.0000	Placebo	0.0000	0.0000	0.0000	0.0000	0.0000	1.000

Figure 5: ranking of treatments based on SUCRA for the primary outcome.

Risk of bias in the included studies

For the vast majority of studies, it was not possible to reach precise conclusions regarding risk of bias due to the high prevalence of "unclear" judgment. The full assessment of risk of bias is shown in **Figure 6**.

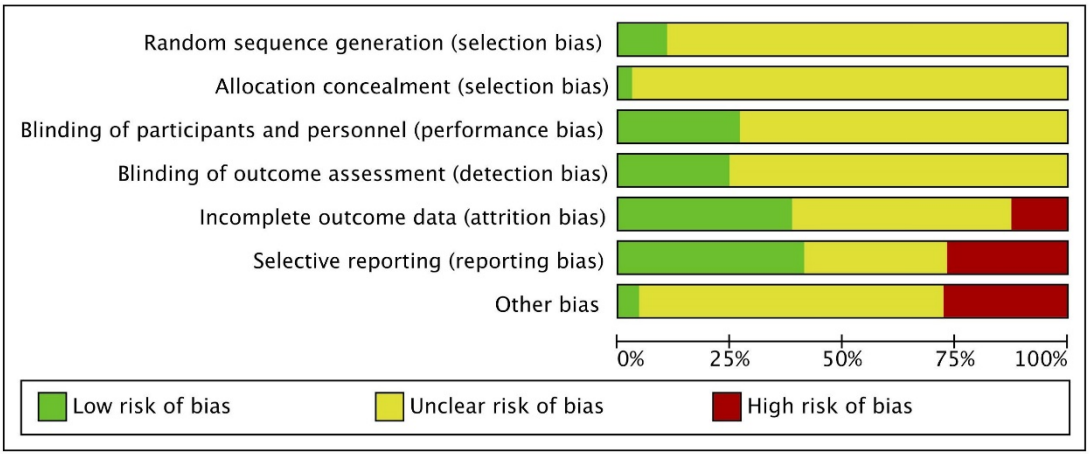

Figure 6: Risk of bias classification according to the RoB 1.0 Cochrane tool.

Asymmetry of evidence

Asymmetry of evidence was assessed through visual inspection of the funnel plot and the formal Begg's and Egger's tests whenever reasonable. No evidence of asymmetry was found by visual inspection nor by Begg's and Egger's tests. This suggests that there is no evidence of publication bias.

DISCUSSION

Hypertension is a major public health problem, affecting a significant proportion of the world's population, with a linear increase with advancing age[48]. In this sense, it is estimated that over 70% of adults over 70 years are hypertensive[49], and more than one billion adults worldwide have hypertension, with this high prevalence being consistent across all socioeconomic levels. Hypertension is associated with a significant increase in risk of adverse cardiovascular outcomes. Based on the risks identified by the Prospective Studies Collaboration[50], the attributable risk for BP equal or higher than 115/75 mmHg was estimated to be 49% for CHD and 62% for stroke[51]. The amount of blood pressure reduction is the major determinant of reduction in cardiovascular risk in patients with hypertension[52]. Thus, there is general agreement that the most appropriate drugs for initial therapy in patients with hypertension are those with the highest blood pressure lowering efficacy. The landmark ALLHAT trial randomly assigned over 41,000 hypertensive patients to one of four regimens: chlorthalidone, amlodipine, lisinopril, or doxazosin (this arm was prematurely terminated due to an increased risk of heart failure)[53]. Although the primary outcome (fatal coronary heart disease or nonfatal myocardial infarction) was the same in the three arms, participants in the chlorthalidone arm had a lower rate of heart failure than amlodipine and lisinopril and a lower rate of combined cardiovascular disease outcomes than lisinopril. Since thiazide diuretics were

superior in preventing primordial events, they have been advocated as preferred first-line antihypertensive therapy[54]

Our study is based on 307 double-blind RCTs (101 for the primary analysis), which included a total of 62,906 patients randomly assigned to thiazides (alone or in combination with a potassium-sparing diuretic) or a comparator (either placebo or any other antihypertensive drug). This comprehensive network meta-analysis, which included a large number of studies obtained through exhaustive search for published and unpublished information, not limited by language nor year of publication, allowed us to further investigate the blood pressure lowering efficacy among thiazide diuretics.

We found that all thiazides (alone or in combination with a potassium-sparing diuretic) included in this metanalysis were more efficacious than placebo, for both systolic and diastolic blood pressure, in adults with hypertension. For systolic blood pressure, high dose thiazide alone provided a greater blood pressure reduction compared to low dose thiazide alone. Additionally, thiazide plus potassium-sparing diuretic (both low dose and high dose) was more effective than low dose thiazide alone in reducing systolic blood pressure. Considering diastolic blood pressure, both high dose thiazide alone and low dose thiazide plus potassium-sparing diuretic provided a greater blood pressure reduction compared to low dose thiazide alone.

The findings of this study provide new and clinically relevant information regarding the additional antihypertensive effect with the addition of a potassium-sparing diuretic to thiazide monotherapy. Heran et al have conducted a systematic review to determine the effects of potassium-sparing diuretics, specifically epithelial sodium channel (ENaC) blockers, on blood pressure when given as a first-line or second-line therapy[28]. Six double-blind RCTs with 496 participants were included, evaluating the blood pressure lowering efficacy of low doses of amiloride and triamterene as a second drug to hydrochlorothiazide and chlorthalidone. In this review, the addition of low doses of amiloride and triamterene did not significantly reduce

blood pressure. The conclusions of their study were severely limited by the small number of included trials. In contrast, our network meta-analysis suggests that the addition of a potassium-sparing diuretic can further reduce blood pressure of low dose thiazide monotherapy.

This network meta-analysis has several strengths. First, the analysis was based on a large number of RCTs, included after a comprehensive search of available literature. This translates into a broader collection of the available evidence on the topic. Second, to the best of our knowledge, no prior network meta-analysis evaluated the antihypertensive efficacy of thiazides alone and associated with potassium sparing diuretics. Third, our findings show that the combination of potassium-sparing diuretics appears to increase the antihypertensive potency of thiazide monotherapy, especially at low doses of the latter. This may serve as a useful input to policy-making for patients with hypertension.

Our study has some limitations. First, the risk of bias could not be assessed in all studies due to incorrect reporting. This may have affected the results of the primary studies and their estimates; readers should thus interpret our findings in light of these limitations. Finally, potassium-sparing diuretics were administered primarily in low dosage, and the blood pressure lowering efficacy with their use at the upper limit of the recommended dose range is not well established. To better address this topic, our group is currently conducting a factorial RCT comparing thiazides (hydrochlorothiazide and chlorthalidone) combined with amiloride at higher doses (10 mg and 20 mg) in relation to antihypertensive efficacy using ABPM[55].

CONCLUSIONS

The combination of potassium-sparing diuretics and higher thiazide dose are associated with increased antihypertensive efficacy compared to low-dose thiazide diuretics. These findings suggest that potassium-sparing diuretics should be added to treatment of hypertension with diuretics.

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ARTIGO 2

Efficacy of chlorthalidone and hydrochlorothiazide in combination with amiloride in multiple doses on blood pressure in patients with primary hypertension: a protocol for a factorial randomized controlled trial.

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Trials

STUDY PROTOCOL Open Access

Efficacy of chlorthalidone and hydrochlorothiazide in combination with amiloride in multiple doses on blood pressure in patients with primary hypertension: a protocol for a factorial randomized controlled trial

Vítor Magnus Martins[1*], Lucas Helal[1], Filipe Ferrari[1], Leonardo Grabinski Bottino[1], Sandra Costa Fuchs[1] and Flávio Danni Fuchs[1,2]

Abstract

Background: Thiazide diuretics have demonstrated favorable blood pressure lowering efficacy, but the equivalent doses of their more common agents, chlorthalidone and hydrochlorothiazide, are still unclear. Further, concerns exist regarding adverse metabolic effects, which may be attenuated with the concomitant administration of a potassium-sparing diuretic, such as amiloride. This trial aims to investigate the efficacy of chlorthalidone and hydrochlorothiazide, in combination with amiloride at different doses, for initial management of patients with primary hypertension.

Methods/design: This is a factorial (2 × 2) randomized double-blinded clinical trial comparing the association of a thiazide diuretic (chlorthalidone 25 mg/day or hydrochlorothiazide 50 mg/day) with a potassium-sparing diuretic (amiloride 10 mg/day or amiloride 20 mg/day) in patients with primary hypertension. The primary outcome will be the mean change from baseline in 24-h systolic and diastolic blood pressure measured by ambulatory blood pressure monitoring. The secondary outcomes will be the mean change from baseline in daytime and nighttime systolic and diastolic blood pressure measured by ambulatory blood pressure monitoring, mean change from baseline in systolic and diastolic blood pressure measured by office blood pressure, incidence of adverse events, variation of laboratory parameters, and proportion of patients who achieved blood pressure control. The follow-up will last 12 weeks. For a P alpha of 0.05, power of 80%, standard deviation of 9 mmHg, and absolute difference of 6 mmHg on systolic blood pressure on 24-h ambulatory blood pressure monitoring, it will be necessary to study a total of 76 patients. The sample size will be increased by 10% to compensate for losses, resulting in 84 patients being randomized.

(Continued on next page)

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(Continued from previous page)
Discussion: Diuretics are pivotal drugs for the treatment of hypertension. Chlorthalidone and hydrochlorothiazide, in combination with amiloride in multiple doses, will be tested in terms of blood pressure lowering efficacy and safety. Since the intensity of blood pressure reduction is the major determinant of reduction in cardiovascular risk in hypertensive patients, this study will help to determine which combination of diuretics represents the most appropriate treatment for this population.

Trial registration: ClinicalTrials.gov, NCT03928145. Registered on 25 April 2019. Last update on 29 April 2019.

Keywords: Diuretics, Thiazides, Amiloride, Blood pressure, Hypertension, Treatment

Background

Thiazide diuretics have been commonly used as pharmacological agents for the treatment of hypertension for over five decades [1, 2], remaining the cornerstone of antihypertensive treatment due to their favorable blood pressure (BP) lowering efficacy, safety profile, and low cost. In patients with primary hypertension, thiazide diuretics have been demonstrated to be effective at low doses [3–10], while higher doses produce more side effects, often with little further reduction in BP [4]. Chlorthalidone (CTD) has been shown to provide greater antihypertensive efficacy than hydrochlorothiazide (HCTZ) at similar dose levels [11–15] with no evidence of higher incidence of side effects [15]. CTD is 1.5 to 2 times as effective as HCTZ at lowering BP at the same dose [12]. The smaller efficacy of HCTZ may be explained by a shorter duration of action compared to CTD [11, 12, 16]. Thus, when compared to HCTZ, these characteristics of CTD could promote better results in reducing BP and cardiovascular outcomes [17].

The use of thiazide diuretics may be associated with adverse metabolic effects, such as hypokalemia, hyponatremia, hyperuricemia, hyperglycemia, hyperlipidemia, and hypomagnesemia [4, 18, 19]. The incidence of these metabolic complications increases in a dose–response manner [3, 4, 20, 21]. It is estimated that less than half of the patients receiving thiazide diuretics develop hypokalemia (serum potassium < 3.5 mEq/L) [22]. The beneficial effect of chlorthalidone in the prevention of major cardiovascular events in the SHEP trial was lost when potassium dropped below 3.5 mEq/L [23]. The risk of hypokalemia may be minimized by combining thiazides with blockers of the epithelial sodium channel (e.g., amiloride and triamterene), which may also mitigate the impaired glucose tolerance associated with thiazides [24]. The blockers of the epithelial sodium channel are commonly referred to as potassium-sparing diuretics. Although the antihypertensive properties of the thiazide diuretics have been well documented [3–10], the BP lowering effect of potassium-sparing diuretics has not been as clearly determined [25]. However, some studies suggest that amiloride may be valuable in treating resistant hypertension [26] and may have a more potent antihypertensive effect in higher doses [24, 27].

It remains unknown whether different diuretics are associated with different clinical outcomes. Both CTD and indapamide have been shown to reduce cardiovascular events in landmark randomized trials [28, 29], whereas there is no evidence that HCTZ alone reduces cardiovascular events [30]. Despite opinions on the preference of CTD and indapamide over classic thiazide diuretics (e.g., HCTZ) [31], no randomized controlled trials have directly compared HCTZ versus CTD in relation to cardiovascular outcomes in hypertensive patients. This scenario supports the relevance of comparative testing of these drugs. Substantial clinical evidence concluded that the amount of BP reduction is the major determinant of reduction in cardiovascular risk in hypertensive patients [21, 32–34], which renders the BP lowering effect among diuretics an appropriate surrogate outcome.

So, we designed a factorial trial to compare the BP-lowering efficacy and safety profile of CTD and HCTZ, in combination with amiloride in multiple doses, in patients with primary hypertension. The mean change from baseline in 24-h systolic and diastolic BP measured by ambulatory blood pressure monitoring (ABPM) is the primary outcome. The mean change from baseline in daytime and nighttime systolic and diastolic BP measured by ABPM, mean change from baseline in systolic and diastolic BP measured by office BP, incidence of adverse events, variation of laboratory parameters, and proportion of patients who achieved BP control are the secondary outcomes.

Primary objectives

To compare CTD 25 mg with amiloride 20 mg versus other combinations of thiazide with amiloride, with respect to BP-lowering efficacy, in subjects with primary hypertension.

Secondary objectives

To compare, in subjects with primary hypertension, CTD 25 mg with amiloride 20 mg versus other combinations of thiazide with amiloride, with respect to the incidence of adverse events, variation of laboratory parameters, and proportion of patients who achieved BP control.

Methods/design

Study design

This is a randomized double-blind single-center superiority trial, controlled by active treatment, with factorial design (2 × 2), with a 1:1:1:1 allocation ratio, follow-up period of 12 weeks, and a primary endpoint of mean change from baseline in 24-h systolic and diastolic BP measured by ABPM. Eligible participants will be randomized to receive two simultaneous interventions: a thiazide diuretic (CTD 25 mg/day or HCTZ 50 mg/day) and a potassium-sparing diuretic (amiloride 10 mg/day or amiloride 20 mg/day).

Study setting

The study will be conducted in the Center for Clinical Research of Hospital de Clínicas de Porto Alegre (HCPA), which aims to establish guidelines and policies regarding the conduct of clinical research as a whole. In this sense, it provides adequate infrastructure for the development of all stages of clinical and epidemiological studies, in line with the public health needs of Brazil.

Inclusion criteria:

- Adults (aged 30 to 75 years) with diagnosis of primary hypertension based on ABPM (mean 24-h systolic BP ≥ 130 mmHg or mean 24-h diastolic BP ≥ 80 mmHg)
- No current use of antihypertensive medication
- Written consent for participation in the study

If the patient is on antihypertensive monotherapy prior to randomization and has BP below 160/100 mmHg (as measured by office BP), he may have his medication suspended for 2 weeks to confirm the inclusion criteria (washout phase).

Exclusion criteria:

- Low life expectancy
- Other indications for the use of diuretics
- Intolerance or contraindications to the study drugs
- Cardiovascular disease (heart failure, myocardial infarction or stroke)
- Secondary hypertension
- Chronic kidney disease and/or abnormal renal function (creatinine > 1.5 mg/dL)
- Hyperkalemia (serum potassium > 5.5 mEq/L)
- Gout
- Previous antihypertensive treatment with more than one drug
- Systolic BP ≥ 160 mmHg or diastolic BP ≥ 100 mmHg measured through office BP
- Pregnancy or prospective pregnancy during the study
- Lactating women

Interventions

The trial has a factorial design, where participants will receive two simultaneous interventions: a thiazide diuretic (CTD 25 mg or HCTZ 50 mg) and a potassium-sparing diuretic (amiloride 10 mg or amiloride 20 mg). Participants will be randomly assigned to four parallel groups:

- CTD 25 mg + amiloride 10 mg
- CTD 25 mg + amiloride 20 mg
- HCTZ 50 mg + amiloride 10 mg
- HCTZ 50 mg + amiloride 20 mg

The thiazide diuretic and amiloride will be combined in a single capsule, which will be provided by a compounding pharmacy. The medication will be administered as fixed-dose combinations. Patients will be instructed to take the medication orally in the morning upon waking. Adherence to trial medication will be assessed by means of pill count.

See Additional file 1 for the Template for Intervention Description and Replication (TIDieR) checklist.

Outcomes

Primary outcomes:

- Difference between the treatment arms in mean change from baseline in 24-h systolic and diastolic BP measured by ABPM at 12 weeks

Secondary outcomes:

- Difference between the treatment arms in mean change from baseline to 12 weeks in: daytime and nighttime systolic and diastolic BP measured by ABPM; systolic and diastolic BP measured by office BP; laboratory parameters.
- Difference between treatment arms in the proportion of participants reporting adverse events in the 12 weeks following randomization.
- Difference between treatment arms in the proportion of participants achieving BP control at 12 weeks. BP control will be defined as < 140/90 mmHg and < 130/80 mmHg for office BP and 24-h ABPM, respectively.

Participant timeline

Participants will be recruited from outpatient clinics and from Basic Health Units (public health system) in Porto Alegre, Brazil, and then invited to participate in the study.

The first visit will consist of (1) informed consent signing, (2) eligibility assessment, and (3) sociodemographic and clinic data collection. If the patient is taking an

antihypertensive drug and has BP below 160/100 mmHg (as measured by office BP), he will have his medication suspended for 2 weeks to confirm the eligibility criteria (washout phase, which allows most of the effects of the BP drug to vanish). If no antihypertensive medication is being used, BP measurements will be carried out in the office (average of three measurements) and ABPM will be placed. Then, participants will be instructed to return the next day after fasting (12 h) for laboratory tests.

