Clinical Benefits and Harms of Diuretics for Primary Prevention of Cardiovascular Outcomes in Black People With Essential Hypertension: A Protocol for a Systematic Review of Randomized Clinical Trials With Meta-analysis and Trial Sequential Analysis

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Protocol

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Abstract

Background

The overall mortality attributable to cardiovascular diseases (coronary heart disease, sudden cardiac death/sudden cardiac arrest, stroke/transient ischemic attack, and peripheral arterial disease) is higher in the Black population when compared to the White population. Essential hypertension (EH) is the most important modifiable risk factor for cardiovascular diseases. The prevalence of hypertension among Black adults is also higher. Diuretics are antihypertensive drugs, and their role in the primary prevention of clinical cardiovascular outcomes in the Black population with essential hypertension remains unknown. To assess the clinical benefits and harms of diuretics, as a primary prevention approach, compared with placebo or any other antihypertensive medications.

Methods

We will search the Cochrane Central Register of Controlled Trials (to update), OVID MEDLINE (1946 to update), Embase (1980 to update), LILACS (1986 to update), and Web of Science (to update). We will manually search the reference lists of the included papers and contact researchers in the field. There will be no language restrictions in the search. We will include parallel-design and crossover randomized clinical trials that has adult Black people with essential hypertension as the population. The primary outcomes are all-cause mortality, myocardial infarction, stroke, and serious adverse events. Pregnant women will be excluded from the study.

We will perform study selection, risk of bias assessment, and data extraction in duplicate. We will estimate risk ratios (RRs) with a 95% confidence interval (95% CI) for dichotomous outcomes. For continuous outcomes, such as health-related quality of life, systolic blood pressure, and diastolic blood pressure, we will calculate the mean difference with 95% CI or the standardized mean difference with 95% CI. We will measure statistical heterogeneity using the I^2 statistic and use a fixed-effects and random-effects model. We will conduct a sequential trial analysis.

Discussion

Our aim is to provide external validity and try to solve conflicts about the evidence regarding use of diuretics as a primary prevention of cardiovascular outcomes in Black people with essential hypertension to guide appropriate clinical practice.

Systematic review registration

PROSPERO registration number: CRD42021240864

Background

Description of the condition

Cardiovascular diseases (CVDs) include coronary heart disease (CHD), sudden cardiac death, sudden cardiac arrest, stroke/transient ischemic attack, and peripheral arterial disease [1]. Mortality and morbidity from CVDs are considered a global public health concern, being the leading cause of death globally, with an estimated 17.9 million deaths each year [2, 3]. The overall rate of death attributable to CVDs was 236.1/100,000 in 2009, and the Black population was disproportionally affected; the disease-specific mortality rate was 387.0/100 000 in Black males and 267.9/100 000 in Black females, compared to 281.4/100,000 and 190.4/100,000 in White males and females, respectively [4].

Hypertension (HTN) is the most important modifiable risk factor for CVDs [3, 5]. Prospective cohort studies have shown that hypertension is a risk factor for several types of heart diseases [6, 7]. According to the International Society of Arterial Hypertension, HTN is diagnosed when the systolic blood pressure (systolic/diastolic) in the clinic office is ≥ 140/90 mmHg on the following visit [8]. Table 1 shows classification of hypertension based on office blood pressure measurements. Table 2 shows the criteria for hypertension based on office, ambulatory, and home blood pressure measurements.

Table 1
Classification of hypertension based on office blood pressure measurement

Category	Systolic blood pressure		Diastolic blood pressure
Normal blood pressure	< 130 mm Hg	and	< 85 mm Hg
High-normal blood pressure	130–139 mm Hg	and/or	85–89 mm Hg
Grade 1 hypertension	140–159 mm Hg	and/or	90–99 mm Hg
Grade 2 hypertension	≥ 160 mm Hg	and/or	≥ 100 mm Hg
Source: Unger 2020			

Table 2
Criteria for hypertension based on office, ambulatory, and home blood pressure measurement

