PROTOCOL:

Effects of SGLT-2 Inhibitors on Arterial Blood Pressure:

A Stratified Systematic Review and Meta-Analysis Comparing Diabetic and Non-Diabetic Etiologies

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Administrative Information

Identification

This supplement contains the systematic review and meta-analysis protocols regarding statistical analysis, source inclusion and exclusion methodology and is made by using the PRISMA-P checklist.

Registration and Contact Details

In accordance with guidelines, this systematic review protocol is registered with the International Prospective Register of Systematic Reviews (PROSPERO).

Name	**Institutional affiliation**	**Contact**	**Role**
Josef Toma Alyas (JTA) ORCID: 0009-0006-7989-7640	Aarhus University, Medical Student	E-mail: au712937@uni.au.dk	*Main author.* Also, analyst and guarantor of protocol, PROSPERO and review. JTA is the guarantor. JTA is the main developer of the selection criteria, methodology, risk of bias assessment, search strategy, PROSPERO-registration, protocol-drafting and statistical analysis. JTA will write, read and provide feedback. JTA will approve the final manuscript.
Niels Henrik Buus (NHB) ORCID: 0000-0001-7972-8181	Aarhus University, Department of Biomedicine	E-mail: nhb@biomed.au.dk	*Corresponding author.* NHB provides feedback and is the main supervisor of all sections. NHB is the corresponding author.
Steffen Flindt Nielsen (SFN) ORCID: 0009-0002-5410-1088	Aarhus University Hospital, Department of Renal Medicine	E-mail: steffen.nielsen@midt.rm.dk	*Co-reviewer and co-supervisor* SFN will independently screen articles for inclusion and exclusion where there is uncertainty by JTA, and will provide valuable feedback in analytical methods and in writing the manuscript.

Amendments

Any future amendments to the protocol will be noted in this section, with a corresponding rationale of changes, and the date of when the change took place.

Date	Reason for amendment
26.08.2025	Under "Review Rationale": • Clarified language to better fit intended meaning (e.g. systolic blood pressure → arterial blood pressure) • Clarified the stratifications, to match "Outcomes" Under "Study Design": • Removed blanket exclusion reason: "Loss-To-Follow Up exceeds 20%" to disregard studies. Replaced with a more nuanced rule under "Report characteristics". Under "Outcomes" • Clarified language to fit intended meaning (e.g. systolic BP is necessary, but DBP is also preferred) • Better clarified how stratifications will take place. Originally, we wrote that the outcome will be stratified by diabetic status, but did not mention how secondary and exploratory results will also be included in the analysis Under "Report characteristics" • Clarified how LTFU will be treated Under "Data management" • Refined readability • Clarified how citation searching will be performed to better define how we intend to retrieve articles Under "Data extraction" • Removed unnecessary / irrelevant data points Under "Risk of Bias assessment" • Refined readability
30.08.2025	Under "Data management" • Clarified how the screening process will take place. Changed from 2 independent reviewers to 1 human + 1 hybrid-human/LLM for independent screening + 1 human for unblinded screening.

Support

No financial support has been given. The review is authored in the free time of the main author, Josef Toma Alyas. Funding for Open Access release may be included here.

Introduction

Review Title

"Effects of SGLT-2 Inhibitors on Arterial Blood Pressure: A Stratified Systematic Review and Meta-Analysis Comparing Diabetic and Non-Diabetic Etiologies"

Review Rationale

Hypertension is a prevalent condition globally, affecting over a billion people. It is a major, but modifiable, risk factor, for cardiovascular events. It is particularly common in patients with type 2 diabetes mellitus (T2DM), and in patients with chronic kidney disease (CKD) and/or cardiovascular disease (CVD). A significant number of patients rely on standard antihypertensive therapies with good effectiveness. However, a significant portion of these high-risk patients develop resistant hypertension, where the blood pressure remains elevated despite treatment with multiple drugs.

Sodium-Glucose Cotransporter 2 (SGLT-2) Inhibitors are a class of medications that are approved for blood glucose reduction in T2DM. Pleiotropic effects have been demonstrated, such as cardio- and nephroprotective effects. One key secondary effect of these agents is the observed reduction in blood pressure, specifically systolic blood pressure (SBP), possibly also in treatment-resistant hypertension. This effect is likely to be multifactorial, stemming from osmotic diuresis, natriuresis, weight loss, and potentially modifications of vascular function and sympathetic nerve activity.

