Withdrawal of renin-angiotensin system inhibitors' effect on estimated glomerular filtration rate in adults with advanced kidney disease: the STOP-ACEi RCT

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Disclosure of interests

Full disclosure of interests: Completed ICMJE forms for all authors, including all related interests, are available in the toolkit on the NIHR Journals Library report publication page at (https://doi.org/10.3310/TTMC6210).

Primary conflicts of interest: The authors have no conflicts of interest related to this trial and all other potential conflicts of interest are detailed in each individual ICMJE form submitted.

Published March 2024
DOI: 10.3310/TTMC6210

Scientific summary

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Efficacy and Mechanism Evaluation 2024; Vol. 11: No. 5
DOI: 10.3310/TTMC6210

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Background

Renin–angiotensin system (RAS) inhibitors, both angiotensin-converting enzyme inhibitors (ACEi) and angiotensin receptor blockers (ARB), slow the progression of mild and moderate chronic kidney disease (CKD). However, some evidence suggests that discontinuation of RAS inhibitors in patients with advanced CKD might increase estimated glomerular filtration rate (eGFR) or slow its decline.

Primary objective

To test the hypothesis that discontinuing ACEi or ARB treatment, or a combination of both, compared with continuing on these treatments, improves or stabilises kidney function in patients with progressive stage 4 or stage 5 CKD based on assessment of kidney function using the modification of diet in renal disease (MDRD) four-variable eGFR at 3 years follow-up.

Secondary objectives

To test whether in each of the randomised groups.

Clinical outcomes

- The number of participants starting kidney replacement therapy (KRT) (dialysis or transplantation) or sustaining a > 50% decline in eGFR differs.
- There is a difference in the time taken to reach end-stage kidney disease (ESKD) or need for KRT.
- Hospitalisation rates from any cause are different.
- Participant quality of life and well-being [measured using the kidney disease quality of life (KDQoL)-SF™ v1.3 questionnaire] differs.
- Participant physical function (measured using the 6-minute walk test) differs.
- Withdrawal of these treatments does not cause excess harm [e.g. increased cardiovascular (CV) events such as heart failure, hypertension, myocardial infarction, stroke] and is not associated with an increase in adverse effects.
- Participant survival in each group is similar.
- Blood pressure (BP) control is the same.
- Cystatin-C levels differ.

Mechanistic outcomes

- There is a change in urine protein excretion [urinary protein-to-creatinine ratio (uPCR)].
- Discontinuation of ACEi/ARB affects haemoglobin concentration.
- Discontinuation of ACEi/ARB affects the requirement for erythropoietin stimulating agents.

Methods

An investigator-initiated, multicentre, open-label randomised trial where people with advanced and progressive CKD (eGFR < 30 ml/minute/1.73 m^2) were randomised to either discontinue or continue RAS inhibitors, and then followed up every 3 months for 3 years.

Patients underwent screening at 39 centres in the UK. Adults (≥ 18 years of age) with stage 4 or stage 5 CKD (eGFR, < 30 ml/minute/1.73 m^2 of body-surface area) were eligible to participate in the trial if they were not receiving dialysis and had not undergone kidney transplantation. All eligible patients were required to have had a decrease of more than 2 ml/minute/1.73 m^2 per year in the eGFR during the previous 2 years and to have been receiving treatment with an ACEi, an ARB, or both for more than 6 months. We calculated the eGFR using the four-variable equation used in the MDRD study, as updated in 2005 ($MDRD_{175}$). Exclusion criteria included uncontrolled hypertension or a history of myocardial infarction or stroke within the previous 3 months. All the patients provided written informed consent.

Patients were randomly assigned in a 1 : 1 ratio to either discontinue or continue RAS inhibitors. Randomisation used a centralised internet-based system with minimisation to ensure balance between groups for the following variables: age (< 65 or ≥ 65 years), eGFR (< 15 or ≥ 15 ml/minute/1.73 m^2), diabetes (type 1, type 2, or none), mean arterial pressure (< 100 or ≥ 100 mmHg) and proteinuria [protein-to-creatinine ratio (PCR), < 100 or ≥ 100 mg/mmol]. In the group that discontinued RAS inhibitor, any guideline-recommended antihypertensive agent other than a RAS inhibitor could be used to control BP. In the group that continued RAS inhibitors, the responsible clinician chose the agent and dose of the RAS inhibitor and could combine it with any other guideline-recommended antihypertensive agent.

The primary outcome was the eGFR at 3 years as calculated according to the $MDRD_{175}$ four-variable equation. Secondary outcome measures included the time until the development of ESKD or initiation of KRT; a composite of a decrease of more than 50% in the eGFR, the development of ESKD, or the initiation of KRT; hospitalisation for any cause; measures of cystatin C and BP; quality of life (as measured on the KDQoL 36-Item Short Form Survey, version 1.3); exercise capacity (as assessed by the 6-minute walk test); and CV events and death. At the time of this report, the transfer and processing of samples for cystatin C measurement had not yet occurred, so the results are not provided here. Secondary mechanistic outcomes included measures of haemoglobin and urinary protein excretion (PCR).