Setting	Systolic and Diastolic Blood Pressure, (mm Hg)
Office blood pressure	≥ 140 and/or ≥ 90
Ambulatory blood pressure measurements	
24-h average	≥ 130 and/or ≥ 80
Day time (or awake) average	≥ 135 and/or ≥ 85
Night time (or asleep) average	≥ 120 and/or ≥ 70
Home blood pressure measurement	≥ 135 and/or ≥ 85
Source: Unger 2020	

It is estimated that 1.13 billion people worldwide have hypertension [3], with 10.4 million deaths reported in 2017 [9]. Compared with high-income countries, low- and middle-income countries show considerable disparities in the regional burden of HTN, due to low level of awareness, treatment, and control rates [8]. The estimated direct and indirect cost of HTN for 2009 was $51.0 billion, which is projected to increase to an estimated $343 billion by 2030 [4, 10].

According to two reports from the National Health and Nutrition Examination Survey (NHANES) from 1988–1994 and 1999–2002, the prevalence of hypertension in Black adults increased from 35.8–41.4%, compared to from 24.3–28.1% in White adults [4, 11]. The NHANES report showed that HTN was particularly high among Black women (44.0%) [4]. Additionally, the Black population developed HTN earlier in life, and their average blood pressure was much higher [4, 12]. Consequently, the Black population is more likely to be over-burdened with morbidity and mortality associated with HTN; the risk of non-fatal stroke, fatal stroke, and death was 1.3 times, 1.8 times, and 1.5 times higher in Blacks compared to Whites. The rate of death attributable to heart diseases and rate of end-stage

kidney disease was 4.2 times higher [4]. Genetic factors, differences in body composition and fat tissue distribution, and nutritional intake, dietary ratio of sodium to potassium, and education level have all been proposed as underlying the increase in hypertension-related deaths in the Black population [13–15].

There is evidence that higher cumulative blood pressure levels may contribute to racial differences in cognitive decline later in life, with systolic blood pressure-related cognitive decline being more significant in Black adults than in whites [16–18]. Furthermore, there are potential differences between African Americans and other populations that are considered essential for effective precision-guided medical therapy with high blood pressure [18].

The response to antihypertensive drugs varies across race groups, with Black people having a higher risk of developing resistant hypertension [12]. Genome-wide analysis identified chromosome 2 locus to be associated with thiazide and thiazide-like-diuretic blood pressure response [19, 20]. In Black people with high blood pressure, ventricular hypertrophy is associated with molecular determinants of the antihypertensive response to thiazide diuretics [20, 21]. Therefore, the treatment of HTN in Black patients is complicated, necessitating a multidisciplinary approach to achieve the most significant clinical benefit with the least number of adverse events [8, 22]. More research should be directed towards improvement in the control and treatment of HTN in Black patients [23, 24].

There are five classes of antihypertensive drugs: diuretics, sympatholytic drugs, calcium (Ca^{2+}) channel blockers, vasodilators, and renin-angiotensin antagonists [25]. This systematic review will focus on diuretics to treat essential hypertension in the Black population and will exclude isolated systolic hypertension and secondary hypertension.

Importance of this review

This review is relevant for several reasons. First, hypertension-related mortality and morbidity disproportionately affects the Black population [16, 17, 26–28], who are at a higher risk of polypharmacy due to the higher prevalence of comorbidities associated with or caused by HTN [29]. Second, a critical appraisal of the current evidence on the clinical benefits and harms for Black people with EH is required. A previously published systematic review and meta-analysis on antihypertensive drug therapy in patients of African and South Asian ethnicity had several pitfalls [30]; the Jadad scale used was inadequate to assess the study quality, the certainty of evidence was not assessed according to the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) methodology [31, 32], crossover design trials with pitfalls were included in the analysis, and the review did not specify the primary and secondary outcomes [33, 34]. Additionally, the review did not conduct a trial sequential analysis to adjust for random error risk due to repetitive testing of accumulating data. This proposed analysis would assist physicians, academics, stakeholders, and consumers in making better clinical practice decisions [35]. The clinical research question of this review is: what are the clinical benefits and harms of diuretics for primary prevention of cardiovascular outcomes in Black people with essential hypertension?

Objectives

To assess the clinical benefits and harms of diuretics as a primary prevention in Black people with essential hypertension.