The next visit will consist of removal of ABPM, confirmation of primary hypertension through ABPM (mean 24-h systolic BP ≥ 130 mmHg or mean 24-h diastolic BP ≥ 80 mmHg), office BP measurement (average of three measurements), anthropometric evaluation, and laboratory tests. After confirming the eligibility criteria, randomization and delivery of the study drug will be performed.

The intermediate visit (week 6) will consist of office BP measurement (average of three measurements), evaluation of adherence to treatment, investigation of adverse events, and delivery of study medication. Participants will be instructed to return in 6 weeks after fasting (12 h) for laboratory tests.

The close-out visit (week 12) will consist of office BP measurement (average of three measurements), anthropometric evaluation, evaluation of adherence to treatment, investigation of adverse events, laboratory tests, and placement of ABPM. Participants will be instructed to return the next day for removal of ABPM, verification of laboratory test results, and termination of study participation.

The schedule of enrollment, interventions, and assessments is presented in Fig. 1. The allocation of participants and timeline are presented in Fig. 2.

Sample size

For an absolute difference of 6 mmHg in systolic BP on 24-h ABPM, with an alpha of 0.05, power of 80%, and standard deviation of 9 mmHg, it will be necessary to study 76 patients in total. The sample size will be increased by 10% to account for possible losses in follow-

	STUDY PERIOD			
	Enrollment	Allocation	Post-allocation	Close-out
TIMEPOINT (weeks)	-4	0	6	12
ENROLLMENT:				
Eligibility screen	X			
Informed consent	X			
Washout	X			
Allocation		X		
INTERVENTIONS:				
Chlorthalidone 25 mg + amiloride 10 mg		←	—	→
Chlorthalidone 25 mg + amiloride 20 mg		←	—	→
Hydrochlorothiazide 50 mg + amiloride 10 mg		←	—	→
Hydrochlorothiazide 50 mg + amiloride 20 mg		←	—	→
ASSESSMENTS:				
ABPM	X			X
Office BP	X	X	X	X
Blood collection		X		X
Anthropometric measurements		X		X
Pill count			X	X
Adverse events questionnaire			X	X

Fig. 1 Schedule of enrollment, interventions and assessments. *ABPM* ambulatory blood pressure monitoring, *BP* blood pressure

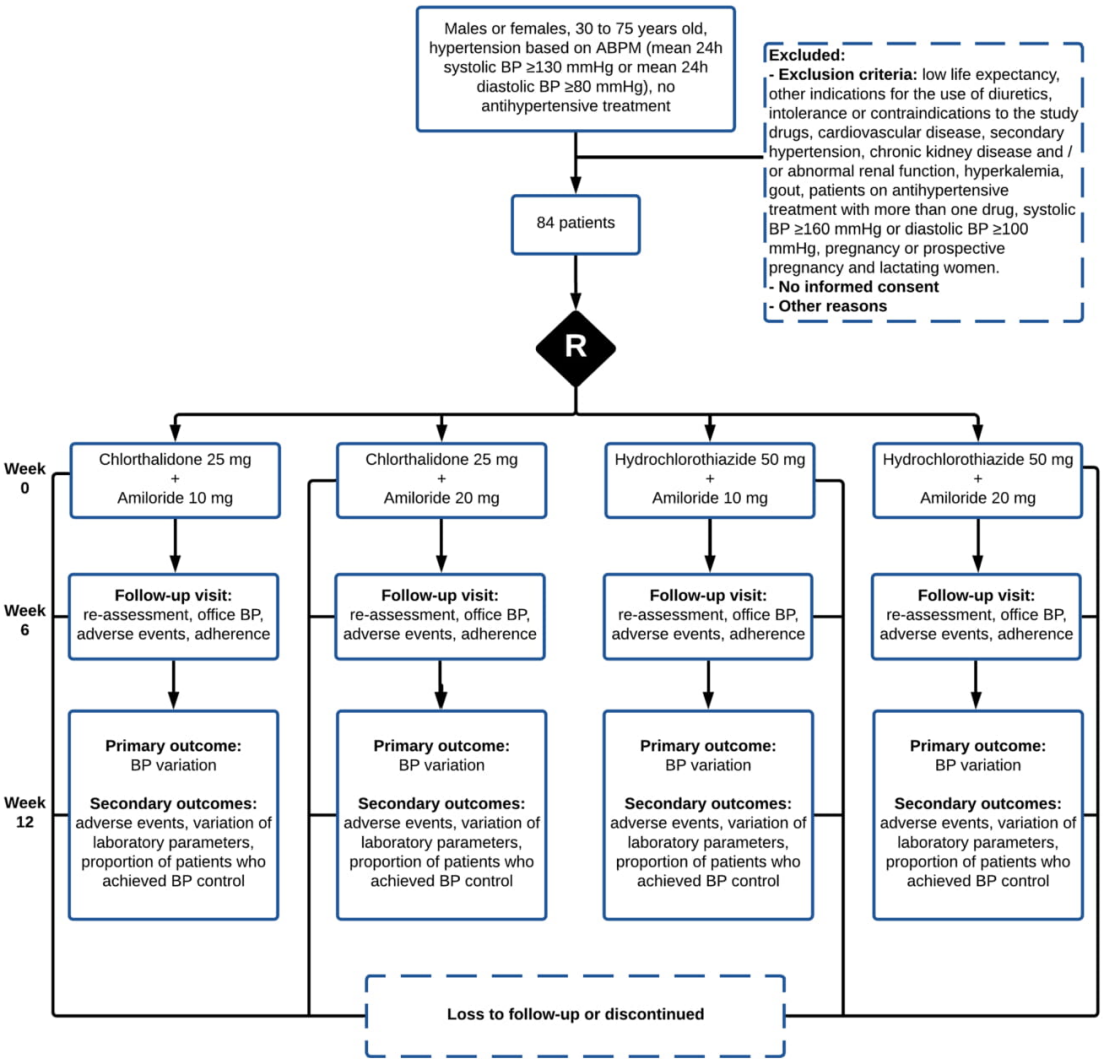

Fig. 2 Allocation of participants and timeline. *ABPM* ambulatory blood pressure monitoring, *BP* blood pressure

up, resulting in 84 patients being randomized (42 for each arm).

Recruitment

Participants will be recruited from outpatient clinics in HCPA and Instituto de Cardiologia do Rio Grande do Sul, Brazil, and from Basic Health Units (public health system). Patients potentially eligible for the study will be contacted by telephone by the trial investigator, who will explain the study and ascertain the patient's interest. If interested, the patient will be seen in the Center for Clinical Research of HCPA, where the study consultations will be made. The enrollment period is expected to extend over 24 months.

Allocation

A computer-generated sequence created by the Random Allocation Software [35] will be used to randomly assign patients to the four interventions, stratified by 24-h systolic BP on ABPM (< 140 or ≥ 140 mmHg), with a 1:1:1:1 allocation using random block sizes to generate equal allocation ratio and parallel groups. The block sizes will not be disclosed, to ensure concealment. The randomization process will be performed before the beginning of the trial, with the random allocation sequence registered in Research Electronic Data Capture (REDCap) [36]. To guarantee concealment of the allocation list, randomization will be implemented through a web-based automated

system. All patients who give consent for participation and who fulfill the inclusion criteria will be randomized. An independent researcher not involved in the enrolment will produce the randomization sequence. The research team will be blinded to the randomization sequence and it will be concealed from the researchers enrolling and assessing participants. The interventions will be delivered by researchers with extensive knowledge of the study medication.

Blinding

The study medication in all groups will have the same color, taste, consistency, odor, and appearance. In this way, patients, care providers, outcome assessors, and the entire research team will be blinded regarding the allocation to treatment groups throughout the study. Unblinding will occur only when knowledge of the actual treatment is absolutely essential for further management of the patient, particularly in the occurrence of serious adverse events.

Data collection

The research team will be trained to perform anthropometric and BP measurements as well as the application of questionnaires. A laboratory technician will collect blood samples after 12-h fasting. These samples will be forwarded for analysis and discarded shortly after. No biological specimens will be stored for future studies. Study data will be collected and managed using REDCap tools hosted at HCPA.

Anthropometric measurements

The following anthropometric measurements will be collected at baseline and close-out visit: body weight, height, waist circumference, and body mass index (BMI). Body weight and height, measured by anthropometric scales, will be used to calculate the body mass index (BMI) using the formula BMI = Weight (kg)/Height squared (m2). BMI values of 18.5 to 24.9 kg/m2 are considered eutrophic values, while individuals with BMI values of 25.0 to 29.9 kg/m2 are overweight and ≥ 30 kg/m2 are obese. The waist circumference, measured at the midpoint between the iliac crest and the lower costal margin, is the most representative anthropometric index of intra-abdominal fat and the simplest reproducible measurement.

Office blood pressure

Office blood pressure (OBP) will be measured at all visits with the participant sitting quietly in a chair with feet on the floor, back supported, and arm resting on a desk for > 5 min, according to standardized guidelines [37]. The patient should avoid caffeine, exercise, and smoking for at least 30 min before measurement. The cuff size will be used according to arm circumference. Three measurements will be taken (separated by 1–2 min) with a validated automatic oscillometric BP measuring device (HBP-1100, OMRON Healthcare) and the average recorded. Baseline OBP and final OBP will be considered as the mean of six measurements in two separate visits.

24-h ABPM

ABPM is a method that allows the indirect and intermittent recording of BP for 24-h while patients perform their usual activities during the day. Monitoring requires patients to maintain their normal daily activities with the BP being measured automatically at 15 min intervals (daytime) and 20 min intervals (nighttime) for an entire 24-h period. The systolic BP and diastolic BP will be obtained by ABPM, with the mean values for the 24-h period, daytime, and nighttime being considered for analysis. The normal nocturnal dip will be defined as a drop of > 10% in systolic BP from wakefulness to the period of sleeping. Participants will be evaluated by ABPM at the baseline and at the end of the follow-up. ABPM will be performed using portable monitors (Spacelabs 90,207, Redmond, WA, USA).

Laboratory tests

Blood samples will be drawn from all patients at the first and last visits after fasting for 12 h. The following laboratory parameters will be assessed: serum total cholesterol (TC), HDL cholesterol (HDL-C), LDL cholesterol (LDL-C), triglycerides (TG), creatinine, urea, potassium, sodium, magnesium, uric acid, fasting plasma glucose, and hemoglobin A1c (HbA1c). The LDL fraction is calculated in mg/dL, using the Friedewald formula [LDL = TC – HDL – TG/5 (for TG < 400 mg/dL)].

Adverse events

Patients will be interviewed at each visit about the occurrence of any adverse events using open questions and a semi-structured questionnaire, including time of onset, duration, and severity; all information will be recorded on an electronic case report form (eCRF). The causal relation to the study drug and the intensity of adverse events will be evaluated by the investigators. Serious adverse events (SAE) must be reported to the institutional review board by the principal investigator within 24 h after the SAE becomes known. Laboratory adverse events, such as hypokalemia, hyperuricemia, and hyperglycemia will be investigated at the final visit.

To improve participant retention, study researchers will make efforts to monitor patients during the study period, including telephone reminders for upcoming visits. Telephone calls will be made to inquire about adverse events if a participant misses a scheduled visit.

Furthermore, all participants will be requested to promptly report possible adverse events by telephone. The participant will be advised on the importance of adhering to the treatment protocol not only for validation of the study results, but mainly for their safety and possible health benefits. In order to improve adherence to intervention protocols, we will use pill count to monitor patient compliance. Participants can withdraw from the trial at any time for any reason without their medical care being affected. Data already collected will continue to be used, and the patients will be asked if they are still willing to provide follow-up data. The reason for withdrawal will be documented whenever possible.

Data collection forms

Study data will be collected and managed using REDCap tools hosted at HCPA. REDCap is a secure, web-based application designed to support data capture for research studies, providing: 1) an intuitive interface for validated data entry; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for importing data from external sources. An eCRF will be constructed for data registration. Data integrity will be enforced through valid values and range checks. For data analysis, subject-related data from REDCap will be exported and analyzed in statistics software (IBM SPSS). Before data export, all patient identifiers will be removed.

Data management

Each participant will be given an identification number at enrolment, and each identification number will have an eCRF. The list over identification codes will be deleted at the end of the study. All trial data, including Trial Master File, eCRF, the source datasheet of the eCRF, and the list of identification codes will be stored in the external server of REDCap with continuous backup. REDCap data are kept for 10 years. Study-related patient documentation and the signed informed consent form will be stored in a patient-specific folder.

Statistical methods

All data will be analyzed according to the intention-to-treat principle, considering all patients as randomized regardless of whether they received the randomized treatment. Analyses will be performed with the software SPSS for Windows (version 17; SPSS Inc., Chicago, Illinois, USA). A P value < 0.05 will be considered statistically significant.

The sample characteristics will be presented by descriptive statistics, and the results will be expressed as mean, standard deviation, and percentage. The comparison of levels of BP among treatment groups at each visit will be done using a t-test for independent samples, and a random-effects linear model fitted to systolic and diastolic BP will be used to compare BP by treatment group during follow-up. The random-effects model will include an intercept and a slope to adjust for the within-participant correlation among the longitudinal data with test for interaction. An attempt to measure BP at the end of trial even for participants that abandoned the treatment will be undertaken. The cumulative incidence of adverse events will be analyzed by Chi-square test. Adverse events will be reported with relative risk and 95% confidence intervals. No subgroup or adjusted analyses are planned for this study.

Assuming there will be no interaction between thiazides and amiloride, we intend to carry out pooled analysis of the differences between CTD (CTD 25 mg with amiloride 10 mg and CTD 25 mg with amiloride 20 mg) versus HCTZ (HCTZ 50 mg with amiloride 10 mg and HCTZ 50 mg with amiloride 20 mg) and the differences between amiloride in a lower dose (amiloride 10 mg with CTD 25 mg and amiloride 10 mg with HCTZ 50 mg) versus amiloride in a higher dose (amiloride 20 mg with CTD 25 mg and amiloride 20 mg with HCTZ 50 mg).

Data monitoring

Due to the short duration of the trial and minimal risks associated with the interventions, a Data Monitoring Committee will not be established, and interim analyses will not be performed. Committees involved in trial coordination and conduct are to be decided elsewhere and will be described in amendments or in the final text.

Harms

At all follow-up visits, adverse events will be investigated by spontaneous reporting and by a directed questionnaire. An adverse event is considered to be any undesired medical occurrence in a clinical trial participant who has received a pharmaceutical product, even if it does not necessarily have a causal relationship to that treatment. A severe adverse event is considered to be any unfavorable medical occurrence that results in death, threat to life, hospitalization or its prolongation, or persistent or significant disability. The causal relationship to the study drug and the intensity of adverse events will be evaluated by the investigators. The communication of adverse events classified as severe or unexpected will be reported to the Ethics Committee. SAE must be reported by the principal investigator within 24-h after the SAE becomes known. The participant who presents with a severe adverse event will be withdrawn from the study. Withdrawal may also occur in the event of intolerance of the participant to non-severe adverse events. In this case, the procedures for the last visit will be carried out. Laboratory adverse events, such as

hypokalemia, hyperuricemia, and hyperglycemia, will be investigated at the final visit. All adverse events and withdrawals due to adverse events will be reported, irrespective of severity, with no frequency threshold.

Auditing

A quality assurance audit/inspection of this study may be conducted by the competent authority. The quality assurance auditor/inspector will have access to all medical records, the investigator's study related files and correspondence, and the informed consent documentation that is relevant to this clinical study. The investigator will allow the persons being responsible for the audit or the inspection to have access to the source data/documents and to answer any questions arising. All involved parties will keep the patient data strictly confidential.

Standard Protocol Items: Recommendations for Interventional Trials checklist

This article followed the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) 2013 statement on the writing of a study protocol for a clinical trial [38]. The filled SPIRIT checklist can be found in Additional file 2. The World Health Organization Trial Registration Data Set is provided in Additional file 3.

Protocol amendments

Any modifications to the protocol which may impact on the conduct of the study or potential benefit to the patient or may affect patient safety, including changes of study objectives, study design, patient population, sample sizes, study procedures, or significant administrative aspects, will require a formal amendment to the protocol. Such amendments will be approved by the Ethics Committee of HCPA prior to implementation. Amendments will be disclosed in the new version of the protocol with reasons.

Consent

Trained physicians responsible for eligibility will supply informed consent forms to patients willing to participate in the trial. The consent form includes institutional affiliation, the objectives of the study, a description of the testing procedures, explanation about interventions and its randomized allocation nature, information about expected length of time for participation, the potential risks and benefits involved in the study, the costs to the participants, information on anonymized data sharing, and an explanation of the patient's right to refuse participation or to withdraw consent at any time. A copy of the consent form is given to the participant, and this fact is documented in the subject's record. The investigator in charge of providing clarification on the study and seeking the participant's ethical consent must allow the subject sufficient time to decide whether or not to participate in the trial. Once a subject decides to participate, a signed and personally dated informed consent form is obtained from the subject before any trial-related procedure. As there are no plans for use of data from this trial in ancillary studies, no additional consent will be required.

Confidentiality

Study data will be collected and managed using REDCap tools. All laboratory specimens, reports, data collection, processes, and administrative forms will be identified by a coded identification number to maintain participant confidentiality. After full data analysis, all subject identifiers will be erased. The principal investigator will grant the relevant personnel user rights to view, edit, or overwrite data entries by password as applicable. All edits will be automatically documented in the change history log. Direct access to source data may be granted in the case of monitoring, audit, or inspections. All personnel must treat patient data as confidential. As far as possible, encoded data will be used.