Previously published meta-analyses have shown systolic blood pressure modification in patients using SGLT-2 inhibitors against a placebo group, however, this is mainly in a broader T2DM population. There is a lack of meta-analyses that address populations that have other comorbidities (e.g. CVD, CKD) either without T2DM or concurrently with T2DM.

The systematic review and meta-analysis, therefore, seeks to address the knowledge gap by systematically evaluating and quantifying the efficacy of SGLT-2 inhibitors in modifying the arterial blood pressure when compared to a placebo. This includes both 24-hour ambulatory blood pressure, and office blood pressure measurements.

The review will conduct two primary subgroup analyses: first, comparing patients with and without type 2 diabetes, and second comparing patients with and without end-organ damage (e.g. CVD/CKD).

As a secondary outcome, a more specified analysis will be performed across eight specific patient profiles to explore nuances within these broader categories. These analyses seek to clarify the potential of this agent as an adjuvant medication for hypertension across different patient populations.

Methods

Eligibility Criteria

Study Designs

We will include trials if:

(1) Randomized controlled trials (RCT) comparing SGLT-2 inhibitors against placebo in patients of any subpopulation, both diabetic and non-diabetic.
(2) The minimum follow-up period in the trial was at least 4 weeks.
(3) The trial describes how blood pressure was measured.

We will exclude trials if:

(1) The trial's target population is individuals with type 1 diabetes.
(2) Medication used is a SGLT-1 and SGLT-2 dual inhibitor, such as sotagliflozin.
(3) Trial changes initial background medication dosage in placebo and trial group asymmetrically.
(4) Trial employs a multi drug intervention group.
(5) Trial is a crossover design.

Participants

We will include all studies that are examining the general adult human population (18 years+) regardless of T2DM-status. If a trial has data sets for multiple populations (e.g. one group has T2DM, another group does not), they will be considered separate data sets, if no analytical bias arises (e.g. non-independent data sets). Data sets containing populations with type 1 diabetes (T1DM) are excluded, if the inclusion criteria of the trials necessitate positive T1DM status.

Interventions

Any trials that use any Sodium-Glucose Cotransporter 2 inhibitor are included, if the drug is an isolated SGLT-2 inhibitor, and not a dual-inhibitor (e.g. Sotagliflozin). Trials that employ a multi-drug approach, introducing both an SGLT-2 inhibitor and another drug simultaneously, are excluded.

Comparators

Only randomized controlled trials that employ a placebo group as a comparator will be included.

Outcomes

Any trial that directly provides the quantitative modification of at least systolic blood pressure (SBP) will be included in the analysis, if it follows the other inclusion and exclusion criteria. Preferably these trials will include diastolic blood pressure (DBP) information also. Trials that do not provide the outcome directly, can still be included, if the outcome is synthesizable through other statistical methods (e.g. a 95% confidence interval via the standard error). The main outcome we will analyze is the quantitative modification of blood pressure measured in mmHg adjusted for the placebo effect. Both 24-hour ambulatory BP (24hBP) measurements and office blood pressures (OBP) are included, but 24hBP will be prioritized if a trial provides both.

The primary outcomes of this meta-analysis will be the effect of SGLT-2 inhibitors on arterial blood pressure in the following pre-specified subgroups:

- Patients with type 2 diabetes (T2DM) vs. patients without T2DM
- Populations with end-organ damage (e.g. established CVD or CKD) vs. populations with no end-organ damage

The secondary outcomes of this meta-analysis will be the effect of the SGLT-2 inhibitors on arterial blood pressure, with more specified subgroups:

- T2DM patients with CVD
- T2DM patients with CKD
- T2DM patients with pre-existing hypertension
- T2DM patients without other major comorbidities

- Non-T2DM patients with CVD
- Non-T2DM patients with CKD
- Non-T2DM patients with pre-existing hypertension
- Non-T2DM patients without other major comorbidities

If possible, we will also assess the potential interactions between diabetes status and concurrent end-organ damage. Therefore, we will try to assess the following four exploratory subgroups:

- T2DM with end-organ damage
- T2DM without end-organ damage
- No T2DM with end-organ damage
- No T2DM without end-organ damage

If a subgroup has less than 3 trials, the analysis will not be described quantitatively, but rather narratively, if possible. A table describing the number of trials and data sets in each subgroup will be created for ease of readability for the reader.