Methods

We have registered the protocol for this systematic review on the International Prospective Register of Systematic Reviews (PROSPERO) with the registration number: CRD42021240864.

Criteria for considering studies for this review

Types of studies

We will include randomized clinical trials (RCTs) on essential hypertension among Black people, irrespective of the publication status and design. There will be no limitations on language, country, or follow-up duration. Non-randomized clinical trials, including quasi-randomized trials, will be excluded.

Types of participants

We will include Black adults (18 years old) with essential hypertension, without a history of cardiovascular outcomes (myocardial infarction, stroke, heart failure, and unstable angina). We will include participants with or without comorbidities (diabetes mellitus, metabolic syndrome, and chronic renal disease). Studies including exclusively pregnant women will be excluded from the review.

Types of interventions

- Intervention

Diuretic drugs of any type, alone or in combination, administered at any dose and for any duration.

- Comparison

Placebo, no intervention or other types of antihypertensive drugs. See Appendix 1 for further details.

Types of outcome measures

The primary outcomes will include the following:

1. All-cause mortality.
2. Myocardial infarction (fatal/non-fatal). We will accept any definition of myocardial infarction [36].
3. Stroke (ischemic/hemorrhagic, fatal/ non-fatal). We will accept any definition of a stroke. We will include cerebrovascular events diagnosed based on imaging procedures [37].
4. Serious adverse events (assessed according to the recommendations from Lineberry et al [38]). The number of patients reporting adverse events or the number of adverse events reported will be measured.
5. Health-related quality of life (any validated scale used by trialists, such as Short Form (SF)-36) [39].

The secondary outcomes of interest include:

1. Hospitalizations due to heart failure at any stage.
2. Systolic blood pressure (continuous, mmHg).
3. Diastolic blood pressure (continuous, mmHg).

Search methods for identification of studies

We will perform a preliminary search strategy for inclusion in the protocol. The preliminary search strategy for MEDLINE will be adapted for use in other databases (Appendix 1). The Cochrane sensitivity-maximizing RCT filter [40] will be applied to MEDLINE and adaptations to other databases, except CENTRAL. We will search all databases from their inception to the present and impose no restriction on language of publication or publication status.

Electronic searches

We will search in the following electronic databases:

1. Cochrane Central Register of Controlled Trials (CENTRAL; latest issue) in the Cochrane Library;
2. OVID MEDLINE (from 1948 to update);
3. Embase (from 1974 to update);
4. LILACS (Latin American and Caribbean Health Science Information database; 1982 to update).
5. Web of Science (to update).
6. Scielo (to update).

We will also search the following ongoing trials registries:

1. World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) (www.who.int/ictrp/en);
2. U.S. National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (www.clinicaltrials.gov).

We will also search the following sites to identify unpublished information submitted for marketing approval of new antihypertensive drugs:

1. Food and Drug Administration (www.fda.gov);
2. European Medicines Agency (www.ema.europa.eu/en).

We will screen the reference lists of relevant studies, randomized clinical trials, and systematic reviews. We will contact trialists and companies for further information.

Data collection and analysis

Data collection and analysis will be conducted according to the Cochrane Handbook for Systematic Reviews of Interventions [41].

Selection of studies

Four review authors (Arturo Martí-Carvajal [AMC], Diana Monge [DM], Andrea Correa [AC], and Cristina G. de Leonardo [CGL]) will independently screen titles and abstracts of the references obtained from our searching strategies. The records identified by the search strategy will be collected in a reference manager tool for removal of duplicates and then uploaded into COVIDENCE. This is an online software that manages the initial phases of systematic reviews. COVIDENCE also enables independent screening and logs disagreements and consensus among reviewers. According to the eligibility criteria mentioned above, the selection processes of the studies will be implemented in two stages. The first stage will involve the screening of each title and abstract by at least two independent reviewers to determine its eligibility for full-text screening. Each article will be categorized into one of three categories (yes, maybe, no) to assess the relevance and probability of full-text retrieval. In the second stage, all studies except those categorized as “No” (excluded) will be retrieved in full text for further analysis. Disagreements between reviewers will be resolved by a third review author (Eduardo Alegría-Barrero [EAB]).