Access to data

All trial investigators will be given access to the cleaned data sets. Project data sets will be stored in the external server of REDCap hosted at HCPA, and all data sets will be password protected. To ensure confidentiality, data dispersed to project team members will be blinded of any identifying participant information.

Ancillary and post-trial care

The study drugs have been used for a long time to treat hypertension and are considered safe. The risks of the study are mainly due to the possibility of adverse effects with the drugs. The most frequent adverse effects are anorexia, dyspepsia, dizziness, headache, cramps, and increased urine volume, and usually do not require discontinuation of treatment. In case of adverse effects or problems related to participation in the study that require medical treatment, the investigators will be responsible for the care such that participant do not incur costs.

Discussion

Thiazide diuretics have good tolerability and proven BP-lowering efficacy, although there is concern about metabolic complications with these agents (e.g., hypokalemia), which can be mitigated by the association of a potassium-sparing diuretic, such as amiloride. This is the first double-blind, randomized controlled trial comparing CTD versus HCTZ combined with amiloride in different doses in relation to BP-lowering efficacy and adverse metabolic effects in patients with primary hypertension. Although the primary outcome (change from

baseline in BP) is not a clinical endpoint, BP has been a valid surrogate of the beneficial effects of BP-lowering drugs. Thus, by identifying the diuretic treatment with greater antihypertensive efficacy and lower incidence of adverse effects, this study will provide evidence-based information that could help in the accomplishment of a more effective hypertension treatment.

Trial status

This is the first version of the protocol (issue date 28 June 2019). The study has not started recruiting participants. We anticipate the study will start by November 2019 and be completed by November 2021.

Supplementary information

Supplementary information accompanies this paper at https://doi.org/10.1186/s13063-019-3909-z.

Additional file 1. TIDieR checklist.

Additional file 2. SPIRIT 2013 checklist: Recommended items to address in a clinical trial protocol and related documents.

Additional file 3. World Health Organization Trial Registration Data Set.

Abbreviations

ABPM: Ambulatory blood pressure monitoring; BMI: Body mass index; BP: Blood pressure; CAPES: Coordenação de Aperfeiçoamento de Pessoal de Nível Superior; CTD: Chlorthalidone; eCRF: Electronic case report form; FIPE: Fundo de Incentivo à Pesquisa e Eventos; HbA1c: Hemoglobin A1c; HCPA: Hospital de Clínicas de Porto Alegre; HCTZ: Hydrochlorothiazide; HDL-C: HDL cholesterol; ICMJE: International Committee of Medical Journal Editors; INCT PREVER: National Institute of Science and Technology for Prevention of Cardiovascular Disease; LDL-C: LDL cholesterol; OBP: Office blood pressure; REDCap: Research Electronic Data Capture; SAE: Serious adverse events; SHEP: Systolic Hypertension in the Elderly Program; SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials; TC: Total cholesterol; TG: Triglycerides; TIDieR: Template for Intervention Description and Replication

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Not applicable.
Guarantor of the trial data: Flávio Danni Fuchs, MD, PhD - ffuchs@hcpa.edu.br
Note: the guarantor of the trial data will handle any issue related to the data sharing policy of this research.

Sponsorship

The trial is sponsored by HCPA, Universidade Federal do Rio Grande do Sul.
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Disclosures

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Authors' contributions

FDF and VMM conceived the study. SCF and FDF provided statistical expertise in clinical trial design. VMM, LH, FF, LGB, SCF, and FDF prepared the data collection plan and the draft of the manuscript. FDF prepared the final version of the manuscript. All authors contributed to refinement of the study protocol and approved the final version of the manuscript.

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The trial is supported by a grant from the Fundo de Incentivo à Pesquisa e Eventos (FIPE), HCPA, Brazil. There will be no financial sponsorship for this study. However, the National Institute of Science and Technology for Prevention of Cardiovascular Disease (INCT PREVER) will provide logistical and human resources necessary for this research project. This study will be conducted by an academic institution and a research group that has no relationship with the pharmaceutical industry. The funding source had no role in the design of this study and will not have any role during its execution, analyses, interpretation of the data, or decision to submit results.

Availability of data and materials

This trial is in accordance with the compliance of the reproducibility standards according to the International Committee of Medical Journal Editors (ICMJE) [39]. Authorship will be determined according to the guidelines of the ICMJE. All trial results, whether positive, negative, or neutral, will be disseminated in peer-reviewed journals, at scientific conferences, and in a public trial data repository. The trial is registered at ClinicalTrials.gov, improving clinical trial transparency and reducing publication bias and selective outcome reporting. We intend to publish the results in an open-access journal, indexed at the Directory of Open Access Journals, with the copyrights transferred to the authors. Also, all materials, raw and treated data, statistical code, and outputs will be publicly shared without restrictions to access the data without an expiration date. Individual participant data will be shared in a de-identified manner, accompanied by a glossary of variables. Only the study guarantor will have the key for re-identification. The repository has not been chosen yet and will be provided in further amendments or in the final report of this study.

Ethics approval and consent to participate

The project and the informed consent form were approved by the Ethics Committee of Hospital de Clínicas de Porto Alegre (2016–0553), which is accredited by the Office of Human Research Protections as an institutional review board. All participants will be asked to sign the informed consent form prior to participation in the study.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Publisher's Note

ADDITIONAL FILE 1

TIDieR Checklist

Efficacy of chlorthalidone and hydrochlorothiazide in combination with amiloride in multiple doses on blood pressure in patients with primary hypertension: description of interventions of a factorial randomized controlled trial.

1. Brief name

Chlorthalidone and hydrochlorothiazide in combination with amiloride in multiple doses.

2. Why

Thiazide diuretics, including chlorthalidone and hydrochlorothiazide, have been commonly used as pharmacological agents for the treatment of primary hypertension, with demonstrated blood pressure lowering efficacy at low doses [1-8]. However, there exist concerns regarding adverse metabolic effects such as hypokalemia, hyperglycemia and hyperlipidemia [2, 9, 10], which may be attenuated with the concomitant administration of a potassium-sparing diuretic, such as amiloride [11]. Also, the inclusion of a new diuretic to control adverse effects could offer an additional blood pressure control, especially in higher doses [11, 12]. Amiloride is commonly administered with hydrochlorothiazide, although other fixed-dose combinations of thiazides and potassium-sparing agents are available. It remains unknown whether different diuretics are

associated with different clinical outcomes. The amount of blood pressure reduction is the major determinant of reduction in cardiovascular risk in hypertensive patients [13-16], which renders the blood pressure lowering effect among diuretics an appropriate surrogate outcome. This trial aims to investigate the antihypertensive efficacy of chlorthalidone and hydrochlorothiazide, in combination with amiloride in different doses, for the initial management in patients with primary hypertension.

3. What (materials)

Participants will receive two simultaneous interventions: a thiazide diuretic (chlorthalidone 25 mg or hydrochlorothiazide 50 mg) and a potassium-sparing diuretic (amiloride 10 mg or amiloride 20 mg). Randomization will be done in 1:1:1:1 ratio, and participants will be randomly assigned to four groups: chlorthalidone 25 mg + amiloride 10 mg, chlorthalidone 25 mg + amiloride 20 mg, hydrochlorothiazide 50 mg + amiloride 10 mg and hydrochlorothiazide 50 mg + amiloride 20 mg. The thiazide diuretic and amiloride will be combined in a single capsule, which will be provided by a compounding pharmacy. The medication will have the same color, taste, consistency, odor and appearance. In this way, patients, researchers, evaluators and the entire research team will be blinded regarding the allocation to the treatment groups throughout the study. The vials containing the capsules of the study drug will be identified only with the study logo, number of capsules dispensed, randomization code and expiry date. The code will be confidentially stored in two independent places, without access by study members.

4. What (procedures)

At the time of provision of the medication, the participant will receive a vial containing capsules of the drug and will be advised on the dosage and observation of any symptoms (adverse events) that appear after starting the drug so that it can report on the subsequent consultation. The physician will ensure the understanding of orientations on the administration of the study drug. The participant will be instructed to bring the vial of the medicine in use in the next consultation, even if empty. The patient will also be advised not to take the study medication on the next consultation day, as it should do so during the medical consultation when requested. If the participant attends the consultation, the blood pressure measurement will be performed before the patient takes the study drug. If the patient has forgotten the study drug vial at home, the physician should use one tablet from the next vial to be dispensed to the patient and arrange for delivery of the previously provided vial. The participant will be advised that in case he forgets to take the medicine, he should not take two tablets to compensate for omission and should continue to take normally.

5. Who provided

The interventions will be delivered by researchers with extensive knowledge of the study medication and will provide guidance on adherence, dosage, and adverse events to participants at each delivery.

6. How

The study medication will be delivered by the researcher to each participant in the scheduled clinical consultation, with sufficient treatment until the next appointment.

7. Where

Participants will be recruited from outpatient clinics in Hospital de Clínicas de Porto Alegre and Instituto de Cardiologia do Rio Grande do Sul, Brazil, and from Basic Health Units (public health system) through the review of medical records of patients in the desired age range. Study consultations will take place in the Center for Clinical Research of Hospital de Clínicas de Porto Alegre.

8. When and how much

The vials containing capsules of the study drugs will be delivered to patients at randomization (week 0) and intermediate consultation (week 6), with sufficient treatment until the end of the follow up (week 12). Each vial will contain enough capsules for 6 weeks of treatment, when the next appointment will occur. Considering possible variations in the dates of the consultation, depending on holidays or weekends, will be provided 5 additional capsules, totaling 47 capsules in each bottle. Patients will be instructed to take the medication orally in the morning upon waking.

9. Tailoring

The medication will be administered as fixed-dose combinations.

10. Modifications

Cannot be described until the study is complete.

11. How well (planned)

Adherence to trial medication will be assessed by means of pill count. Participants will be instructed to bring the bottles with the remaining capsules in follow up consultations. Since capsule counting will be used as a measure of adherence to treatment, the importance of this will be reinforced even if the vial is empty. The count of capsules will be made by the physician from the bottles brought by the participant. A participant who has used 80% or more of the prescribed drug will be considered a good adherent.

12. How well (actual)

Cannot be described until the study is complete.

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ADDITIONAL FILE 2

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/ item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	3
	2b	All items from the World Health Organization Trial Registration Data Set	Provided in Additional file 3
Protocol version	3	Date and version identifier	23
Funding	4	Sources and types of financial, material, and other support	25
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1, 25, 26
	5b	Name and contact information for the trial sponsor	26
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	25

	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	18, 19
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	3-5
	6b	Explanation for choice of comparators	3-5
Objectives	7	Specific objectives or hypotheses	5, 6
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	6
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	6
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	6, 7
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	Refer to TIDieR checklist
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	Refer to TIDieR checklist
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	Refer to TIDieR checklist

	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	Refer to TIDieR checklist
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	8, 9
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	9-12
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	12
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	12, 13
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	13
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	13
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	13

Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	13, 14
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	14
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	14-16
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	16, 17
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	17
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	17, 18
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	18
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	18
Methods: Monitoring			

Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	18, 19
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	18, 19
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	19
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	19, 20
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	24
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	20
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	20
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	21
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	21
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	25

Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	21, 22
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	22
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	24, 25
	31b	Authorship eligibility guidelines and any intended use of professional writers	24
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	24, 25
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	20, 21
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	14

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

ADDITIONAL FILE 3

World Health Organization Trial Registration Data Set

Data category	**Information**
Primary Registry and Trial Identifying Number	ClinicalTrials.gov NCT03928145
Date of Registration in Primary Registry	April, 2019
Secondary Identifying Numbers	Not applicable
Source(s) of Monetary or Material Support	Fundo de Incentivo à Pesquisa e Eventos (FIPE) and National Institute of Science and Technology for Prevention of Cardiovascular Disease (INCT PREVER).
Primary Sponsor	Hospital de Clínicas de Porto Alegre, Universidade Federal do Rio Grande do Sul
Secondary Sponsor(s)	Not applicable
Contact for Public Queries	Principal Investigator: Flávio Danni Fuchs, MD, PhD Address: Division of Cardiology, Hospital de Clínicas de Porto Alegre, R. Ramiro Barcellos 2350, Porto Alegre/RS, ZIP 90035-903, Brazil Telephone: +55 51 3359.8344 Email: ffuchs@hcpa.edu.br Affiliation: Hospital de Clínicas de Porto Alegre, Universidade Federal do Rio Grande do Sul
Contact for Scientific Queries	Principal Investigator: Flávio Danni Fuchs, MD, PhD Address: Division of Cardiology, Hospital de Clínicas de Porto Alegre, R. Ramiro Barcellos 2350, Porto Alegre/RS, ZIP 90035-903, Brazil

	Telephone: +55 51 3359.8344 Email: ffuchs@hcpa.edu.br Affiliation: Hospital de Clínicas de Porto Alegre, Universidade Federal do Rio Grande do Sul Guarantor of the trial: Flávio Danni Fuchs, MD, PhD Address: Division of Cardiology, Hospital de Clínicas de Porto Alegre, R. Ramiro Barcellos 2350, Porto Alegre/RS, ZIP 90035-903, Brazil Telephone: +55 51 3359.8344 Email: ffuchs@hcpa.edu.br Affiliation: Hospital de Clínicas de Porto Alegre, Universidade Federal do Rio Grande do Sul
Public Title	Efficacy of chlorthalidone and hydrochlorothiazide in combination with amiloride in multiple doses on blood pressure in patients with primary hypertension.
Scientific Title	Efficacy of chlorthalidone and hydrochlorothiazide in combination with amiloride in multiple doses on blood pressure in patients with primary hypertension: a factorial randomized controlled trial.
Countries of Recruitment	Brazil
Health Condition(s) or Problem(s) Studied	Hypertension, antihypertensive treatment
Intervention(s)	Active intervention: chlorthalidone 25 mg + amiloride 20 mg (one capsule per day for 12 weeks) Active intervention: chlorthalidone 25 mg + amiloride 10 mg (one capsule per day for 12 weeks) Active intervention: hydrochlorothiazide 50 mg + amiloride 20 mg (one capsule per day for 12 weeks) Active control: hydrochlorothiazide 50 mg + amiloride 10 mg (one capsule per day for 12 weeks)

Key Inclusion and Exclusion Criteria	Inclusion criteria: adults (age 30 to 75 years) with diagnosis of primary hypertension based on ABPM (mean 24-h systolic BP ≥130 mmHg or mean 24-h diastolic BP ≥80 mmHg) and without current use of antihypertensive medication. Exclusion criteria: low life expectancy, other indications for the use of diuretics, intolerance or contraindications to the study drugs, cardiovascular disease (heart failure, myocardial infarction or stroke), secondary hypertension, chronic kidney disease and / or abnormal renal function (creatinine >1.5 mg/dL), hyperkalemia (serum potassium >5.5 mEq/L) or gout. Patients on antihypertensive treatment with more than one drug, with systolic BP ≥160 mmHg or diastolic BP ≥100 mmHg measured through office BP, with pregnancy or prospective pregnancy during the study and lactating women will also be excluded.
Study Type	Interventional Allocation: randomized Allocation concealment mechanism: randomization will be implemented through a web-based automated system Sequence generation: computer generated sequence created by the Random Allocation Software Masking: double blind (patients, researchers, evaluators and the entire research team will be blinded regarding the allocation to the treatment groups) Assignment: factorial Primary purpose: treatment Phase III
Anticipated date of First Enrollment	November 2019
Sample Size	Planned: 84

	Enrolled: 0
Recruitment Status	Pending
Primary Outcome(s)	1 - Difference between the treatment arms in mean change from baseline in 24-h systolic blood pressure measured by ambulatory blood pressure monitoring at 12 weeks. 2 - Difference between the treatment arms in mean change from baseline in 24-h diastolic blood pressure measured by ambulatory blood pressure monitoring at 12 weeks.
Key Secondary Outcomes	1 - Difference between the treatment arms in mean change from baseline in daytime and nighttime systolic and diastolic blood pressure measured by ambulatory blood pressure monitoring at 12 weeks. 2 - Difference between the treatment arms in mean change from baseline in systolic and diastolic blood pressure measured by office blood pressure at 12 weeks. 3 - Difference between treatment arms in the proportion of participants reporting adverse events in the 12 weeks following randomization. 4 - Difference between the treatment arms in mean change from baseline in laboratory parameters measured at 12 weeks. 5 - Difference between treatment arms in the proportion of participants achieving BP control at 12 weeks.
Ethics Review	1 - Status: approved 2 - Date of approval: April 2019 3 - Name and contact details of Ethics committee: Ethics Committee of Hospital de Clínicas de Porto Alegre. R. Ramiro Barcellos 2350, Porto Alegre/RS, Brazil. Telephone: +55 51 3359.7640. Email: cep@hcpa.edu.br.
Completion date	Trial not completed.
Summary Results	Not applicable.

IPD sharing statement	Plan to share IPD: yes Plan description: all materials, raw and treated data, statistical code and outputs will be publicly shared without restrictions to access the data neither expiration date. The repository was not chosen yet and will be provided in further amendments or in the final report of this study.