Report Characteristics

For any trial to be considered, the trial must be written in English and published. Therefore, trials that are exclusively written in another language will be excluded. If an ad-hoc trial is not yet published, it can still be included, if all relevant data sets (e.g. systolic blood pressure modification) are available and no further measurements will be taken, otherwise it is excluded. For the primary analysis, the latest follow-up time point with a Loss-To-Follow-Up (LTFU) of less than 20% will be extracted from each trial. If a trial has no follow-up time points with an LTFU below this threshold, the time point with the lowest LTFU will be chosen, provided the follow-up duration is at least 4 weeks post-baseline, and blood pressure measurements are available for this time point.

Search Strategy and Information Sources

In general, the literature search strategy consists primarily of three main databases, namely PubMed, Cochrane's Library and Embase. The search strings used in these indexes will be implemented by using the same MeSH-terms and other keywords to find relevant trials. To supplement the electronic database search, the reference lists of included trials will be scanned for relevancy, and potential inclusion by method of "Citation Searching". There is no time frame limit for the databases, but the search strings will exclude non-English trials and only select randomized controlled trials (RCTs), either included in the search string itself, or as a filter on the corresponding website.

PubMed

Search string	Number of results
(("Sodium-Glucose Transporter 2 Inhibitors"[MeSH Terms] OR "dapagliflozin"[Title/Abstract] OR "Sodium-Glucose Transporter 2 Inhibitors"[Pharmacological Action] OR "sodium glucose transporter 2 inhibitor*"[All Fields] OR "ertugliflozin"[Title/Abstract] OR "Empagliflozin"[Title/Abstract] OR "Canagliflozin"[Title/Abstract] OR "sglt 2 inhibit*"[Title/Abstract] OR "sglt2 inhibit*"[Title/Abstract] OR "sodium glucose transporter 2 inhibit*"[Title/Abstract]) AND ("Hypertension"[MeSH Terms] OR "hypertensi*"[Title/Abstract] OR "blood pressure"[Title/Abstract] OR "High blood pressure"[Title/Abstract])) AND (randomizedcontrolledtrial[Filter]) AND (english[Filter])	278 Searched on the 15th of August 2025

Using PubMed's advanced search engine, the abovementioned search string yields 278 results. The usage of asterisks in certain terms (wildcards) allows for a wider search, to find all grammatical variations of the same term. Example: "SGLT 2 inhibit*" will allow for both "SGLT 2 Inhibitors" and "SGLT 2 Inhibitor" to be found under one search entry.

EMBASE

Search string	Number of results
('sodium glucose cotransporter 2 inhibitor'/exp OR 'sodium glucose cotransporter 2 inhibitor' OR 'dapagliflozin':ti,ab,kw OR 'sodium glucose transporter 2 inhibitor*' OR 'ertugliflozin':ti,ab,kw OR 'empagliflozin':ti,ab,kw OR 'canagliflozin':ti,ab,kw OR 'sglt 2 inhibit*':ti,ab,kw OR 'sglt2 inhibit*':ti,ab,kw OR 'sodium glucose transporter 2 inhibit*':ti,ab,kw) AND ('hypertension'/exp OR 'hypertension' OR 'hypertensi*':ti,ab,kw OR 'blood pressure':ti,ab,kw OR 'high blood pressure':ti,ab,kw) AND [randomized controlled trial]/lim AND [english]/lim	1249 Searched on the 15th of August 2025

Similar to PubMed, the following string yielded 1249 results. However, EMBASE implements a slightly different terminology to describe an umbrella term, using Emtree Terms Exploded (/exp) as an alternative to MeSH terms.

