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Outcomes of discontinuing renin-angiotensin system inhibitors: a study protocol for conducting systematic review and meta-analysis

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ABSTRACT

Introduction Renin-angiotensin system (RAS) plays a key role in various types of cardiovascular disease and many kinds of RAS inhibitors have been developed. The effect of discontinuation of RAS inhibitors on clinical outcomes is still controversial. This study aims to evaluate the effects of discontinuing RAS inhibitor medication on the clinical outcomes of patients continuously taking these agents.

Methods and analysis This article presents a systematic review protocol described in accordance with Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols guidelines. We will include randomised controlled trials in which the effects of RAS inhibitor withdrawal were evaluated. Initially, four authors will search for eligible studies in MEDLINE, EMBASE, the Cochrane Database Trial Register, European trial registry and ClinicalTrials.gov. Abstracts and full-text screenings will be performed by the four authors with data extraction performed by each author independently. We will include patients taking RAS inhibitors—including ACE inhibitor, angiotensin receptor blocker and angiotensin receptor neprilysin inhibitor and exclude the patients undergoing renal replacement therapy (RRT), adolescents (under 18 years of age) and patients with acute infectious diseases. Our search will be performed on 1 May 2023. Studies in which the patients discontinued RAS inhibitors due to any reason will be included. Patients who continuously took RAS inhibitors under conditions in which the intervention group discontinued these agents will be considered eligible as the comparison group. Death (any cause), Death (cardiovascular disease (CVD)) and CVD events will be set as primary outcomes. Secondary outcomes will be set as RRT, acute kidney injury, renal function (analysis of the change in estimated glomerular filtration rate), hyperkalaemia, proteinuria and blood pressure.

Ethics and dissemination Research ethics approval was not required in this study due to it being a systematic review, and any data belonging to individuals cannot be identified. The results of this study will be disseminated through peer-reviewed journals and conferences.

Trial registration number PROSPERO CRD42022300777.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This systematic review protocol was complied with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols checklist.
⇒ Our study was registered with the International Prospective Register of Systematic Reviews (PROSPERO).
⇒ Subgroup analysis was performed to determine the effects of renin-angiotensin system inhibitor withdrawal in patients with and without heart failure, CVD, diabetes mellitus and chronic kidney disease.
⇒ In this study, we analysed the estimated glomerular filtration rate according to the definition of each study. It might affect the results and downstream analysis given the variability in the definition of estimated glomerular filtration rate inherent to each study.

INTRODUCTION

The renin-angiotensin system (RAS) plays a key role in many types of cardiovascular diseases (CVDs). Many basic and clinical studies have shown that excessive stimulation of RAS results in severe outcomes; thus, the control of RAS has been a major focus in recent decades in the management of CVD. To date, many kinds of medications focusing on the regulation of RAS have been developed and are comprised of aldosterone antagonist, ACE inhibitor (ACEI), angiotensin receptor blockers (ARBs) and angiotensin receptor neprilysin inhibitor (ARNI). These RAS inhibitors are administered to patients with hypertension,[1] heart failure[2] and chronic kidney disease (CKD).[3] Several clinical studies have found that these interventions for RAS could decrease the risk of primary outcomes, including death, hospitalisation and CVD.[4] As such, these medications have been widely accepted in clinical settings worldwide.

Although the effectiveness of RAS blockers has been confirmed, they can be discontinued due to events, such as planned surgery, as well as due to their own side effects, such

as over-suppression of blood pressure, hyperkalaemia and impairment of renal function. Even after recovery from adverse side-effects, there are instances when these agents are not readministered to patients. It has not been fully validated that RAS inhibitors could be administered to patients without discontinuation when these adverse events occur, and it is still controversial if the withdrawal of RAS inhibitors might affect major outcomes. Some randomised trials and prospective longitudinal studies have focused on the effects of RAS inhibitor withdrawal; however, a limited number of meta-analyses have validated the impact of withdrawing RAS inhibitors.

In this systematic review, we will investigate the effects of withdrawal of RAS blockers on several outcomes, including death, CVD events, and renal function.

METHODS AND ANALYSIS

Patient and public involvement

This study will be conducted without patient and public involvement.

Protocol and registration

This protocol is carried out in accordance with[5] the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols statement. The current protocol has been registered with the International Prospective Register of Systematic Reviews database (CRD42022300777).

Search source and strategy

The electronic databases will be used to identify the relevant articles published in MEDLINE, EMBASE, Cochrane Database Trial Register (CENTRAL), European trial registry and ClinicalTrials.gov. The search strategy was designed according to the advice of a librarian with experience in systematic reviews. Searches will be conducted using a standardised set of keywords: ACEI, ARB, ARNI, discontinuation and withdrawal. Our searches will not be restricted by any language and publication period criteria. The search strategy for each electronic database is shown in online supplemental table 1. Our search will be performed on 1 May 2023.

Eligibility criteria

Types of study

We will include clinical trials with randomised, placebo-controlled, individual and cluster randomised controlled trials (RCTs). Non-randomised studies, in vitro studies, animal studies, extended abstracts, and observational studies will be excluded.

Inclusion criteria for study selection

Patients

We will include patients taking RAS inhibitors—including ACEI, ARB, aldosterone antagonists and ARNI. We will exclude adolescents (under 18 years of age), patients undergoing renal replacement therapy (RRT) and patients with acute infectious diseases. We will also exclude patients who discontinued RAS inhibitors prior to the coronary angiography (CAG) or cardiac surgery.

Intervention

Studies in which the patients discontinued RAS inhibitors as an intervention will be included.