CONCLUSÕES E CONSIDERAÇÕES FINAIS

Esta metanálise em rede, com grande número de ensaios clínicos randomizados incluídos, mostrou que diuréticos tiazídicos combinados com poupadores de potássio são superiores na redução da pressão arterial, quando comparados a tiazídicos em monoterapia, no tratamento de pacientes com hipertensão arterial. Este efeito foi evidenciado principalmente no grupo tratado com tiazídico em dose baixa. Adicionalmente, tiazídico em dose alta se mostrou mais eficaz na redução da pressão arterial quando comparado ao tratamento em dose baixa, condizente com o esperado efeito dose-resposta. Os resultados deste estudo fornecem informações clinicamente relevantes sobre o efeito anti-hipertensivo alcançado com a adição de um diurético poupador de potássio, porém estes achados devem ser interpretados à luz do risco de viés incerto em grande parte dos estudos avaliados.

A continuidade da análise dos dados extraídos permitirá a avaliação de outros desfechos previstos, como variação de parâmetros metabólicos, ampliando o conhecimento em relação à segurança e tolerabilidade do tratamento com tiazídicos. Por fim, nesta metanálise os diuréticos poupadores de potássio foram administrados principalmente em doses baixas, e a eficácia anti-hipertensiva com seu uso em doses mais elevadas não está bem estabelecida. O ensaio clínico randomizado do nosso grupo, que está atualmente recrutando pacientes, pretende preencher esta lacuna do conhecimento.

APÊNDICE 1

Network meta-analysis protocol publicly deposited in Open Science Framework

(https://osf.io/tezf8; DOI 10.17605/OSF.IO/TEZF8)

Version II
Date: 12.30.18
Open Science Framework: **https://osf.io/tezf8**; DOI 10.17605/OSF.IO/TEZF8

Study Protocol

Thiazide diuretics alone or in combination with a potassium-sparing diuretic on blood pressure lowering in patients with primary hypertension: protocol for a systematic review and network metanalysis

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Statement

This protocol was written guided by Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols Statement (PRISMA-P) and the PRISMA Explanation and Elaboration article for guidance. The final report will be written with the PRISMA Extension for Network Meta-Analysis, for Abstracts and for Harms.

Registration

This systematic review and network metanalysis is prospectively registered at the PROSPERO database (CRD4220181203, ID 118492).

Affiliations

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Senior Roles

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Note: the guarantor of the review will handle with any issue related to the data sharing policy of this research.

Contributions

Conception of the study: VM, LH, SCF, FDF
Major Drafters of the protocol: VM, FF, MB,
Minor Drafters of the protocol: SCF, FDF, LH
Provided feedback to the protocol: SCF, FDF, LH

Future Contributions

Data extraction and synthesis: Patrícia Klarmann Ziegelmann (PKM), PhD (*senior statistician*)

Amendments

This is the second version of this protocol. The new version of this protocol have already been updated at Open Science Framework. Amendments are disclosed bellow with reasons.

Amendment 01 (date: 12.30.18)
Change: Inclusion of the following eligibility criteria: Thiazides with potassium supplementation will not be considered an eligible intervention, but this combination may be eligible as a comparator.
Rationale: As potassium chloride may have antihypertensive effect, it was deemed inappropriate for analysis in combination with the interventions of interest.
Affected Protocol Section: Methods - Eligibility criteria - Interventions.

Amendment 02 (date: 12.30.18)
Change: Inclusion of the following eligibility criteria: Studies in which blood pressure measurements were not taken under resting condition will be excluded.
Rationale: For diagnosis and management of hypertension, resting measurement of blood pressure is essential to categorize an individual's true level of blood pressure.
Affected Protocol Section: Methods - Eligibility criteria - Outcomes - Primary outcome.

Amendment 03 (date: 12.30.18)
Change: Inclusion of the following eligibility criteria: Studies with step up therapy in non-responders (i.e., addition of another antihypertensive drug as second-line therapy in patients not meeting a target goal blood pressure level) will be included, as long as pre-step up blood pressure measurements are provided.
Rationale: In case of blood pressure measurement before step-up, it can be used to evaluate the interventions of interest, without the influence of co-intervention.
Affected Protocol Section: Methods - Eligibility criteria - Study designs.

Amendment 04 (date: 12.30.18)
Change: Studies with double dummy technique will be included, not excluded.
Rationale: Double dummy trials will be included in order to retain the double blinding, if necessary.
Affected Protocol Section: Methods - Eligibility criteria - Study designs.

Support

Sponsor

There will be no financial sponsorship for this study. However, the PREVER Group will provide logistical and human resources necessary for this research project. This study is conducted by an academic institution and a research group that has no relationship with any pharmaceutical industry.

Role of the sponsor

The sponsor will act on the planning, conducting, reporting, data-sharing and post-publication issues of this study.

Compliance with the reproducibility standards

This network metanalysis and systematic review (NMA-SR) is in accordance with the compliance of the reproducibility standards. We intend to publish the results in an open-access journal, indexed at the Directory of Open Access Journals, with the copyrights transferred to the authors. Also, all materials, search strategies, raw and treated data, statistical code and outputs will be publicly shared without restrictions to access the data neither expiration date. The repository was not chosen yet and will be provided in further amendments or in the final report of this study.

Disclosures

VM is supported by the PREVER Group (Porto Alegre, Brazil)
FF is supported by the Conselho Nacional de Pesquisa e Desenvolvimento (Brazil)
LH is supported by the Coordenação de Aperfeiçoamento de Pessoal de Nível Superior - Brasil (CAPES) - Finance Code 001, PDSE - 88881.189100/2018-01 (Brazil), member of the Canadian EQUATOR Centre (Ottawa, Canada) and member of the Cochrane Collaboration - Bias Method Group (UK)
SCF is the director of the PREVER Group and Study (Porto Alegre, Brazil), and 1A Researcher from the Conselho Nacional de Pesquisa e Desenvolvimento (Brazil)
FDF is the director of the PREVER Group and Study (Porto Alegre, Brazil), and 1A Researcher from the Conselho Nacional de Pesquisa e Desenvolvimento (Brazil)

Introduction

Background and Rationale

Thiazide diuretics have been used for the treatment of hypertension for more than five decades, becoming the first oral antihypertensive agents with an acceptable side-effect profile [1,2]. Agents of this class derived from benzothiadiazine are called "thiazide-type diuretics", such as hydrochlorothiazide and bendroflumethiazide. Drugs with a similar pharmacologic action on the kidney but that do not have the thiazide chemical structure (e.g., indapamide, chlorthalidone and metolazone) are termed "thiazide-like diuretics". Despite chemical structural variations, the term "thiazide diuretic" covers all diuretics that have a primary action in the distal tubule.

In patients with primary hypertension, thiazide diuretics have been demonstrated to be effective at low doses [3-9], where the steepest part of the dose-response curve is typically seen [10]. Chlorthalidone and indapamide, both thiazide-like diuretics, have been shown to provide greater antihypertensive efficacy than hydrochlorothiazide, a thiazide-type diuretic, at similar dose levels [11-15]. Chlorthalidone is 1.5 to 2 times as effective as hydrochlorothiazide at lowering blood pressure at the same dose [13]. The lower efficacy of hydrochlorothiazide may be explained by a shorter duration of action compared to chlorthalidone and indapamide [12,13,16].

The use of thiazide diuretics may be associated with adverse metabolic effects, specially hypokalemia and hyperglycemia, but also hyponatremia, hyperuricemia, hyperlipidemia and hypomagnesemia [3,17,18]. The incidence of these metabolic effects occurs in a dose-response manner [3,10,19], and even sudden death may happen with high doses of thiazide-type diuretics when a potassium-sparing association lacks [20]. The risk of hypokalemia may be minimized by combining thiazides with potassium-sparing diuretics - mineralocorticoid receptor antagonists (eg, spironolactone and eplerenone) or blockers of the epithelial sodium channel (eg, amiloride and triamterene), which may also mitigate the impaired glucose tolerance associated with thiazides [21]. However, we should acknowledge that potassium-sparing diuretics may have also some side effects, such as hyperkalemia, and spironolactone have been associated with gynecomastia [22].

Although the antihypertensive properties of spironolactone and eplerenone have been well documented [23-27], the blood pressure lowering effect of amiloride and triamterene has not been as clearly determined. A previous systematic review reported no significant effects on blood pressure at low doses of amiloride and triamterene [28]. In contrast, some studies suggest that amiloride may be effective in resistant hypertension [29], and may have stronger antihypertensive effect at higher doses in non-resistant hypertension [21, 30].

It remains unknown whether different diuretics are associated with different clinical outcomes. Both chlorthalidone and indapamide have been shown to reduce cardiovascular events in benchmark randomized trials [31, 32], whereas there is no evidence that hydrochlorothiazide alone reduces cardiovascular events [33]. There are no randomized controlled trials that directly compared different thiazides (alone or in combination with potassium-sparing diuretics) on primordial cardiovascular outcomes in hypertensive patients, and previous indirect comparisons by metanalysis and evidence from observational studies provided conflicting results [34-38]. Given the plethora of drug types among thiazides, no between-drugs comparison has been conducted at the level of a primary study - randomized controlled trial - (and it is also unfeasible), whereas decision-makers may need the best evidence to choose the first line therapy when opting by thiazides. Since substantial clinical evidence concluded that the amount of blood pressure reduction is the major determinant of reduction in cardiovascular risk in hypertensive patients [10, 39-41], the blood pressure lowering effect among diuretics becomes an appropriate surrogate outcome. For this purpose, a network metanalysis of randomized controlled trials seems to be justifiable since it will allow comparisons of the available drugs even if not included in the same randomized controlled trial, and may also provide a probability of success among the tested treatments.

This said, we will conduct a systematic review with a network metanalysis through a mixed-treatment comparison model, in which direct and indirect evidence will be incorporated and merged whenever possible, to compare the efficacy of thiazides alone or in combination with a potassium-sparing diuretic in patients with primary hypertension, as well the safety of such drugs through the measurement of drug-related adverse events.

Objectives

Primary objective

To investigate, quantitatively summarize and compare the blood pressure lowering efficacy of thiazide diuretics alone or in combination with potassium-sparing diuretics among themselves and to classify the treatment in which the probability of success and adverse events is the highest.

Secondary objectives

To investigate, quantitatively summarize and compare the impact of the thiazide diuretics alone or in combination with a potassium-sparing diuretic in relation to the following laboratorial markers concentrations as harm outcomes: serum potassium, LDL cholesterol (LDL-C), uric acid and fasting plasma glucose.

To investigate, quantitatively summarize and compare the impact of the thiazide diuretics alone or in combination with a potassium-sparing diuretic in relation to major adverse cardiovascular events - MACE (e.g., all-cause mortality, cardiovascular mortality, fatal or non-fatal stroke, fatal or non-fatal myocardial infarction). We will synthesize MACEs as a composite outcome and also individually whenever reported.

Withdrawals, falls and hypotension events among the eligible treatments will be summarized quantitatively.

Methods

Eligibility criteria

Participants

We will include only studies in adults (18 years old or more) regardless of sex and race, diagnosed with primary hypertension (as stated by the authors), and without secondary causes of hypertension identified (e.g., primary aldosteronism, renovascular disease or obstructive sleep apnea. **Note:** other secondary causes will be stated by us in the final report). Patients need necessarily to be in monotherapy and naive to the new drug. As naive, we are considering patients recently diagnosed with primary hypertension or those in which received drug withdrawal to be randomized. Trials targeting blood pressure in patients with hypertension but in which blood pressure is not the primary therapeutic target (e.g., a randomized controlled trial targeting blood pressure with antihypertensive agents in type 2 diabetes, in which the common clinical target is glycated haemoglobin - HbA1c, e.g., the ACCORD trial [42]) will not be excluded if the patients are treated with one of our eligible interventions. Any other comorbid not below mentioned will not restrict our study eligibility. Studies that also included children are eligible only if the provided data for adults was reported separately.

We will exclude trials in the last fashion for some specific clinical entities: patients with heart failure with reduced ejection fraction (≤ 40%); patients with heart failure with preserved ejection fraction and New York Heart Association (NYHA) functional class II–IV; chronic renal disease requiring dialysis; or a documented serum creatinine level more than 1.5 times the normal range, as thiazide diuretics are considered to be less effective in patients with impaired kidney function [43].

Interventions

Our eligible interventions will be antihypertensive agents from the class of diuretics (classification above mentioned), as follows:

a) Thiazide diuretics alone, specifically: hydrochlorothiazide, chlorothiazide, butizide, bendroflumethiazide, hydroflumethiazide, trichlormethiazide, methyclothiazide, polythiazide, cyclothiazide, cyclopenthiazide, chlorthalidone, metolazone, quinethazone, fenquizone, clorexolone, clopamide, indapamide, diapamide, isodapamide, mefruside, xipamide, bemetizide, benzthiazide and chlorazanil;

b) Thiazide diuretics in combination with a potassium-sparing diuretic, specifically: spironolactone, eplerenone, amiloride and triamterene.

Studies with fixed-dose and flexible doses of the drugs of interest will be permitted. If patients in the study receive a force-titrated dose, regardless of blood pressure, we will include blood pressure measurements under the highest administered dose. Participants taking medications that affect blood pressure, other than the interventions of interest, will be excluded (e.g., doxazosin for benign prostatic hyperplasia, which also has an antihypertensive effect. As potassium chloride may have antihypertensive effect, thiazides with potassium supplementation will not be considered an eligible intervention, but this combination may be eligible as a comparator. **Note**: further confounding medications to exclude trials will be provided in the final manuscript will a rationale.

Comparators

By the nature of this study, the eligible interventions will be compared among themselves. However, we will include treatments out of interest to expand our geometry and so add potentially indirect comparisons for our mixed treatment comparison. Comparisons with (or between) no eligible treatment will be presented at the supplementary file. Here are the additional treatments: placebo or any other antihypertensive drug, alone or in combination, regardless of the pharmacological class, including angiotensin-converting enzyme inhibitors (ACEi), angiotensin receptor blockers (ARB), beta-blockers (BB), calcium channel blockers (CCB), renin inhibitors, centrally-acting drugs and diuretics other than the interventions of interest (eg, loop diuretics) - **note:** we will present effects of pair of drugs included to expand geometry, whenever found, in our supplementary file.

Outcomes

Primary outcome

Our primary outcome is the blood pressure lowering effect of eligible treatments on the office systolic and diastolic blood pressure by means of trough blood pressure. Trough blood pressure is defined as the blood pressure measurement taken before the next dosing schedule. If timing of measurement is not reported, blood pressure will be assumed to have been taken at trough. When blood pressure measurement data are available in more than one position, sitting blood pressure will be the first preference, followed by standing and

supine position. If blood pressure measurements are available more than once within the accepted follow-up window, the last measurement will be used. Studies in which blood pressure measurements were not taken under resting condition will be excluded.

Secondary outcomes

Efficacy outcomes

Ambulatory blood pressure monitoring (ABPM). We will qualitatively synthesize data about daytime, nighttime and 24h blood pressure (systolic and diastolic).

Major adverse cardiovascular events - MACE (e.g., all-cause mortality, cardiovascular mortality, fatal or non-fatal stroke, fatal or non-fatal myocardial infarction). We will synthesize MACEs as a composite outcome and also individually whenever reported.

Note: when studies with both office and ambulatory blood pressure measurements are available, they will be considered eligible, and data from all methods will be analyzed. In studies in which blood pressure was measured by only one method, we will collect data from that method. If several measurements are available within the acceptable window, the last measurement will be used.

Safety (harms) outcomes

We will quantitatively analyze changes in serum potassium, LDL-C, uric acid and fasting plasma glucose. Number of withdrawals, falls and hypotension events among the eligible treatments will be analyzed qualitatively. If several measurements are available within the acceptable window, the last measurement will be used.

Study designs

We will include only double-blind randomized controlled trials as our unit of analysis. Studies will be considered suitable for inclusion if the following criteria are met: randomized controlled trials with parallel or crossover design, double-blind, controlled by placebo or active treatment. We will limit trials for those beginning with 3 weeks of follow up last to 52 weeks, because trials designed with longer follow-up often target primordial cardiovascular outcomes (e.g., cardiovascular mortality) and thus blood pressure measurement is at higher risk to be inaccurate due to a lesser relevance given in those designs.

Intensification studies in which the antihypertensive drugs of interest were used for this purpose will be excluded; thus, only studies with treatment-naive patients at the time of randomization will be included.

Studies with step up therapy in non-responders (i.e., addition of another antihypertensive drug as second-line therapy in patients not meeting a target goal blood pressure level) will be included, as long as pre-step up blood pressure measurements are provided.

Crossover studies will be included entirely if there is a clear history of at least 2 weeks of washout among the treatments tested. If not, only the first period of the study will be included, as long as pre-crossover data are provided. Factorial designs will be also considered whenever interaction between treatments are absent. We will include studies

that measure office blood pressure or ABPM at baseline and at one or more time points between 3 and 52 weeks after initiation of treatment.

We will exclude the following designs: open-label randomized controlled trials, non-randomized controlled trials, observational studies, case report or case series studies, open-label studies, studies with thiazides in combination with drug classes other than potassium-sparing diuretics, and studies in patients with secondary causes of hypertension. Quasi-experimental studies (such as those that allocate using alternate days of the week or that do not have a comparator group) will also be excluded. Studies with double dummy technique will be included.

No restriction will be imposed for the language of publication, date of publication, publication status or sample size. Whenever possible, any report (e.g., conference abstracts) in which partial data are sufficient to be analyzed (quantitatively or qualitatively) will be included - for sufficient data, we will consider the sample size for each group; the point-estimate within or between-groups; its related dispersion, precision or type 1 error variable.