- We will retrieve the full-text articles for the remaining references and, independently, four review authors (AMC, DM, AC, and CGL) will screen the full-text articles and identify studies as potential inclusion trials. At the stage of full-text assessment, the main reason for exclusion of each excluded study will be recorded. Any disagreements will be resolved through discussion or, if required, another review author (EAB) will be consulted.

We will collate multiple reports of the same study as each study, not the reference, is the unit of interest in the review. We will record the selection process and complete the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram [42].

Data extraction and management

Data extraction will be performed independently by four authors (AMC, DM, Susana Nicola [SN], and Mohamed Abd El Aziz [MAA]). In addition, Agustín Ciapponi (ACI), CGL, and CMA will check the data extracted for each study. We will develop an Excel spreadsheet for data extraction. One author (MAA) will supervise this collection. Basically, we plan to extract data regarding the methods (type of design-trial, country, number of arms, follow-up, duration of treatment, type of phase, type of RCTs, i.e., superiority, inferiority, or equivalence), participants (number of randomized, dropout number, age, sex, physiological variables related to blood hypertension, inclusion and exclusion criteria), interventions (medication study and control), outcomes prefixed in each trial, and other notes (sample size estimation a priori, percentage of Black population if trial included many ethnicities. identifier trial number, interval time for conducting trial, sponsor, founder, and role of sponsor). For cross-design trials, we will adapt the data extraction form for the crossover trials template [43]. We will describe the details of the intervention according to the recommendations of Hoffmann et al. [44, 45] (See Appendix 2 for the details of the intervention description). Furthermore, we plan to recollect adverse event information using an Excel spreadsheet according to Li, 2019 [46] (see Appendix 3). We plan to report the adverse events reported in each trial.

Assessment of risk of bias in included studies

Independently, three review authors (AMC, DM, AV) will assess the risk of bias (RoB) for each study using the RoB criteria outlined in the Cochrane Handbook for Systematic Reviews of Interventions [47, 48]. We will resolve any disagreements by discussion or by involving another review author (Jesús López Alcalde [JLA]).

We will assess the risk of bias according to the following seven domains:

1. Random sequence generation (selection bias).
2. Allocation concealment (selection bias).
3. Blinding of participants and personnel (performance bias)
4. Blinding of outcome assessment (detection bias)
5. Incomplete outcome data (attrition bias)
6. Selective reporting (reporting bias)
7. Other bias, that is, design bias, for RCTs that estimated no sample size a priori.

We will use the Cochrane Handbook for Systematic Reviews of Interventions' recommendations to assess the risk of bias in cross-design trials [49].

We will grade the risk of bias for each domain as high, low, or unclear, and provide information from the study report together with a justification for our judgment in the 'Risk of bias' tables. We will include company funding under other bias. See Appendix 4 for details on the domains.

Measures of treatment effect

For binary outcomes, such as all-cause mortality, myocardial infarction, stroke, serious adverse events, and heart failure (rehospitalization), we plan to calculate the risk ratio (RR) with a 95% confidence interval (CI). With the

exception of all-cause mortality, if the other dichotomous outcomes are reported as incidence rate (count data), we will report them with rate ratio (RR) and 95% CI.

For continuous outcomes, such as health-related quality of life, systolic blood pressure, and diastolic blood pressure, we plan to calculate the mean difference (MD) with 95% CI. If different scales are used for measuring the same outcome, such as health-related quality of life, we plan to use the standardized mean difference with 95% CI [50]. We will also estimate the ratio of means (RoM) with 95% CI from the mean difference [51].

As recommended in the Cochrane Handbook for Systematic Reviews of Interventions, if necessary, we will multiply the mean values from one set of studies by -1 to ensure that all the scales point in the same direction [52]. If statistical information is missing (such as standard deviations), we will try to extract them from other relevant information in the paper, such as P values and CIs.

For binary outcomes in crossover trials, we will use the odds ratio (95% CI), which is based on the BeckerBalagtas approach [43, 53–55]. For continuous outcomes, we plan to use the mean and standard deviation (or standard error) of participant-level differences between experimental intervention (E) and comparator intervention (C) measurements, the mean difference and one of the following: (i) t-statistic from a paired t-test; (ii) P value from a paired t-test; and (iii) a confidence interval from a paired analysis [48]. We will follow the recommendations for assessing crossover design trials according to the Cochrane Handbook for Systematic Reviews of Interventions [43, 48].