Comparison

Patients who continuously took RAS inhibitors under conditions in which the intervention group discontinued these agents will be considered as eligible comparison group.

Outcomes

Primary outcomes

We will examine the following outcomes as the primary outcomes:

- Death (any cause).
- Death (CVD).
- CVD events.

Secondary outcomes

The following outcomes will be included in addition:

- Hospitalisation due to heart failure.
- RRT (haemodialysis, peritoneal dialysis, and renal transplantation).
- Acute kidney injury (diagnosed according to[6] the definition of kidney disease improving global outcomes (KDIGO)).
- Renal function (analysis of the change in estimated glomerular filtration rate (eGFR)).
- Serum potassium levels.
- Proteinuria.
- Blood pressure.
- Incidence of hyperkalaemia.

Study selection

Initially, four authors will independently screen the titles and abstracts (if available) of the articles selected using the search engine according to the selected search criteria. The full text of the articles will then be reviewed to be either included or excluded in the review. If any disagreements on the inclusion or exclusion of an article occur, the authors might then relegate the final decision to the fifth author as a tie breaker.

Data extraction and management

Four authors will independently extract studies that meet the set standard: study design, author name, follow-up period, country of recruitment and treatment, year of publication, sample characteristics (population, size, ethnicity, gender, age, duration of taking RAS inhibitors, case definition/diagnostic criteria of disease condition, inclusion and exclusion criteria, intervention (I) and control (C)), and clinical data before and after the intervention. The fifth author will resolve any differences between the primary reviewers. Example of data extraction sheet is shown in online supplemental table 2.

Assessment of certainty of the evidence and risk of bias

The certainty of the evidence will be assessed using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach, which has four levels of evidence: very low, low, moderate and high. The evidence of RCTs starts at high quality. Using the GRADE approach, the certainty of the evidence is increased or decreased for reasons such as bias risk. The risk of bias in our analysis will be assessed using the tools described in Chapter 8 of the Cochrane Handbook for Systematic Reviews of Interventions, V.6.2.[7] Seven domains will be assessed: (1) sequence generation, (2) allocation concealment, (3) blinding of participants and personnel, (4) blinding of outcome assessment, (5) incomplete outcome data, (6) selective outcome reporting and (7) other biases, such as baseline imbalance. The risk of bias will either be determined to be high, unclear or low. Four authors will perform the quality assessment independently, and a fifth author will resolve any disagreement.

Strategy for data analysis and synthesis

For the synthesis analyses, we will use the Review Manager (RevMan) software, V.5.4 (Cochrane Collaboration, Oxford, UK). We will apply the DerSimonian-Laird-type random-effects model for synthesis analyses to address heterogeneity between studies. Statistical heterogeneity among the trials was evaluated using the heterogeneity variance τ^2, Higgins' I^2 statistic and Q-statistic (Cochrane's test). In addition, we will assess potential small-study effects using the Egger test.

Analysis of subgroups

To assess clinical heterogeneity by potential effect modifiers, we will conduct subgroup or meta-regression analyses. The subgroup analyses will be performed for patients with heart failure, CVD, CKD and patients with diabetes mellitus (DM). RAS inhibitors are basically administered to patients with heart failure and CVD. We expect heart failure and CVD to affect the outcomes, thus we will perform subgroup analysis pertaining to these states. For the subgroup analysis, we will adopt the definition of CKD in the KDIGO guideline.[8] Patients undergoing RRT will be excluded. Although RAS inhibitors are administered to patients with CKD, they are often discontinued due to their side effects such as lowering eGFR and/or hyperkalaemia. The withdrawal of these medications may induce different adverse events. DM strongly affects chief outcomes, including CVD and renal impairment. Accordingly, we distinguished patients with DM from those without DM in our analysis.

DISCUSSION

RAS inhibitors are accepted as effective medications in various clinical settings; however, these agents must be withdrawn under specific conditions such as before a planned surgery and under occurrences of acute heart failure, hyperkalaemia and renal failure. Several retrospective studies have evaluated the effects of discontinuing RAS inhibitors.[9 10] Many of these studies have indicated favourable results concerning the continuation of RAS inhibitors. It has been reported that withdrawal of RAS inhibitors in patients with CKD might not contribute to the avoidance of end-stage kidney disease and increase the risk of major adverse cardiac events.[11]

Whiting *et al* conducted a systematic review focusing on temporary discontinuation of ACEI and ARB.[12] The study included three RCTs[13–15] and three prospective cohort studies.[16–18] All studies included in this systematic review evaluated the effects of discontinuing the agents before CAG or cardiac surgery. They concluded that the discontinuation of ACEI/ARBs prior to CAG and cardiac surgery may reduce the incidence of AKI. The clinical settings that the systematic review analysed were limited, and further studies with expanded scope, other than trials on CAG or surgeries should be included. Thus, we have included only RCTs performed in clinical settings other than CAG and surgeries to evaluate the comprehensive effects of RAS inhibitor withdrawal. Additionally, we have included patients using not only ACEI and ARB, but also ARNI—which is a new RAS inhibitor. We expect that our systematic review will provide further evidence for the management of RAS inhibitors.

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Contributors Conception was drafted by TS. TS, HNi, EO, HNo and TH designed this study. Study selection will be performed by TS, HNi, YA and YW. Risk of bias will be assessed by TS, HNi, YA and YW. TS, HNi, YA and YW will analyse the data statistically. Interpretation of data will be performed by TS, HNi, YA, YW, EO, HNo and TH. The manuscript was drafted or revised by TS, HNi, YA, YW, EO, HNo, HH and TH.

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Competing interests None declared.

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