Information sources

Electronic searches

For an extensive and comprehensive survey of the literature, we will search six electronic bibliographic databases from database inception to the data of the search (PubMed/MEDLINE, Cochrane Library, Embase, Web of Science, Scopus, Lilacs), a registration database (ClinicalTrials.gov) for potential results in unpublished studies and

Educational Resources Information Center (ERIC [ProQuest]) for results in non-indexed journals or other forms of reporting (thesis, clinical report, conference summary, monograph, etc.). The main electronic search strategy was designed for MEDLINE and will be adapted as appropriate for each of the databases. Literature search strategies will be developed using MeSH terms and their synonyms, and boolean operators (where possible) to improve searches. Keywords and terms of MeSH include: "hydrochlorothiazide", "chlorothiazide", "bendroflumethiazide", "hydroflumethiazide", "trichlormethiazide", "methyclothiazide", "polythiazide", "cyclopenthiazide", "chlorthalidone", "metolazone", "clopamide", "indapamide", "mefruside", "xipamide", "bemetizide", "benzthiazide", "chlorazanil", "spironolactone", “eplerenone”, "amiloride", "triamterene", "thiazide diuretics", “inhibitor of the epithelial sodium channel”, “potassium sparing diuretic” and "hypertension". In addition, we will check reference lists of included studies or relevant reviews identified to the data through the survey so as to ensure that no eligible studies are missed out. Bibliographic research will not be limited by languages. For articles not published in English, Spanish or Portuguese, we will use Google Translator. Results from the search and retrieved references will be imported and managed in Clarivate Analytics Endnote X9® (2018) reference management software. Comprehensive search strategies for all the bases that will be consulted are included in Appendix 1.

Note (limitation): clinical study reports from regulatory agencies and pharmaceuticals industry will need to be excluded by feasibility. The evidence shows barriers, time frames and predictors (e.g., the sharing only for recognized institutions such as the Cochrane Collaboration - authority fallacy) that points out for our inability to handle with it [44].

Therefore, we acknowledge it as a limitation of our search strategy and also from our study since its inception.

Study records

After the queries, each electronic database will be exported to a reference manager software (EndNote X9) and duplicates will be removed. Other found sources will be inserted manually in the reference manager and checked again for duplicates. Then, titles and abstracts will be stored at the reference manager till the beginning of the eligibility process. At the time of the screening process, one author will split the library with the titles and abstracts accordingly to the number of reviewers. Potentially eligible titles and abstracts and the excluded ones will be stored in specific folders. Physical report will be scanned for future purposes or independent researchers checking and deposited in the Google Drive® with specific folders for inclusion and exclusion with reasons. A final list of included and excluded articles in each step will be recorded. If a trial suspected to have unpublished outcomes of blood pressure efficacy, authors will be contacted to seek for any potential unpublished outcome.

Then, we will extract the data and they will be stored in a piloted spreadsheet for data synthesis. For the assessment of the risk of bias of included studies, we will use the Cochrane Collaboration spreadsheet settled for the Risk of Bias 2.0 tool and final decisions will be stored at the RoB 2.0 spreadsheet. All of the materials used in this NMA-SR will be shared thereafter in a public repository, after the publication of the manuscript.

Screening Process

The screening for eligible randomized controlled trials will be conducted in a two-step manner. First, we will check the reports on the level of titles and abstracts. For this purpose, we will undergo the liberal accelerated approach[45], in which one author will flag the potentially eligible reports and the excluded ones, and a second author will review records excluded by the first reviewer. Disagreements will be solved by consensus. On the level of the titles and abstracts, the reports will be stored in only two folders after the final decision - only for potentially eligible reports and a second one for excluded reported.

After the first step, the remaining potentially eligibility records will be checked by their full-texts in duplicate by pairs of independent reviewers. Disagreements will be solved by consensus or by a third reviewer decision. On this level, reports will be flagged as eligible or ineligible with their respective reasons. In case of any physical report to be checked, they will be separated in the same manner as digital records after final decision, but they will be checked for eligibility directly by the full-text assessment.

Data collection process

Data extraction will be done in duplicate, with independent reviewers through a piloted data extraction form. The piloting of the form will be done by two experienced reviewers with the first 3 eligible records and amendments will be made accordingly to the

process. Disagreements will be solved by consensus or by the opinion of a third reviewer. Reasons for amendments and versions of the data extraction form will be recorded.

Data items

For the purpose of our NMA-SR, we will extract the following variables whenever available:

1. **Study**
   a. First author
   b. Year of publication

2. **Study characteristics**
   a. Publication type
   b. Study design (parallel, crossover)
   c. Washout period (wk)
   d. Study period (wk)
   e. Number of patients randomized (n)
   f. Industry sponsorship
   g. Countries
   h. Language of publication

3. Patient baseline characteristics
   a. Age (y)
   b. Gender (male/female, %)
   c. Race
   d. BMI (kg/m2)
   e. Marital Status
   f. Smoker
   g. Doses of alcohol per day
   h. BP measurement (e.g., reported as peak or reported as trough)
   i. BP measurement position
   j. Medications under chronic use (type, regimen -e.g., BID - and dose per day)
   k. Number of medications under chronic use (regardless of being an antihypertensive agent)
   l. Comorbidities

4. Interventions and comparators
   a. Name of the thiazide (generic)
   b. Type (thiazide-type or thiazide-like)
   c. Daily dose of thiazide
   d. Name of the association (potassium-sparing diuretic)
   e. Daily dose of potassium-sparing diuretic
   f. Name of the comparator
   g. Drug class of comparator
   h. Daily dose of comparator

Primary outcomes

We will collected data in those domains as presented in the article (e.g., mean or median plus confidence intervals or interquartile ranges) and transform/input them for our data-synthesis method, that will be describe in another section.

For office blood pressure:

i. Systolic blood pressure
ii. Diastolic blood pressure

Blood pressure will be presented and synthesized in mmHg. Whenever presented in another way, we will undergo transformations. Methods will be reported in further protocol amendments or in the final report.

Details of the observations that will be collected to synthesize the data by the change-from-baseline method will be presented at the bottom of this section.

Secondary outcomes

For metabolic variables

a. Serum potassium
b. Serum LDL-C
c. Serum uric acid
d. Fasting plasma glucose
e. Number of withdrawals

f. Number of falls
g. Number of hypotension events

For ambulatory blood pressure

h. Number of hypotension events
i. Daytime systolic blood pressure
j. Nightime systolic blood pressure
k. Daytime diastolic blood pressure
l. Nightime diastolic blood pressure
m. 24h systolic blood pressure
n. 24h diastolic blood pressure
o. Number of hypotension events

For MACE

p. All-cause mortality
q. Cardiovascular mortality
r. Fatal or non-fatal stroke
s. Fatal or non-fatal myocardial infarction

Serum potassium will be presented and synthesized in mEq/L. Fasting plasma glucose, LDL-C and uric acid will be presented and synthesized in mg/dL. Whenever necessary, transformations will be carried on. Methods will be reported in further protocol amendments of in the final report.

Outcomes and prioritisation

Primary Outcome

The quantitative summary effect of the antihypertensive drugs on blood pressure lowering. For the blood pressure outcome, we will put together the office blood pressure measured by any method (auscultatory, oscillometric and others).

Secondary outcomes

The pooled adverse cardiovascular events incidence will be our secondary efficacy outcome.

Secondary outcomes for harms (safety) are as follows: pooled serum potassium, LDL-C, uric acid and fasting plasma glucose. We will also qualitatively synthesize the number of withdrawals, falls and hypotension events of our antihypertensive drugs as well as the effect on the 24h, daytime and nighttime ambulatory blood pressure.

Continuous outcomes data extraction

Continuous outcomes are often presented in a sort of ways in each article. We will use the within group change-from-baseline method, synthesizing the mean and the standard deviation of the first and final observation. If not presented immediately by authors, we will transform the data from the following variables:

a. Within groups presentation

When the baseline and final values are displayed, point estimates and precision measurements

1. Mean or median of baseline and final observations
2. Standard deviation or confidence intervals or standard errors or interquartile ranges, or *P*-values of baseline and final observations
3. **Missing values**: inputations accordingly to the data-extraction sheet using the minor effect size and highest precision estimate to be conservative and to not unfavor out synthesis

When the baseline values are displayed, but the effect size displayed as the difference from baselines

1. Mean or median of baseline observations
2. Standard deviation or confidence intervals or standard errors of *P*-values of baseline observations
3. Effect size with the precision estimate (change from baseline and its related standard deviation or confidence intervals or standard errors of P-values of baseline)
4. **Missing values**: inputations accordingly to the data-extraction sheet using the minor effect size and highest precision estimate to be conservative and to not unfavor out synthesis

b. Between groups presentation

1. Effect size with the precision estimate (between groups change-from-baseline effect size and its related standard deviation or confidence intervals or standard errors of P-values of baseline)
2. **Missing values**: inputations accordingly to the data-extraction sheet using the minor effect size and highest precision estimate to be conservative and to not unfavor out synthesis

Dichotomous outcomes data extraction

For dichotomous outcomes data extraction, we will collect the number of events and the sample size for each treatment arm.

Data synthesis

Main Analyses

Firstly, we will qualitatively synthesize the data to present results in a systematic review manner. We will follow the PICO question to tabulate results and, regardless of metanalysis, the direct-comparison outcomes results (e.g., point-estimates and confidence intervals) will be also presented. A table with a detailed description of the interventions, disclosed conflicts of interest, reporting of disclosures, the presence of funding and the source of funding will be also conducted at this step.

To quantitatively summarize results, we will run a multiple treatment comparison (MTC) network metanalysis combining all available direct and indirect evidence from pairs of treatments. This will be made through the generalized Bayesian linear model proposed by Lu and Ades (2004). For this, a non-informative *priori* will be considered and study's effect sizes will be considerate to formulate the likelihood. The *posteriori* will be then generated to estimate parameters by the Monte-Carlo simulation nested to the Markov-Chain model.

We will check autocorrelation, traceplots and gelmanplots assumptions before continuing analysis to fit the best model. Analysis of inconsistency will be also made before moving forward to MTC estimates, and only those comparisons with no evidence of inconsistency ($P \leq 0.05$) will be maintained in the model and presented. MTC estimates will be assessed combining all direct and indirect available evidences by a random effects

model. Results will be presented as mean differences ± 95% of credible intervals ($P \leq 0.05$) and a frame with the geometry of comparisons will be also provided for continuous outcomes and by risk ratios ± 95% of credible intervals ($P \leq 0.05$) for dichotomous variables. The probability of success for each treatment for each outcome will be calculated by the SUCRA method.

We will also run a random-effects pairwise metanalysis for all available direct evidences. The I^2 statistics will be generated to assess heterogeneity of results and the Begg and Egger test plus the funnel plot visual inspection will be used to assess asymmetry of results whenever 10 or more studies would be available. Results will be presented as mean differences weighted by the study's inverse of variance ± 95% of confidence intervals ($P \leq 0.05$) for continuous outcomes and by risk ratios ± 95% of confidence intervals ($P \leq 0.05$) for dichotomous variables. Adverse events will be only summarized qualitatively. All the statistical analyses will be carried on at the R software (v. 3.5.2) using the packages "meta", "metafor" ane "rjags" that nest the WinBUGS software to the R Package.

Note 1: the statistical method for the exploratory analyses will be provided in the amendment of this protocol version.

Note 2: a medical statistician specialist (PKZ) will provide support for the data extraction and meta-biases adjustments (sensitivity analyses, meta-regression analyses) till the final report.

Note 3: For syntheses, the applied random effects will be the DerSimonian & Lard model for continuous variables. For dichotomous outcomes, the Mantel-Hanzeal random effects model will applied.

Note 4: Results will be presented in forest plots against placebo for the mixed effect. A league table will be also presented with one efficacy outcome and one safety outcome on the sides of the table. Pairwise metanalysis effects, mixed treatment effects, indirect effects will be presented also separately, as well as any further exploratory analysis for all quantitatively assessed outcomes. The geometry of the treatments will be presented for each outcome. The probability of success of treatments for each outcomes will be also presented. All the summarized outcomes (quantitatively) will have their full data provided (point estimate, precision and P-value) and qualitatively summarized outcomes will be intended to be displayed as complete as possible, accordingly to the author's data and further contacts.

Pre-Planned Exploratory Analyses (subgroup, sensitivity and meta-regression analyses)

Pre-planned subgroup analyses will be used to explore possible differences in treatments given such variables:

a. Sex
b. Age: adults (18-69 years), older people (70 years and older)
c. Race: black, white, other
d. Baseline severity of hypertension: < 140 mmHg, 140 to 149 mmHg, 150 to 159 mmHg and 160 mmHg or > (based on systolic blood pressure at baseline) and

< 90 mmHg, 90 to 99 mmHg, 100 to 109 mmHg and 110 mmHg or > (based on diastolic blood pressure at baseline).

e. The presence of comorbidity or not (dichotomic)

In the case of a large heterogeneity (I^2 > 50%) among treatments, we pre-planned some potential variables to re-conducted a metanalysis with adjustments for covariables. That being the case, we will provide a rationale for those conducted and those that we did not conducted at the final report. **Note: being an exploratory analysis by nature, some of the variables to adjust could be further added (with a rationale) to our pre-planned analyses and will be displayed as our deviations from the protocol in the final reported.** Also, a change for fixed effect model and exclusion of potential studies/treatments can be carried to check the accountability of the statistical method or a single particular study in terms of heterogeneity. **Disclaimer: no conclusion or recommendation will be done based on exploratory analyses.**

a. Industry-sponsored vs non-industry sponsored
b. Trials with blood pressure data measured in the sitting position versus other measurement positions.
c. Trials with published standard deviations of blood pressure change versus imputed standard deviations.
d. Trials with fixed-effect versus random-effects model.

Checking for asymmetry and suggestion of publication bias

As mentioned above, we will investigate the asymmetry of results through a contour plot in which point estimates will be inserted against the inverse of their standard error (e.g., a funnel plot). The Begg and Egger test will provide statistical support to any judgment and assessment.

Transitivity and risk of bias between studies (overall metanalysis)

We are considering the analyses for assumptions of transitivity and its accountability for any observed heterogeneity for such characteristics like age or baseline blood pressure levels by the method used at Cipriani et al 2018 [46]. Not pre-planned variables will be provided in updated versions of this protocol before the data analysis, due to any potential characteristics observed during the eligibility and will be displayed in an updated version of this protocol with a rationale. Any other variable not previously tracked that would be needed to explore after data analysis will be reported in the final paper as a deviation from the protocol, with a rationel. We are also intending the check for the risk of bias between studies (e.g., "overall bias of the metanalysis" or "confidence of the evidence of the metanalysis) by the CINeMA tool [47]. However, none of the authors have conducted this

approach before and this analysis could be deferred still at the level of the study conduction, if considered as infeasible due to technical constraints.

Risk of bias within individual studies

We will access the risk of bias of the primary studies with the Risk of Bias for Interventions tool v. 2.0 from the Cochrane Collaboration. We will use the proposed domains and will access each outcome separately. For the purpose of the assessment, we will follow the proposed algorithm and the supporting material of the tool.