Cochrane's Library / CENTRAL

ID	Search string	Number of results
#1	[mh "Sodium-Glucose Transporter 2 Inhibitors"] OR dapagliflozin:ti,ab OR "sodium glucose transporter 2 NEXT inhibitor*":ti,ab OR ertugliflozin:ti,ab OR Empagliflozin:ti,ab OR Canagliflozin:ti,ab OR "sglt 2 NEXT inhibit*":ti,ab OR "sglt2 NEXT inhibit*":ti,ab OR "sodium glucose transporter 2 NEXT inhibit*":ti,ab	5818
#2	[mh "Hypertension"] OR "NEXT hypertensi*":ti,ab OR "blood pressure":ti,ab OR "High blood pressure":ti,ab	112712
#3	#1 AND #2	1211 Searched on the 15th of August 2025

On Cochrane's Library, using the search manager under the advanced search option, we used three separate entries to make the final search. The first search string searches for any article that includes anything related to SGLT-2 inhibitors, while the second string searches for articles that relate to hypertension or blood pressure. The third string combines them, allowing only articles that include both strings to be presented. By using the "Limits" option on the third string, we disallowed non-trial articles to be included, providing the final result of 1209 trials. In our experience, the individual strings yielded a warning that wildcards or asterisks are disallowed unless used in conjunction with "NEXT" before the word with an asterisk. This sometimes led to the third string yielding an "ERROR" result, instead of the 1211 articles. Clicking on the "ERROR" button still yielded the correct number of results.

Data Management

In total, 2738 articles were found via the search strings used on the three databases. This includes duplicates, which later will be screened and removed to prevent the inclusion of multiple renditions of the same trials.

Literature search results are to be uploaded to Covidence[1], a webtool that allows for duplicate screening and facilitates the selection process among all collaborating reviewers. By selecting all yielded search results on EMBASE, PubMed and CENTRAL, and exporting them as an EndNote file (.ris or .nbib), we will be able to convert the file to a list, which in Covidence removes automatically recognized duplicates when imported. After the removal of duplicates is done, the review team will screen the titles and abstracts of all imported articles to determine whether they are relevant to the systematic review and meta-analysis, and if they are qualified for inclusion by the eligibility criteria.

~~The primary review author (JTA) will assess all articles for eligibility. In uncertain cases, if an article is unable to be assessed as relevant by the title and abstract alone, the whole article will be obtained and searched for relevancy. If an article for other reasons is unable to be assessed by the primary review author, the secondary reviewer (SFN) will assess the article independently, and a discussion will take place to build a consensus to determine whether the article will be included or excluded.~~

Articles will be screened using a 5-phased approach:

1. Manual screening by JTA.
2. Hybrid machine-assisted + human screening (JTA) via specialized in-line citation-based large-language-models. JTA blinded for initial screening. A combination of Google's Gemini Pro 2.5 and Perplexity's Sonar will be used. Prompt engineering will take place to optimize the accuracy, prohibiting the usage of external sources, focusing only on the given material (e.g. the trial under assessment and supplementary material + this present protocol).

3. Comparison of screening results from phase 1 vs phase 2. Disagreements resolved with a third, unblinded screening.
4. Second human (SFN) reviewed the results for consistency.
5. Overall disagreements discussed among all the authors.

After the preliminary relevancy screening, all articles that are determined to be excluded in the full-text screening will be recorded and registered with a reason for exclusion, in accordance with PRISMA. None of the review authors will be blind to the article's title, its authors, nor its institution. Citation searching will be performed in non-ad hoc articles that are deemed to be included in the meta-analysis. If the original ad hoc trial is eligible for inclusion, it will be merged with the linking non-ad hoc trial.

If an article is included in the analysis, the whole article will be obtained, and data extraction will take place. To prevent the inclusion of duplicate data sets that are not initially caught by the preliminary screening, a comparison of all data sets will be performed. In cases where two data sets are similar in nature, a check will take place to confirm that they are independent of each other.

Data Extraction

An independent process will take place to extract all relevant details from an article. To minimize possibilities of introducing bias, a PRISMA compliant pilot form will be used to extract the following information from all articles determined to be included in the meta-analysis.

1. STUDY IDENTIFICATION
    - Study ID
    - First Author
    - Publication Year
    - Journal
    - Study Design
    - Registration Number
2. STUDY CHARACTERISTICS
    - Study Duration
    - Sample Size
    - Treatment Group Size
    - Control Group Size
    - Single-center / Multi-center
    - Geographic Location
3. PARTICIPANT BASELINE CHARACTERISTICS
    - Average Age - Treatment
    - Average Age - Control
    - Male Percentage - Treatment
    - Male Percentage - Control
    - BMI - Treatment
    - BMI - Control