Unit of analysis issues

The unit of analysis will be the participants. This review will be complex in terms of the unit of analysis because of the different design trials. This is because all participants will undergo repeated multiple observations (systolic and diastolic blood pressures and number of adverse events reported). Participants included in crossover trials will receive more than one intervention. There is a chance of parallel-design trials with more than one control group. Thus, we propose the following approach: First, all outcomes will be analyzed at a single time point (at the end of the trial). Second, we will not combine trials conducted with different designs. Third, in parallel-design trials with more than one control group, we will not count the same population twice or thrice. Therefore, the meta-analysis will only show the subtotal.

Dealing with missing data

We will assess the percentage of drop-outs for each included trial, and for each intervention group, and evaluate whether an intention-to-treat (ITT) analysis had been performed or could have been performed from the available published information. We will try to contact the study authors to resolve any questions arising on missing data.

For the benefits, we will attempt to undertake an ITT analysis. Thus, we will seek data from the trial authors about the number of participants in the treatment groups, irrespective of their compliance, and whether or not they were later thought to be ineligible, otherwise excluded from treatment, or lost to follow-up. If this information is not forthcoming, we will perform a per-protocol (PP) analysis of those who completed the study, being aware that it may be biased. For harms, we will attempt to perform a PP analysis.

We will include participants with incomplete or missing data in sensitivity analyses by imputing them according to the following scenarios:

- Extreme-case analysis favoring the experimental intervention (best-worst-case scenario): none of the drop-outs/participants lost from the experimental arm, but all of the drop-outs/participants lost from the control arm experienced the outcome, including all randomized participants in the denominator.
- Extreme-case analysis favoring the control (worst case scenario): all drop-outs/participants lost from the experimental arm, but none from the control arm experienced the outcome, including all randomized participants in the denominator [56].
- Gamble-Hollis's analysis, which considers the uncertainty and generates uncertainty intervals for a trial incorporating both sampling error and the potential impact of missing data [57]. This method increases the uncertainty of the trials by using the results from the best-case and worst-case analyses [58].

Assessment of heterogeneity

Statistical heterogeneity will be quantified using the I^2 statistic [50]. We will consider statistical heterogeneity if I^2 is greater than 70% [52].

If there are simultaneous statistical heterogeneity and three or more RCTs, we will determine the 95% prediction interval (PI), which takes into account the whole distribution of the effects [59]. Therefore, prediction intervals show the expected range of true effects in similar studies [60]. We estimated the 95% PI using Stata statistical software (STATA) [61].

If there are 10 or more randomized controlled trials and I^2 is greater than 70% for a primary outcome, we will conduct a meta-regression using Stata statistical software (STATA).

Assessment of reporting biases

If there are 10 or more randomized clinical trials, we will use the contour-enhanced funnel plot to differentiate asymmetry due to publication bias from that due to other factors [62]. We will assess the likelihood of publication bias using Harbord's and Peter's tests [63]. STATA will be used to produce conventional and contour funnel plots.

Data synthesis

We will perform meta-analyses with 95% using both a fixed-effect and random-effects model [64]. In the case of statistical heterogeneity ($I^2 > 70\%$), data will be reported using the random-effects model and prediction interval [52, 59, 60]. We will conduct a meta-analysis using Review Manager 5.4.1 [65].