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Appendix 1
Search strategies

PUBMED

#1 hydrochlorothiazide[MeSH] OR chlorothiazide[MeSH] OR dichlothiazide OR dihydrochlorothiazide OR hctz OR butizide OR buthiazide OR isobutylhydrochlorothiazide OR bendroflumethiazide[MeSH] OR bendrofluazide OR hydroflumethiazide[MeSH] OR trifluoromethylhydrothiazide OR trichlormethiazide[MeSH] OR methyclothiazide[MeSH] OR polythiazide[MeSH] OR cyclothiazide OR cyclopenthiazide[MeSH] OR cyclomethiazide OR chlorthalidone[MeSH] OR chlortalidone OR chlorphthalidolone OR metolazone[MeSH] OR phthalamudine OR quinethazone OR metolazone OR quinethazone OR fenquizone OR clorexolone OR chlorexolone OR clopamide[MeSH] OR indapamide[MeSH] OR metindamide OR diapamide OR mefruside[MeSH] OR xipamide[MeSH] OR bemetizide OR benzthiazide OR benzothiazide OR chlorazanil OR thiazide OR diuretics, thiazide[MeSH] OR thiazide diuretics[MeSH] OR benzothiadiazine diuretic[MeSH] OR sodium chloride symporter inhibitors OR sodium chloride cotransporter inhibitor OR potassium depleting diuretics OR diuretics, potassium depletion OR triamterene[MeSH] OR amiloride[MeSH] OR spironolactone[MeSH] OR eplerenone OR sodium channel blockers OR EnaC blocker OR inhibitor of the epithelial sodium channel[MeSH] OR co-amilozide OR coamilozide OR aldosterone receptor antagonist[MeSH] OR aldosterone antagonist OR mineralocorticoid antagonist OR mineralocorticoid receptor antagonist OR potassium sparing diuretic[MeSH]

#2 hypertension[MeSH] OR “hypertensive patients”[tw] OR “patients, hypertensive” OR “blood pressure”[tiab] OR “systolic blood pressure”[tiab] OR “diastolic blood pressure”[tiab]

#3 randomized controlled trial[pt] OR controlled clinical trial[pt] OR clinical trial[pt] OR randomized controlled trials[mh] OR random allocation[mh] OR double-blind method[mh] OR singleblind method[mh] OR random*[tiab] OR random*[tw] OR ("clinical trial"[tw]) OR drug therapy[sh] OR trial[tiab] OR groups[tiab] OR prospective studies[mh] OR NOT (animal[mh] NOT human[mh]) –

TOTAL #1 AND #2 AND #3

Cochrane Library

#1 MeSH descriptor: [hydrochlorothiazide] explode all trees
#2 MeSH descriptor: [chlorothiazide] explode all trees
#3 MeSH descriptor: [bendroflumethiazide] explode all trees
#4 MeSH descriptor: [hydroflumethiazide] explode all trees

#5 MeSH descriptor: [cyclopenthiazide] explode all trees
#6 MeSH descriptor: [trichlormethiazide] explode all trees
#7 MeSH descriptor: [methyclothiazide] explode all trees
#8 MeSH descriptor: [polythiazide] explode all trees
#9 MeSH descriptor: [chlorthalidone] explode all trees
#10 MeSH descriptor: [indapamide] explode all trees
#11 MeSH descriptor: [thiazide diuretics] explode all trees
#12 MeSH descriptor: [mefruside] explode all trees
#13 MeSH descriptor: [xipamide] explode all trees
#14 MeSH descriptor: [clopamide] explode all trees
#15 MeSH descriptor: [triamterene] explode all trees
#16 MeSH descriptor: [spironolactone] explode all trees
#17 MeSH descriptor: [amiloride] explode all trees
#18 MeSH descriptor: [sodium channel blockers] explode all trees
#19 MeSH descriptor: [mineralocorticoide receptor antagonists] explode all trees

#20 dichlothiazide or dihydrochlorothiazide or hctz or butizide or buthiazide or isobutylhydrochlorothiazide or bendrofluazide or trifluoromethylhydrothiazide or cyclothiazide or cyclopenthiazide or cyclomethiazide or chlortalidone or chlorphthalidolone or metolazone or phthalamudine or quinethazone or metolazone or quinethazone or fenquizone or clorexolone or chlorexolone or metindamide or diapamide or bemetizide or benzthiazide or benzothiazide or chlorazanil or thiazide or diuretics, thiazide or benzothiadiazine or sodium chloride symporter inhibitors or sodium chloride cotransporter inhibitor or potassium depleting diuretics or diuretics, potassium depletion or eplerenone or EnaC blocker or inhibitor of the epithelial sodium channel or co-amilozide or coamilozide or mineralocorticoid antagonist or mineralocorticoid receptor antagonist or aldosterone antagonists or potassium sparing diuretic

#21 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20
#22 MeSH descriptor: [hypertension] explode all trees
#23 “hypertensive patients” or “patients, hypertensive”
#24 #22 or #23
#25 MeSH descriptor: [Randomized Controlled Trial] explode all trees
#26 MeSH descriptor: [Random Allocation] explode all trees
#27 MeSH descriptor: [Randomized Controlled Trials as Topic] explode all trees
#28 double-blind method or controlled clinical trial or clinical trial
#29 #25 or #26 or #27 or #28
#30 #21 and #24 and #29 in Trials

Embase

#1 ‘hydrochlorothiazide’/exp OR ‘chlorothiazide’/exp OR ‘bendroflumethiazide’/exp OR ‘hydroflumethiazide’/exp OR ‘cyclopenthiazide’/exp OR ‘trichlormethiazide’/exp OR ‘methyclothiazide’/exp OR ‘polythiazide’/exp OR ‘chlorthalidone’/exp OR ‘indapamide’/exp OR ‘thiazide diuretic agent’/exp OR ‘mefruside’/exp OR ‘xipamide’/exp OR ‘clopamide’/exp OR dichlothiazide OR dihydrochlorothiazide OR hctz OR butizide OR buthiazide OR isobutylhydrochlorothiazide OR bendrofluazide OR trifluoromethylhydrothiazide OR cyclothiazide OR cyclopenthiazide OR cyclomethiazide OR chlortalidone OR chlorphthalidolone OR metolazone OR phthalamudine OR quinethazone OR metolazone OR quinethazone OR fenquizone OR clorexolone OR chlorexolone OR metindamide OR diapamide OR bemetizide OR benzthiazide OR benzothiazide OR chlorazanil OR thiazide OR diuretics, thiazide OR benzothiadiazine OR sodium chloride symporter inhibitors OR sodium chloride cotransporter inhibitor OR potassium depleting diuretics OR diuretics, potassium depletion OR ‘eplerenone’/exp OR ‘triamterene’/exp OR ‘spironolactone’/exp OR ‘amiloride’/exp OR 'sodium channel blocking agent'/exp OR sodium channel blockers OR ‘aldosterone receptor antagonists’/exp OR aldosterone antagonists OR 'potassium sparing diuretic agent'/exp OR potassium sparing diuretic OR EnaC blocker OR ‘inhibitor of the epithelial sodium channel’/exp OR co-amilozide OR coamilozide OR ‘mineralocorticoid antagonist’/exp OR mineralocorticoid receptor antagonist

#2 ‘hypertension’/exp OR ‘hypertensive patient’/exp OR patients, hypertensive OR blood pressure OR ‘systolic blood pressure’/exp OR ‘diastolic blood pressure’/exp
#3 random$ OR doubl$ adj blind$ OR singl$ adj blind$ OR assign$ OR allocat$ OR 'randomized controlled trial'/exp

#1 AND #2 AND #3

Web of Science

#1 TS=((hydrochlorothiazide OR chlorothiazide OR bendroflumethiazide OR hydroflumethiazide OR cyclopenthiazide OR trichlormethiazide OR methyclothiazide OR polythiazide OR chlorthalidone OR indapamide OR thiazide diuretic agent OR mefruside OR xipamide OR clopamide OR dichlothiazide OR dihydrochlorothiazide OR hctz OR butizide OR buthiazide OR isobutylhydrochlorothiazide OR bendrofluazide OR trifluoromethylhydrothiazide OR cyclothiazide OR cyclopenthiazide OR cyclomethiazide OR chlortalidone OR chlorphthalidolone OR metolazone OR phthalamudine OR quinethazone OR metolazone OR quinethazone OR fenquizone OR clorexolone OR chlorexolone OR metindamide OR diapamide OR bemetizide OR benzthiazide OR

benzothiazide OR chlorazanil OR thiazide OR diuretics, thiazide OR benzothiadiazine OR sodium chloride symporter inhibitors OR sodium chloride cotransporter inhibitor OR potassium depleting diuretics OR diuretics, potassium depletion OR amiloride OR triamterene OR spironolactone OR eplerenone OR sodium channel blockers or aldosterone receptor antagonists or aldosterone antagonists or potassium sparing diuretic or EnaC blocker OR inhibitor of the epithelial sodium channel OR co-amilozide OR coamilozide OR mineralocorticoid antagonist OR mineralocorticoid receptor antagonist)

#2 TS=((hypertension OR hypertensive patients OR patients, hypertensive OR blood pressure OR systolic blood pressure OR diastolic blood pressure))

#3 TS=((randomized controlled trial OR controlled clinical trial OR clinical trial OR randomized controlled trials OR random OR clinical trial))

Lilacs

#1 (tw:(hydrochlorothiazide OR chlorothiazide OR bendroflumethiazide OR hydroflumethiazide OR cyclopenthiazide OR trichlormethiazide OR methyclothiazide OR polythiazide OR chlorthalidone OR indapamide OR thiazide diuretic agent OR mefruside OR xipamide OR clopamide OR dichlothiazide OR dihydrochlorothiazide OR hctz OR butizide OR buthiazide OR isobutylhydrochlorothiazide OR bendrofluazide OR trifluoromethylhydrothiazide OR cyclothiazide OR cyclopenthiazide OR cyclomethiazide OR chlortalidone OR chlorphthalidolone OR metolazone OR phthalamudine OR quinethazone OR metolazone OR quinethazone OR fenquizone OR clorexolone OR chlorexolone OR metindamide OR diapamide OR bemetizide OR benzthiazide OR benzothiazide OR chlorazanil OR thiazide OR diuretics, thiazide OR benzothiadiazine OR sodium chloride symporter inhibitors OR sodium chloride cotransporter inhibitor OR potassium depleting diuretics OR diuretics, potassium depletion OR eplerenone OR amiloride OR triamterene OR spironolactone OR sodium channel blockers OR aldosterone receptor antagonists OR aldosterone antagonists OR potassium sparing diuretic OR EnaC blocker OR inhibitor of the epithelial sodium channel OR co-amilozide OR coamilozide OR mineralocorticoid antagonist OR mineralocorticoid receptor antagonist) AND (hypertension OR hypertensive patients OR patients, hypertensive OR blood pressure OR systolic blood pressure OR diastolic blood pressure))

#2 (tw:(hypertension OR “hypertensive patients” OR “patients, hypertensive” OR “blood pressure” OR “systolic blood pressure” OR “diastolic blood pressure”))

#3 (db:("LILACS"))

#1 AND #2 AND #3

Scopus

#1 KEY(hydrochlorothiazide OR chlorothiazide OR chlorthalidone OR indapamide OR thiazide AND diuretic OR eplerenone OR spironolactone OR triamterene OR amiloride) OR ALL(bendroflumethiazide OR hydroflumethiazide OR cyclopenthiazide OR trichlormethiazide OR methyclothiazide OR polythiazide OR thiazide diuretic agent mefruside OR xipamide OR clopamide OR dichlothiazide OR dihydrochlorothiazide OR hctz OR butizide OR buthiazide OR isobutylhydrochlorothiazide OR bendrofluazide OR trifluoromethylhydrothiazide OR cyclothiazide OR cyclopenthiazide OR cyclomethiazide OR chlortalidone OR chlorphthalidolone OR metolazone OR phthalamudine OR quinethazone OR metolazone OR quinethazone OR fenquizone OR clorexolone OR chlorexolone OR metindamide OR diapamide OR bemetizide OR benzthiazide OR benzothiazide OR chlorazanil OR thiazide OR diuretics, thiazide OR benzothiadiazine OR sodium chloride symporter inhibitors OR sodium chloride cotransporter inhibitor OR potassium depleting diuretics OR diuretics, potassium depletion OR aldosterone antagonists OR EnaC blocker OR co-amilozide OR coamilozide OR mineralocorticoid antagonist OR aldosterone receptor antagonists OR mineralocorticoid AND receptor AND antagonist OR inhibitor AND of AND the AND epithelial AND sodium AND channel OR sodium AND channel AND blockers OR potassium AND sparing AND diuretic)

#2 KEY(hypertension OR hypertensive AND patients)

#3 KEY(randomized AND controlled AND trial OR clinical AND trial) AND NOT review AND NOT (systematic AND review) AND NOT (observational AND study)

ERIC

“hypertension”

Clinical Trials

Condition or disease: Hypertension
Other terms: Hypertensive patients

Study type: Interventional studies (Clinical trials)
Study results: All studies
Status: “Recruiting”, “active, not recruiting”, “terminated”, “completed” and “unknown status”.
Age: Adult (18-64) and older adult (65+)
Sex: All
Intervention/treatment: Diuretics

Additional criteria: Phase 2, phase 3 and phase 4

APÊNDICE 2

Network meta-analysis search strategies.

Search strategies

PUBMED

#1 hydrochlorothiazide[MeSH] OR chlorothiazide[MeSH] OR dichlothiazide OR dihydrochlorothiazide OR hctz OR butizide OR buthiazide OR isobutylhydrochlorothiazide OR bendroflumethiazide[MeSH] OR bendrofluazide OR hydroflumethiazide[MeSH] OR trifluoromethylhydrothiazide OR trichlormethiazide[MeSH] OR methyclothiazide[MeSH] OR polythiazide[MeSH] OR cyclothiazide OR cyclopenthiazide[MeSH] OR cyclomethiazide OR chlorthalidone[MeSH] OR chlortalidone OR chlorphthalidolone OR metolazone[MeSH] OR phthalamudine OR quinethazone OR metolazone OR quinethazone OR fenquizone OR clorexolone OR chlorexolone OR clopamide[MeSH] OR indapamide[MeSH] OR metindamide OR diapamide OR mefruside[MeSH] OR xipamide[MeSH] OR bemetizide OR benzthiazide OR benzothiazide OR chlorazanil OR thiazide OR diuretics, thiazide[MeSH] OR thiazide diuretics[MeSH] OR benzothiadiazine diuretic[MeSH] OR sodium chloride symporter inhibitors OR sodium chloride cotransporter inhibitor OR potassium depleting diuretics OR diuretics, potassium depletion OR triamterene[MeSH] OR amiloride[MeSH] OR spironolactone[MeSH] OR eplerenone OR sodium channel blockers OR EnaC blocker OR inhibitor of the epithelial sodium channel[MeSH] OR co-amilozide OR coamilozide OR aldosterone receptor antagonist[MeSH] OR aldosterone antagonist OR mineralocorticoid antagonist OR mineralocorticoid receptor antagonist OR potassium sparing diuretic[MeSH]

#2 hypertension[MeSH] OR “hypertensive patients”[tw] OR “patients, hypertensive” OR “blood pressure”[tiab] OR “systolic blood pressure”[tiab] OR “diastolic blood pressure”[tiab]

#3 randomized controlled trial[pt] OR controlled clinical trial[pt] OR clinical trial[pt] OR randomized controlled trials[mh] OR random allocation[mh] OR double-blind method[mh] OR singleblind method[mh] OR random*[tiab] OR random*[tw] OR ("clinical trial"[tw]) OR drug therapy[sh] OR trial[tiab] OR groups[tiab] OR prospective studies[mh] OR NOT (animal[mh] NOT human[mh]) –

TOTAL #1 AND #2 AND #3

Cochrane Library

#1 MeSH descriptor: [hydrochlorothiazide] explode all trees

#2 MeSH descriptor: [chlorothiazide] explode all trees

#3 MeSH descriptor: [bendroflumethiazide] explode all trees

#4 MeSH descriptor: [hydroflumethiazide] explode all trees

#5 MeSH descriptor: [cyclopenthiazide] explode all trees

#6 MeSH descriptor: [trichlormethiazide] explode all trees

#7 MeSH descriptor: [methyclothiazide] explode all trees

#8 MeSH descriptor: [polythiazide] explode all trees

#9 MeSH descriptor: [chlorthalidone] explode all trees

#10 MeSH descriptor: [indapamide] explode all trees

#11 MeSH descriptor: [thiazide diuretics] explode all trees

#12 MeSH descriptor: [mefruside] explode all trees

#13 MeSH descriptor: [xipamide] explode all trees

#14 MeSH descriptor: [clopamide] explode all trees

#15 MeSH descriptor: [triamterene] explode all trees

#16 MeSH descriptor: [spironolactone] explode all trees

#17 MeSH descriptor: [amiloride] explode all trees

#18 MeSH descriptor: [sodium channel blockers] explode all trees

#19 MeSH descriptor: [mineralocorticoide receptor antagonists] explode all trees

#20 dichlothiazide or dihydrochlorothiazide or hctz or butizide or buthiazide or isobutylhydrochlorothiazide or bendrofluazide or trifluoromethylhydrothiazide or cyclothiazide or cyclopenthiazide or cyclomethiazide or chlortalidone or chlorphthalidolone or metolazone or phthalamudine or quinethazone or metolazone or quinethazone or fenquizone or clorexolone or chlorexolone or metindamide or diapamide or bemetizide or benzthiazide or benzothiazide or chlorazanil or thiazide or diuretics, thiazide or benzothiadiazine or sodium chloride symporter inhibitors or sodium chloride cotransporter inhibitor or potassium depleting diuretics or diuretics, potassium depletion or eplerenone or EnaC blocker or inhibitor of the epithelial sodium channel or co-amilozide or coamilozide or mineralocorticoid antagonist or mineralocorticoid receptor antagonist or aldosterone antagonists or potassium sparing diuretic

#21 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20

#22 MeSH descriptor: [hypertension] explode all trees

#23 “hypertensive patients” or “patients, hypertensive”

#24 #22 or #23

#25 MeSH descriptor: [Randomized Controlled Trial] explode all trees

#26 MeSH descriptor: [Random Allocation] explode all trees

#27 MeSH descriptor: [Randomized Controlled Trials as Topic] explode all trees

#28 double-blind method or controlled clinical trial or clinical trial

#29 #25 or #26 or #27 or #28

#30 #21 and #24 and #29 in Trials

Embase

#1 ‘hydrochlorothiazide’/exp OR ‘chlorothiazide’/exp OR ‘bendroflumethiazide’/exp OR ‘hydroflumethiazide’/exp OR ‘cyclopenthiazide’/exp OR ‘trichlormethiazide’/exp OR ‘methyclothiazide’/exp OR ‘polythiazide’/exp OR ‘chlorthalidone’/exp OR ‘indapamide’/exp OR ‘thiazide diuretic agent’/exp OR ‘mefruside’/exp OR ‘xipamide’/exp OR ‘clopamide’/exp OR dichlothiazide OR dihydrochlorothiazide OR hctz OR butizide OR buthiazide OR isobutylhydrochlorothiazide OR bendrofluazide OR trifluoromethylhydrothiazide OR cyclothiazide OR cyclopenthiazide OR cyclomethiazide OR chlortalidone OR chlorphthalidolone OR metolazone OR phthalamudine OR quinethazone OR metolazone OR quinethazone OR fenquizone OR clorexolone OR chlorexolone OR metindamide OR diapamide OR bemetizide OR benzthiazide OR benzothiazide OR chlorazanil OR thiazide OR diuretics, thiazide OR benzothiadiazine OR sodium chloride symporter inhibitors OR sodium chloride cotransporter inhibitor OR potassium depleting diuretics OR diuretics, potassium depletion OR ‘eplerenone’/exp OR ‘triamterene’/exp OR ‘spironolactone’/exp OR ‘amiloride’/exp OR 'sodium channel blocking agent'/exp OR sodium channel blockers OR ‘aldosterone receptor antagonists’/exp OR aldosterone antagonists OR 'potassium sparing diuretic agent'/exp OR potassium sparing diuretic OR EnaC blocker OR ‘inhibitor of the epithelial sodium channel’/exp OR co-amilozide OR coamilozide OR ‘mineralocorticoid antagonist’/exp OR mineralocorticoid receptor antagonist