- Baseline SBP - Treatment
- Baseline SBP - Control
- Baseline DBP - Treatment
- Baseline DBP - Control
- Baseline Heart Rate - Treatment
- Baseline Heart Rate - Control
- HbA1c - Treatment
- HbA1c - Control
- eGFR - Treatment
- eGFR - Control
- Fasting Glucose - Treatment
- Fasting Glucose - Control
- Comorbidity Classification
- Diabetes Status
- Cardiovascular Disease
- Chronic Kidney Disease
- Heart Failure
- Hypertension Severity

4. INTERVENTION DETAILS
    - SGLT-2 Inhibitor Type
    - Dosage
    - Administration Route
    - Control Intervention
    - Concomitant Medications
5. OUTCOME MEASUREMENTS
    - Primary Blood Pressure Outcomes
    - BP Measurement Method
    - SBP Change - Treatment
    - SBP Change - Control
    - DBP Change - Treatment
    - DBP Change - Control
    - Mean Difference SBP
    - Statistical Significance
    - Secondary Outcomes
    - Weight Change - Treatment
    - Weight Change - Control
    - Adverse Events - Treatment
    - Adverse Events - Control
    - Discontinuation Rate - Treatment

    - Discontinuation Rate - Control
6. RISK OF BIAS ASSESSMENT (RoB2)
    - Randomization Process
    - Deviations from Intended Interventions
    - Missing Outcome Data
    - Measurement of Outcome
    - Selection of Reported Result
    - Overall Risk of Bias
7. DATA QUALITY
    - Standard Error (or 95% CI) Reported
    - Intention-to-Treat Analysis
    - Per-Protocol Analysis
    - Baseline Characteristics Balance
    - Loss to Follow-up Rate
8. ADDITIONAL INFORMATION
    - Funding Source
    - Conflicts of Interest
    - Clinical Setting

Risk of Bias Assessment

To assess the risk of bias for individual numerical outcomes within included randomized controlled trials, we will use the Cochrane Risk of Bias 2 (RoB2) tool. This tool evaluates bias at the level of a specific result rather than the trial as a whole, ensuring a precise assessment of potential bias relevant to the outcome of interest.

The RoB2 tool covers five key domains of potential bias:

1. Bias arising from the randomization process
2. Bias due to deviations from intended interventions
3. Bias due to missing outcome data
4. Bias in measurement of the outcome
5. Bias in selection of the reported result

For each domain, a judgment of low risk, some concerns, or high risk of bias will be assigned based on specific signaling questions provided by the tool.

In this review, trials not assessed as "low risk" of bias for the outcome will still be included in the overall primary meta-analysis results to reflect all available evidence. However, a sensitivity analysis in the primary outcome excluding these higher risk trials will be performed to evaluate the robustness of the primary meta-analytic findings. This approach allows for assessment of whether excluding potentially biased evidence materially affects the conclusions, thereby strengthening confidence in the results.

Data Synthesis

The meta-analysis will be performed using a random-effects model. Statistical heterogeneity will also be quantified using the I^2 statistic. Whenever non-essential data is missing, we will not attempt to contact the

original authors but rather attempt to obtain the missing data by synthesizing it, if possible (e.g. 95% confidence intervals via standard deviation).

All outcomes relevant to the meta-analysis will be calculated using Review Manager 5.4 (RevMan 5.4).

A systematic narrative explanation will be provided with all information presented in the text, tables and figures, to describe the characteristics and findings of each result.

To assess publication bias in the meta-analysis, a funnel plot will be generated that enhances the reliability of results by identifying potential selective reporting of studies. The funnel plot functions by displaying each study's effect size (e.g., mean difference) against a measure of its precision (e.g., standard error or inverse variance), creating an inverted funnel shape in the absence of bias, where symmetry indicates that smaller studies with varying results are equally likely to be published. If the funnel plot demonstrates asymmetry, it suggests publication bias usually towards positive outcomes.

Strength of Evidence

The quality of evidence for each primary and secondary outcome will be assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach. GRADE provides a systematic and transparent framework for rating the certainty of evidence across studies, starting from an initial rating based on study design (high for randomized trials, low for observational studies) and adjusting for factors such as risk of bias, inconsistency, indirectness, imprecision, and publication bias. The findings will be discussed in the final manuscript.

Sources

1 Covidence systematic review software, Veritas Health Innovation, Melbourne, Australia. Available at www.covidence.org.