Trial sequential analysis

We will apply trial sequential analysis (TSA), as cumulative meta-analyses are at risk of producing random errors due to sparse data and repetitive testing of accumulating data [35, 66, 67). To minimize random errors, we calculated the required information size (i.e., the number of participants needed in a meta-analysis to detect or reject a certain plausible intervention effect) [35]. The required information size calculation should also account for the heterogeneity or diversity present in meta-analysis [35]. We will use the event proportion in the control group, the assumption of a plausible RR reduction of 20%, or the RR reduction observed in the included trials with low risk of bias, a risk of type I error of 5%, a risk of type II error of 10%, and the empirical diversity of the meta-analysis for estimating the diversity-adjusted required information size (DARIS) [35]. We will add the trials according to the year of publication, and if more than one trial has been published in a year, we will add trials alphabetically according to the last name of the first author. Based on the required information size, we will construct trial sequential monitoring boundaries [68, 69]. These boundaries determine the statistical inference one may draw regarding the cumulative

meta-analysis that has not reached the required information size; if the trial sequential monitoring boundary for benefit or harm is crossed before the required information size is reached, any further trials may turn out to be superfluous. On the other hand, if the boundary is not surpassed, it is necessary to continue conducting trials to detect or reject a certain intervention effect. This can be determined by assessing whether the cumulative Z-curve crosses the trial sequential boundaries for futility. If futility boundaries are crossed, further trials may be unnecessary [70]. We will conduct TSA using software from the Copenhagen Trial Unit [68, 70].

We plan to downgrade our assessment of imprecision in GRADE (please see below) by two levels if the accrued number of participants is below 50% of the DARIS, and by one level if between 50% and 100% of DARIS and the monitoring boundaries for benefit, harm, or futility are not broken by the cumulative Z value. We will not downgrade if the cumulative Z-curve reaches or breaks the monitoring boundaries for benefit, harm, or futility of DARIS.

GRADE and 'Summary of findings' table

We will create a summary of findings (SoF) table using the following outcomes: all-cause mortality, myocardial infarction, stroke, serious adverse events, health-related quality of life, and cardiac heart failure (Table 3). We will use the five GRADE considerations (study limitations, consistency of effect, imprecision, indirectness, and publication bias) to assess the quality of a body of evidence as it relates to the studies that contribute data to the meta-analyses for the predefined outcomes [31]. We will use the methods and recommendations described in Chap. 14 of the Cochrane Handbook for Systematic Reviews of Interventions [32]. We will justify all decisions to downgrade the quality of the evidence using footnotes, and where necessary, we will make comments to aid the reader's understanding of the review.

Table 3

Diuretics compared with placebo or any other comparison as primary prevention of cardiovascular outcomes in Black people with essential hypertension

Diuretics compared with placebo or any other comparison as primary prevention of cardiovascular outcomes in Black people with essential hypertension						
Patient or population: Black people with essential hypertension **Settings**: outpatients (primary prevention) **Intervention**: diuretics **Comparison**: placebo or any other comparison						
Outcomes	**Illustrative comparative risks* (95% CI)**		**Relative effect** (95% CI)	**No of Participants** (studies)	**Quality of the evidence** (GRADE)	**Comments**
	Assumed risk	Corresponding risk				
	Placebo or no intervention	**Diuretic medication**				
All-cause mortality	See comment	See comment	Not estimable	0 (0)	See comment	
Myocardial infarction (fatal/non-fatal)	See comment	See comment	Not estimable	0 (0)	See comment	
Stroke (ischemic/hemorrhage, fatal/non fatal)	See comment	See comment	Not estimable	0 (0)	See comment	
Serious adverse events	See comment	See comment	Not estimable	0 (0)	See comment	
Health-related quality of life		The mean health-related quality of life in the intervention groups was **0 higher** (0 to 0 higher)		0 (0)	See comment	
Heart failure at any stage	See comment	See comment	Not estimable	0 (0)	See comment	
Non-serious adverse events	See comment	See comment	Not estimable	0 (0)	See comment	
*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI). **CI**: Confidence interval; **RR**: Risk ratio;						

Diuretics compared with placebo or any other comparison as primary prevention of cardiovascular outcomes in Black people with essential hypertension
GRADE Working Group grades of evidence **High quality**: Further research is very unlikely to change our confidence in the estimate of effect. **Moderate quality**: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. **Low quality**: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. **Very low quality**: We are very uncertain about the estimate.

We will conduct the imprecision analysis reported in SoF with TSA, as suggested by Castellini et al and Gartlehner et al [71, 72]. We will communicate the findings of interventions following the recommendations of the GRADE Working Group [73].