#2 ‘hypertension’/exp OR ‘hypertensive patient’/exp OR patients, hypertensive OR blood pressure OR ‘systolic blood pressure’/exp OR ‘diastolic blood pressure’/exp

#3 random$ OR doubl$ adj blind$ OR singl$ adj blind$ OR assign$ OR allocat$ OR 'randomized controlled trial'/exp

#1 AND #2 AND #3

Web of Science

#1 TS=((hydrochlorothiazide OR chlorothiazide OR bendroflumethiazide OR hydroflumethiazide OR cyclopenthiazide OR trichlormethiazide OR methyclothiazide OR polythiazide OR chlorthalidone OR indapamide OR thiazide diuretic agent OR mefruside OR xipamide OR clopamide OR dichlothiazide OR dihydrochlorothiazide OR hctz OR butizide OR buthiazide OR isobutylhydrochlorothiazide OR bendrofluazide OR trifluoromethylhydrothiazide OR cyclothiazide OR cyclopenthiazide OR cyclomethiazide OR chlortalidone OR chlorphthalidolone OR metolazone OR phthalamudine OR quinethazone OR metolazone OR quinethazone OR fenquizone OR clorexolone OR chlorexolone OR metindamide OR diapamide OR bemetizide OR benzthiazide OR benzothiazide OR chlorazanil OR thiazide OR diuretics, thiazide OR benzothiadiazine OR sodium chloride symporter inhibitors OR sodium chloride cotransporter inhibitor OR potassium depleting diuretics OR diuretics, potassium depletion OR amiloride OR triamterene OR spironolactone OR eplerenone OR sodium channel blockers or aldosterone receptor antagonists or aldosterone antagonists or potassium sparing diuretic or EnaC blocker OR inhibitor of the epithelial sodium channel OR co-amilozide OR coamilozide OR mineralocorticoid antagonist OR mineralocorticoid receptor antagonist)

#2 TS=((hypertension OR hypertensive patients OR patients, hypertensive OR blood pressure OR systolic blood pressure OR diastolic blood pressure))

#3 TS=((randomized controlled trial OR controlled clinical trial OR clinical trial OR randomized controlled trials OR random OR clinical trial))

Lilacs

#1 (tw:(hydrochlorothiazide OR chlorothiazide OR bendroflumethiazide OR hydroflumethiazide OR cyclopenthiazide OR trichlormethiazide OR methyclothiazide OR polythiazide OR chlorthalidone OR indapamide OR thiazide diuretic agent OR mefruside OR xipamide OR clopamide OR dichlothiazide OR dihydrochlorothiazide OR hctz OR butizide OR buthiazide OR isobutylhydrochlorothiazide OR bendrofluazide OR trifluoromethylhydrothiazide OR cyclothiazide OR cyclopenthiazide OR cyclomethiazide OR chlortalidone OR chlorphthalidolone OR metolazone OR phthalamudine OR quinethazone OR metolazone OR quinethazone OR fenquizone OR clorexolone OR chlorexolone OR metindamide OR diapamide OR bemetizide OR benzthiazide OR benzothiazide OR chlorazanil OR thiazide OR diuretics, thiazide OR benzothiadiazine OR sodium chloride symporter inhibitors OR sodium chloride cotransporter inhibitor OR potassium depleting diuretics OR diuretics, potassium depletion OR eplerenone OR amiloride OR triamterene OR spironolactone OR sodium channel blockers OR aldosterone receptor antagonists OR aldosterone antagonists OR potassium sparing diuretic OR EnaC blocker OR inhibitor of the epithelial sodium channel OR co-amilozide OR coamilozide OR mineralocorticoid antagonist OR mineralocorticoid receptor antagonist) AND (hypertension OR hypertensive patients OR patients, hypertensive OR blood pressure OR systolic blood pressure OR diastolic blood pressure))

#2 (tw:(hypertension OR “hypertensive patients” OR “patients, hypertensive” OR “blood pressure” OR “systolic blood pressure” OR “diastolic blood pressure”))

#3 (db:("LILACS"))

#1 AND #2 AND #3

Scopus

#1 KEY(hydrochlorothiazide OR chlorothiazide OR chlorthalidone OR indapamide OR thiazide AND diuretic OR eplerenone OR spironolactone OR triamterene OR amiloride) OR ALL(bendroflumethiazide OR hydroflumethiazide OR cyclopenthiazide OR trichlormethiazide OR methyclothiazide OR polythiazide OR thiazide diuretic agent mefruside OR xipamide OR clopamide OR dichlothiazide OR dihydrochlorothiazide OR hctz OR butizide OR buthiazide OR isobutylhydrochlorothiazide OR bendrofluazide OR trifluoromethylhydrothiazide OR cyclothiazide OR cyclopenthiazide OR cyclomethiazide OR chlortalidone OR chlorphthalidolone OR metolazone OR phthalamudine OR quinethazone OR metolazone OR quinethazone OR fenquizone OR clorexolone OR chlorexolone OR metindamide OR diapamide OR bemetizide OR benzthiazide OR benzothiazide OR chlorazanil OR thiazide OR diuretics, thiazide OR benzothiadiazine OR sodium chloride symporter inhibitors OR sodium chloride cotransporter inhibitor OR potassium depleting diuretics OR diuretics, potassium depletion OR aldosterone antagonists OR EnaC blocker OR co-amilozide OR coamilozide OR mineralocorticoid antagonist OR aldosterone receptor antagonists OR mineralocorticoid AND receptor AND antagonist OR inhibitor AND of AND the AND epithelial AND sodium AND channel OR sodium AND channel AND blockers OR potassium AND sparing AND diuretic)

#2 KEY(hypertension OR hypertensive AND patients)

#3 KEY(randomized AND controlled AND trial OR clinical AND trial) AND NOT review AND NOT (systematic AND review) AND NOT (observational AND study)

ERIC

“hypertension”

Clinical Trials

Condition or disease: Hypertension

Other terms: Hypertensive patients

Study type: Interventional studies (Clinical trials)

Study results: All studies

Status: “Recruiting”, “active, not recruiting”, “terminated”, “completed” and “unknown status”.

Age: Adult (18-64) and older adult (65+)

Sex: All

Intervention/treatment: Diuretics

Additional criteria: Phase 2, phase 3 and phase 4

APÊNDICE 3

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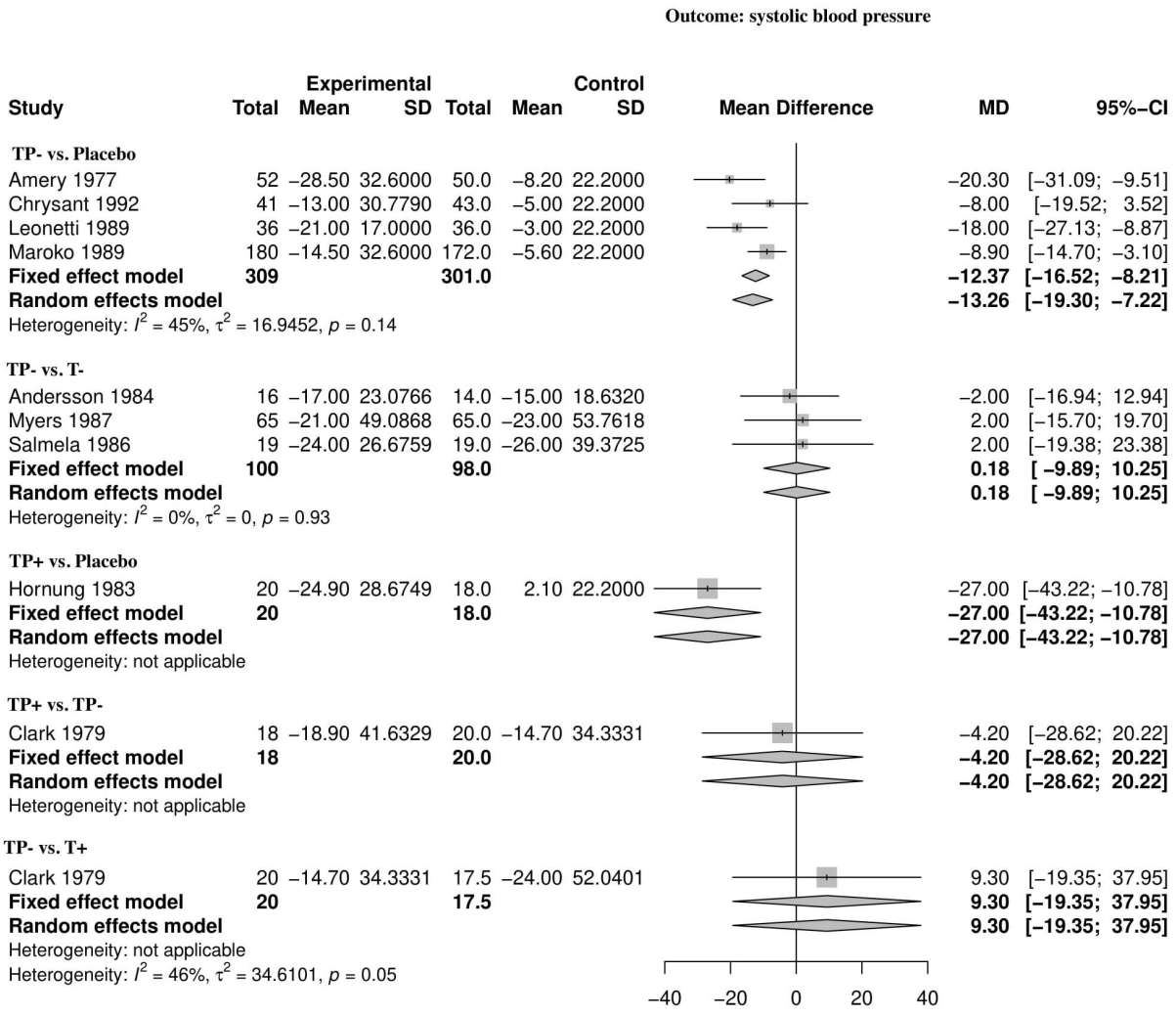
APÊNDICE 4

Pairwise meta-analyses.



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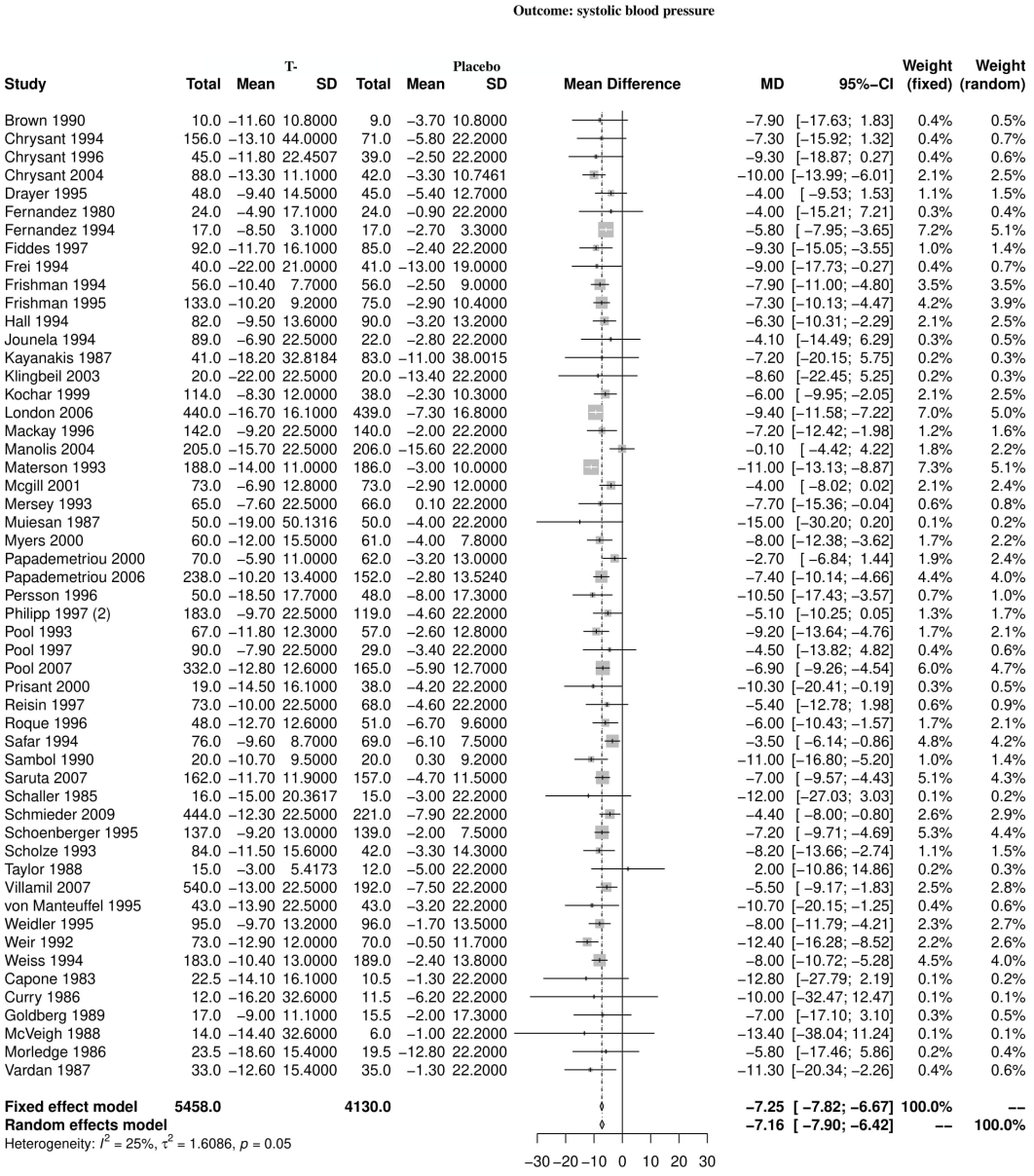

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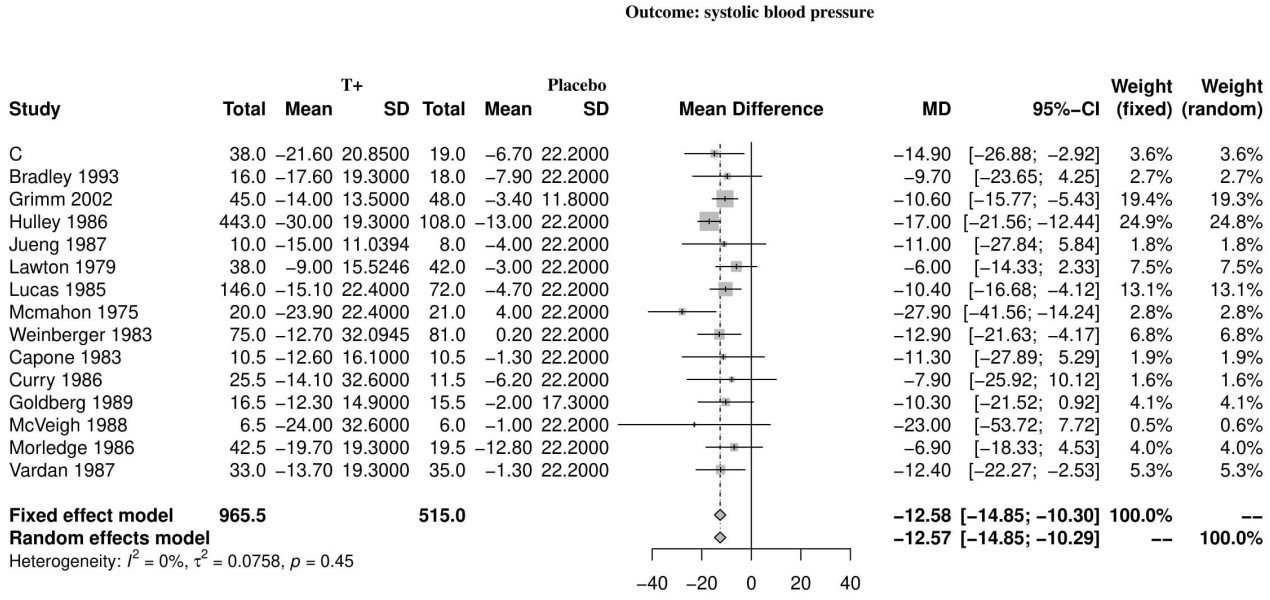

