Study Protocol

Thiazide diuretics alone or in combination with a potassium-sparing diuretic on blood pressure lowering in patients with primary hypertension: a protocol 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 will be prospectively registered at the PROSPERO database. The number of the register will be provided in further amendments of the protocol.

Affiliations

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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 first version of this protocol. Any further amendments will be disclosed with reasons.

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)
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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. **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.

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.

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. Double dummy trials designs will be excluded by combinations of placebo drugs in our eligible treatment arms.

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 from 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 (i.e., "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.

References

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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