Subgroup analysis and investigation of heterogeneity

If we identify enough trials (five or more) by outcome, we will conduct the following subgroup analysis:

1. Male participants versus female participants.
2. Participants aged < 65 years versus participants aged ≥ 65 years.
3. Participants without diabetes mellitus compared to participants with diabetes mellitus.
4. Participants without chronic kidney disease versus participants with chronic kidney disease.
5. Participants without metabolic syndrome compared to participants with metabolic syndrome.

Sensitivity analysis

We will perform the following sensitivity analysis to explore the influence of particular factors on the intervention effect size:

1. Trials with high risk of incomplete outcome data compared to trials with low risk of incomplete outcome data.
2. Trials with low risk of bias compared to trials with high risk of bias.
3. Trials supported by pharmaceutical companies compared to trials without support from pharmaceutical companies.
4. Trials with an observed sample size (OSS) lower than the optimal information size (OIS) compared to trials with an OSS larger than the OIS.

Fragility index

We will calculate the fragility index (FI) when the RR is significant ($P < 0.05$). FI is a measure used to identify the number of events required to change statistically significant results to non-significant results [74]. We will apply the FI only to RCTs that allocate participants in a 1:1 ratio and to binary data (e.g., all-cause mortality). We will estimate the FI using the fragility index calculator [75].

Bayes factors

We estimate the threshold for clinical relevance using Bayes factors [64]. The Bayes factor is a likelihood ratio that indicates the relative strength of evidence for two theories [76–78]. The Bayes factor is a comparison of how well

two hypotheses (the null hypothesis, H0, and the alternative hypothesis, H1) predicts the data [77]. The Bayes factor provides a continuous measure of evidence for H1 over the H0. When the Bayes factor is 1, the evidence is insensitive, the data are equally well predicted by both models, and the evidence does not favor either model over the other (1 means the data are as well predicted by H1 as H0; therefore, it should not be interpreted as favoring H0; rather, the evidence does not point either way). As the Bayes factor increases above 1 (toward infinity), the evidence favors H1 over H0. As the Bayes factor decreases below 1 (toward 0), the evidence favors H0 over H1 [76]. We will estimate the Bayes factor for all outcomes.

Discussion

We aim to provide external validity and try to solve conflicts on the use of diuretics in Black people with essential hypertension to guide appropriate clinical practice. As Gene Glass stated, a meta-analysis was created out of the need to extract useful information from the cryptic records of inferential data analyses in the abbreviated reports of research in journals and other printed sources [79]. According to the criteria established in this protocol, our goal is to decrypt the secrets of RCTs that meet these criteria. Our ultimate aim is to carry out a scientific synthesis of the role of diuretics in controlling blood pressure in Black patients, with or without comorbidities. The inclusion of the RCTs conducted either with the Black population or with various ethnic groups, as long as they report data on the Black population, will provide external validity and clarify doubts about the role of diuretics as a primary prevention approach to treat Black people with hypertension.

Abbreviations

CI, confidence interval; CENTRAL, Cochrane Central Register of Controlled Trials; CVDs, Cardiovascular diseases; DARIS, diversity-adjusted required information size; EH, essential hypertension; FI, fragility index; GRADE, Grading of Recommendations, Assessment, Development and Evaluations; HTN, hypertension; ITT, intention-to-treat; MD, mean difference; NHANES, National Health and Nutrition Examination Survey; OIS, optimal information size; OSS, observed sample size; PP, per-protocol; PI, prediction interval; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; PROSPERO, International Prospective Register of Systematic Reviews; RCTs, randomized clinical trials; RoM, ratio of means; RR, risk ratios; SoF, summary of findings; TSA, trial sequential analysis; WHO, World Health Organization

Declarations

Ethics approval and consent to participate

Not applicable because no primary data were collected.

Consent for publication

Not applicable

Availability of data and materials

The datasets that we will use and/or analyze during the current study will be available from the corresponding author on reasonable request.

Competing interests

AMC is Associate Editor for *Systematic Reviews*.

The rest of the authors declare that they have no competing interests.

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Authors' contributions

AMC and DM conceived and wrote the first draft of the protocol with inputs from all authors (AC, CGL, EAB, RH, SN, MAEA, ACI, AV, CMA, JLA, NA). All authors read and approved the final manuscript.

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