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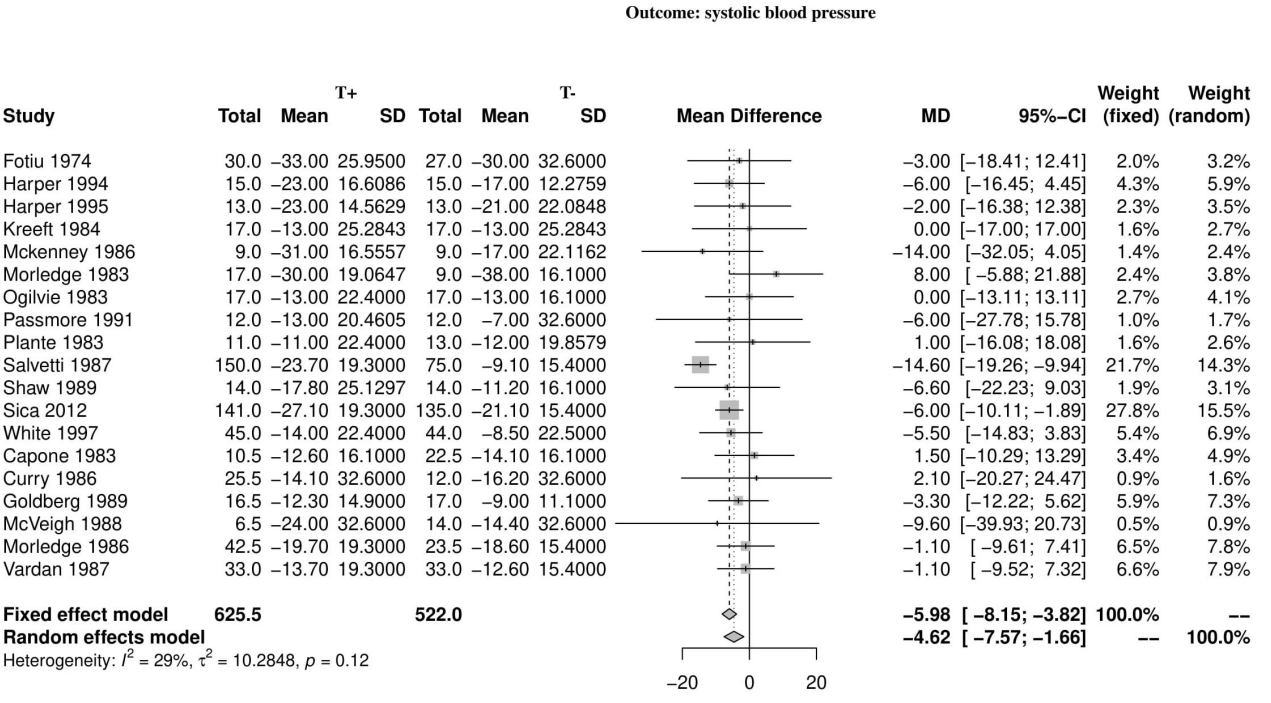
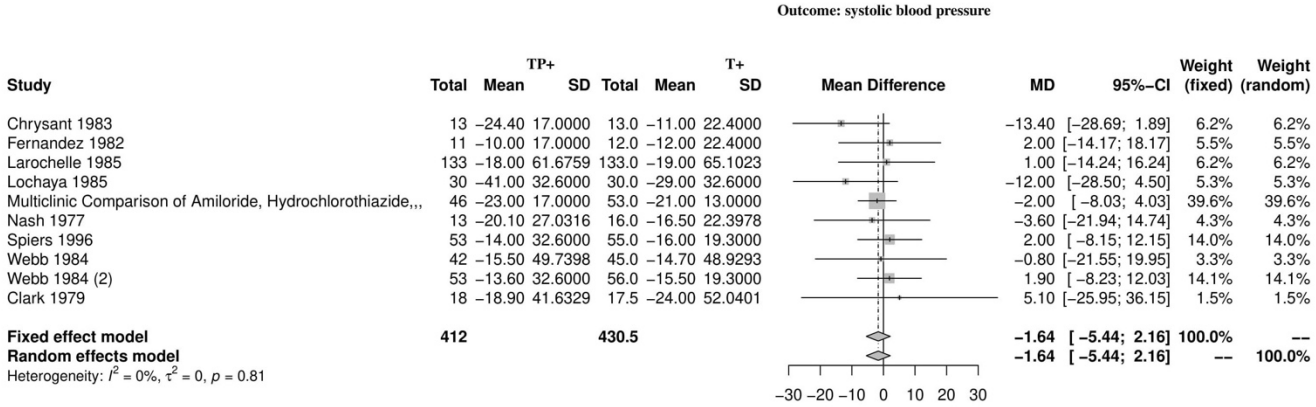
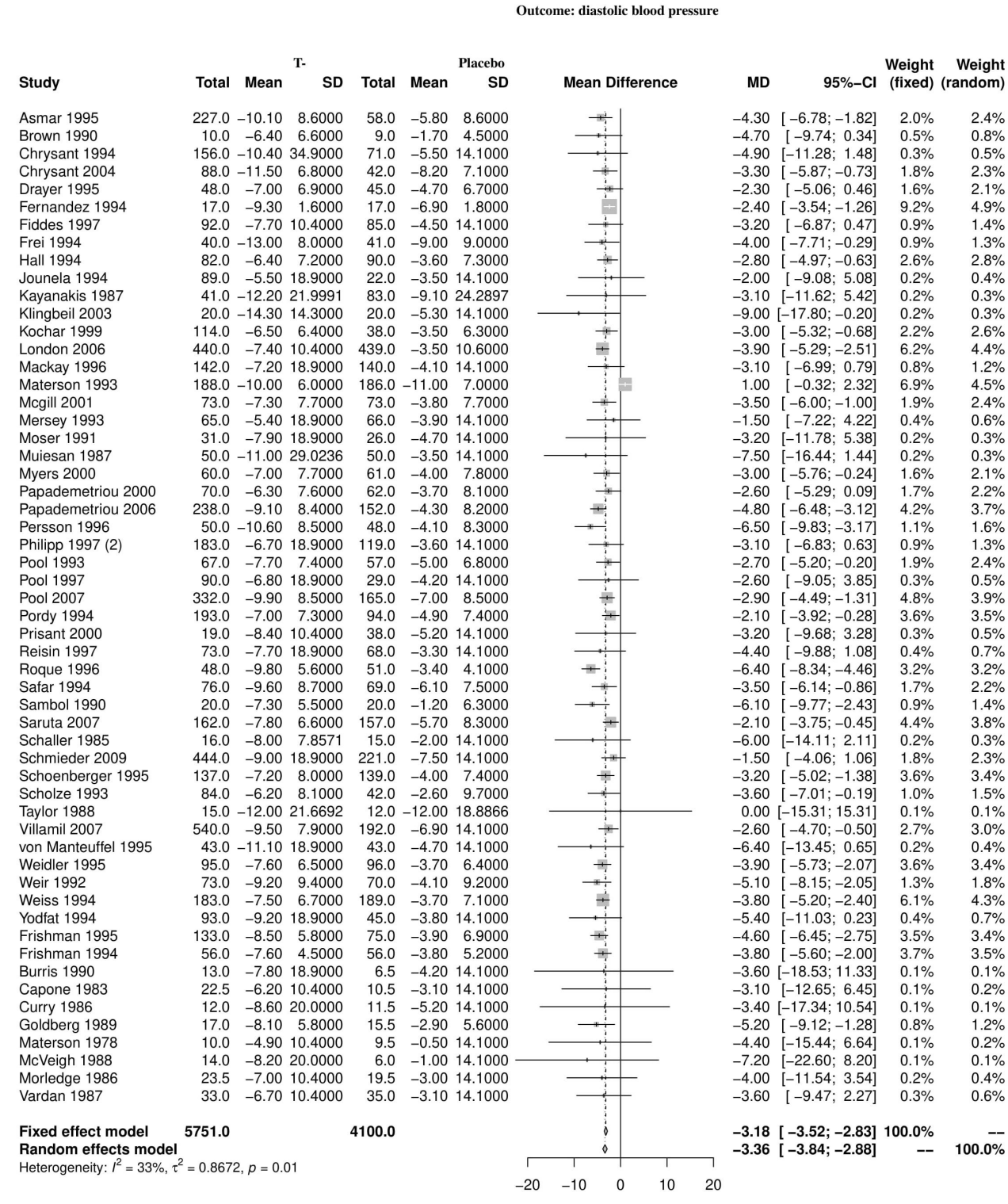


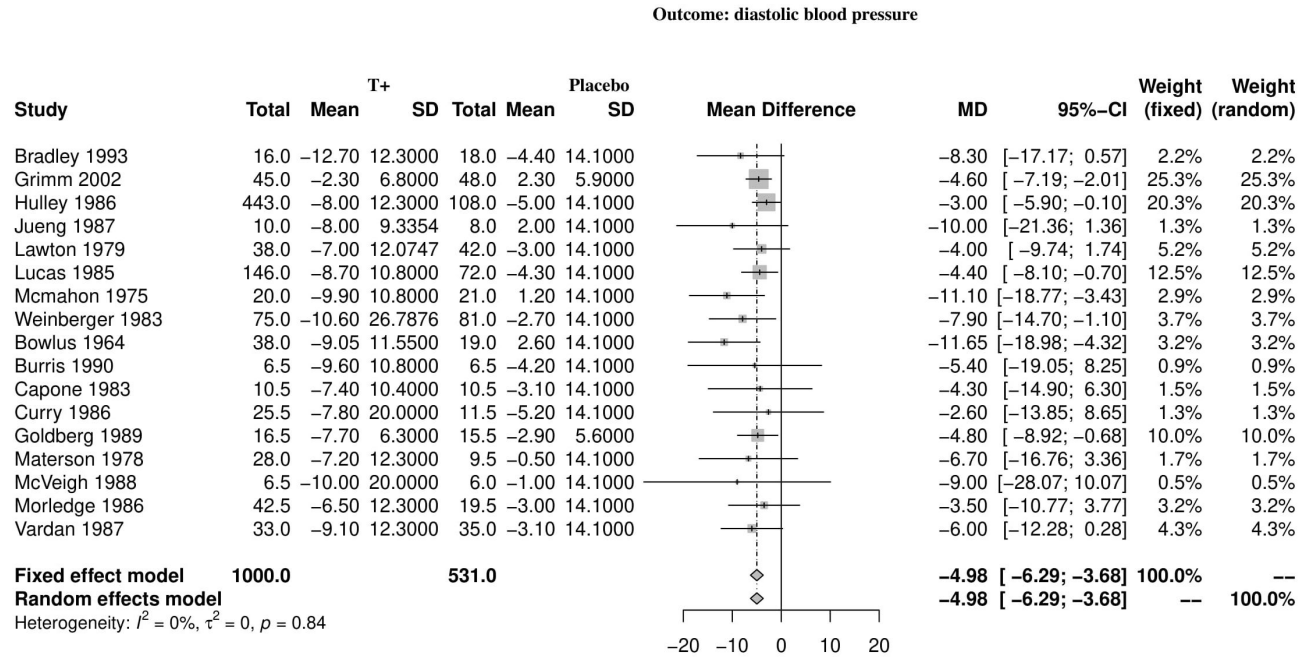
Pairwise meta-analysis of eligible comparisons for office systolic blood pressure.



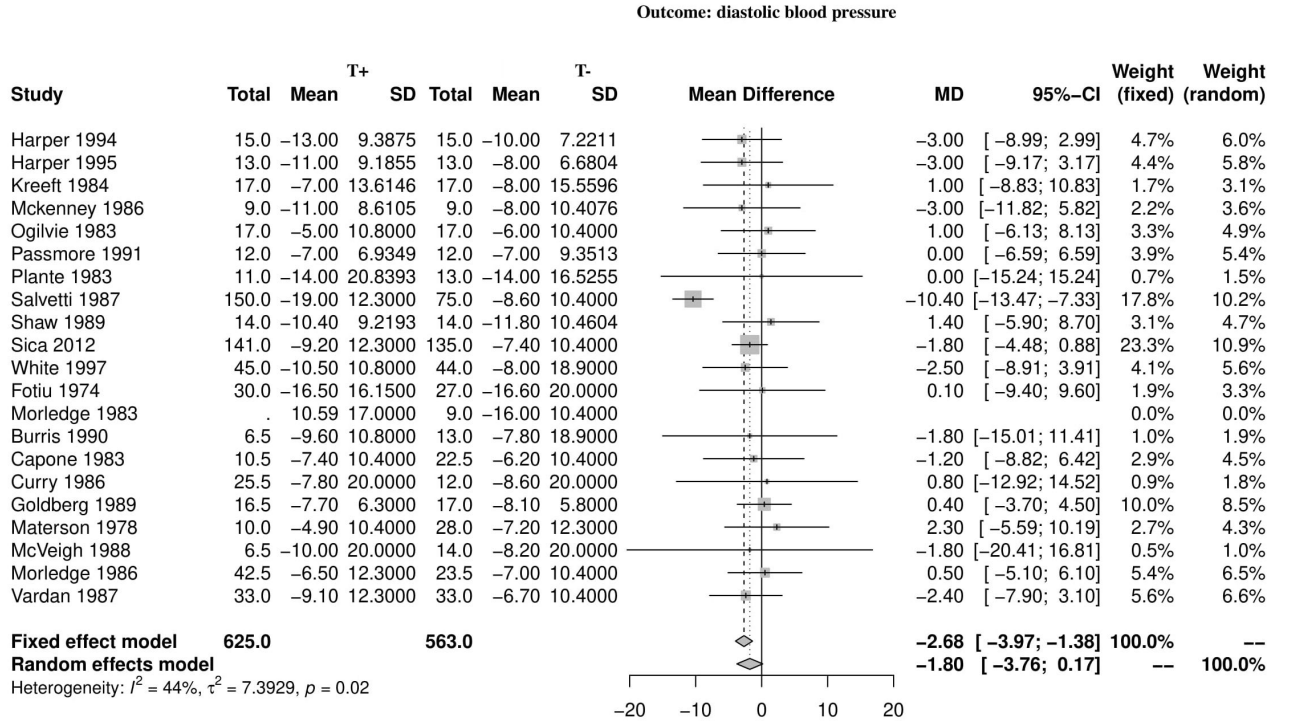
Pairwise meta-analysis of eligible comparisons for office systolic blood pressure.



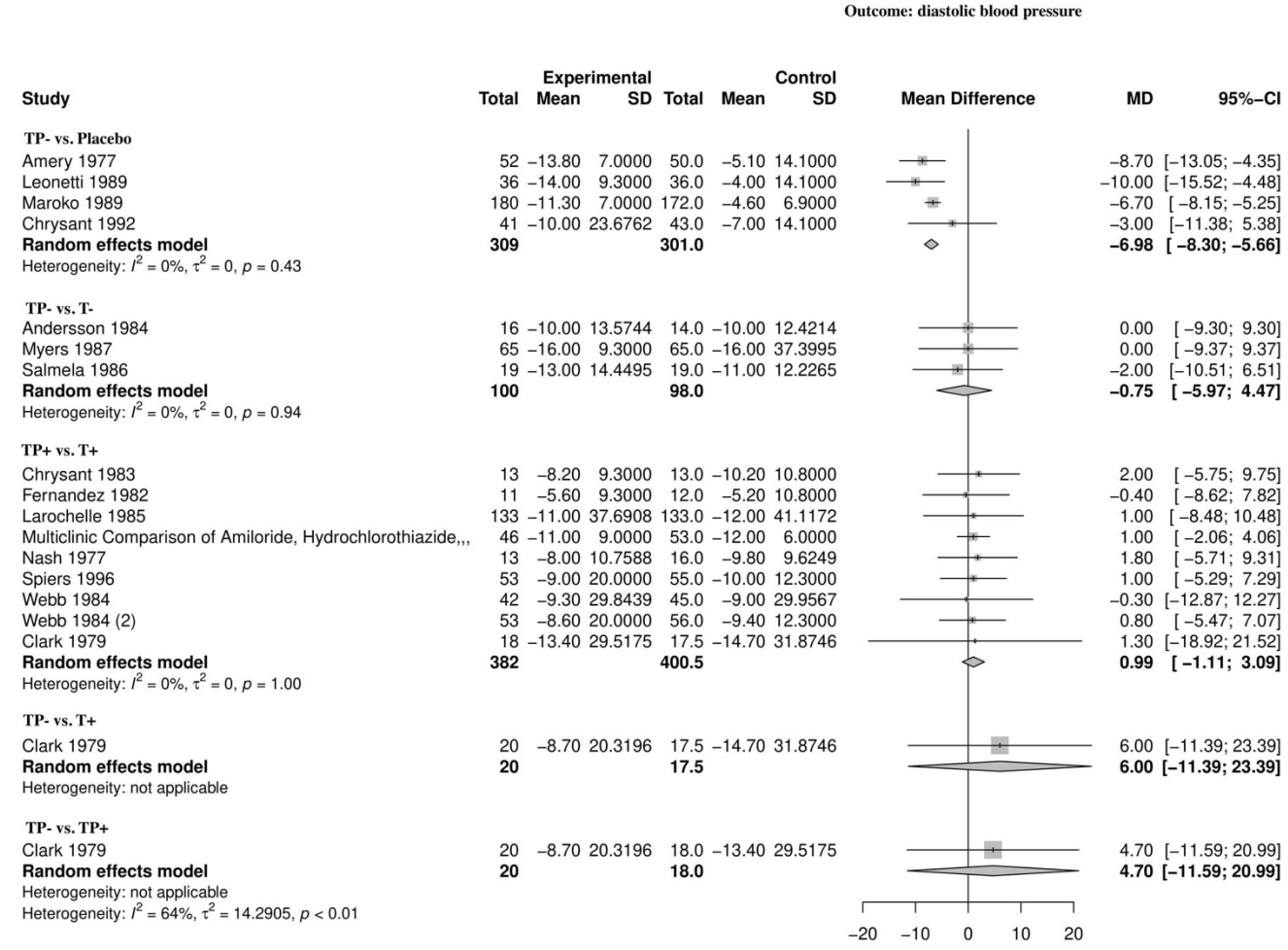
Pairwise meta-analysis of eligible comparisons for office diastolic blood pressure.



Pairwise meta-analysis of eligible comparisons for office diastolic blood pressure.



Pairwise meta-analysis of eligible comparisons for office diastolic blood pressure.



Pairwise meta-analysis of eligible comparisons for office diastolic blood pressure.