The trial aimed to recruit 410 patients (205 patients in each trial group) which would provide 80% power to determine a minimum relevant between-group difference in the eGFR of 5 ml/minute/1.73 m^2 (alpha level of 0.05), assuming an attrition rate of 20%. This difference represents an effect size of 0.31, with a standard deviation of 16 ml/minute/1.73 m^2.

The analyses were based on the intention-to-treat principle and were adjusted for the minimisation variables and baseline values. A repeated-measures, mixed-effects linear regression model was used to estimate the between-group difference in eGFR at 3 years. Any measurements of eGFR that were made after patients had initiated dialysis or undergone kidney transplantation were excluded from the primary analysis. To examine the effect of data that were not missing at random, we performed sensitivity analyses by fitting pattern-mixture and joint models for the primary outcome. We also repeated analyses for the primary outcome with the use of two other four-variable equations for the eGFR calculation: the Chronic Kidney Disease Epidemiology Collaboration 2009 equation and the $MDRD_{186}$ equation. Continuously distributed secondary outcomes, such as BP, were analysed using the same methods as per the primary analysis, but data were not censored at the time of initiation of KRT. Categorical (dichotomous) secondary outcomes were analysed with the use of a Poisson regression model with robust standard errors (SEs) to estimate the relative risk (RR) and 95% confidence interval (CI). A Cox proportional-hazards model was used to calculate hazard ratios (HRs) and 95% CIs for time-to-event outcomes, such as the development of ESKD or the initiation of KRT. Categorical safety outcome

measures (i.e. hospitalisation and serious adverse events) were summarised as the percentage of patients with these events. Data collection for kidney outcomes did not distinguish between ESKD and kidney-replacement outcomes (i.e. both outcomes used the same end-point code), although investigators could note the specific outcome. Prespecified subgroup analyses were performed only for the primary outcome according to the minimisation variables. Time and subgroup were included in the model to allow for the possibility of differential changes over time within subgroups, time according to subgroup and the three-way interaction among the variables of treatment, time and subgroup. Although all data were included in the regression models for the subgroup analyses, only estimates of differences at 3 years are presented. All analyses were performed with the use of SAS software, version 9.4 (SAS Institute), and Stata software, version 17 (StataCorp).

Results

At 3 years, among the 411 patients who underwent randomisation, the least-squares mean (LS-Mean) (±SE) eGFR was 12.6 ± 0.7 ml/minute/1.73 m^2 in the discontinuation group and 13.3 ± 0.6 ml/minute/1.73 m^2 in the continuation group (difference −0.7, 95% (CI −2.5 to 1.0; p = 0.42) with a negative value favouring the continuation group.

End-stage kidney disease or the initiation of KRT occurred in 128 patients (62%) in the discontinuation group and in 115 patients (56%) in the continuation group (HR 1.28, 95% CI 0.99 to 1.65). The number of patients with > 50% decline in eGFR or need to start KRT (including ESKD) was 140/206 (68%) in the discontinue RAS inhibitor group compared to 127/202 (63%) in the continue RAS inhibitor group; RR 1.07, 95% CI 0.94 to 1.22.

The number of hospitalisations were similar between the groups; 414 in the stop RAS inhibitor group versus 413 in the continue RAS inhibitor group. The difference in LS-Mean at 3 years for systolic BP was 0 mmHg, 95% CI −4 to 5 mmHg. The results were similar for diastolic BP; 0 mmHg, 95% CI −2 to 3 mmHg. Adverse events were similar in both the discontinuation group and continuation group with respect to CV events (108 vs. 88) and deaths (20 vs. 22).

Conclusions

Our STOP-ACEi trial showed that discontinuing RAS inhibitors for patients with advanced and progressive CKD does not lead to a clinically relevant change in eGFR or difference in the rate of long-term decline in eGFR, overall or in pre-specified subgroups by age, severity of CKD, diabetes, proteinuria or BP.

Numerically more patients who discontinued RAS inhibitors had progression to ESKD or need for KRT, so a larger trial might have shown an advantage to continuing with RAS inhibition.

The rate of CV events and death was similar.

Systolic and diastolic BP and proteinuria were greater over the first year of follow-up in those randomised to discontinue RAS inhibitors but there was little difference, thereafter, reflecting initiation of antihypertensive agents other than RAS inhibitors.

No differences in quality of life or exercise capacity were observed for those who discontinued or continued RAS inhibitors.

Our trial lacked sufficient power to investigate the effect of withdrawing RAS inhibitors on CV events or mortality. However, because our trial suggests that there is no advantage in discontinuing RAS inhibitors

from the perspective of kidney function, there is little rationale to conduct a larger randomised trial to investigate CV safety.

Future work

Future work should initially focus on updating clinical guidelines in the UK and potentially worldwide. Further analyses, in addition to the prespecified analyses, may be undertaken if new eGFR equations are introduced into routine clinical practice such as the National Institute for Health and Care Excellence recommended removal of black ethnicity correction factor from the eGFR equation. Consideration of subgroup analysis by aetiology of kidney disease and gender will be considered to look for any potential differences in outcome in specific groups which might warrant future studies.

Trial registration

This trial is registered as STOP ACEi EudraCT Number, 2013-003798-82; ISTRCTN62869767.

Funding

This award was funded by the Efficacy and Mechanism Evaluation (EME) programme (NIHR award ref: 11/30/07), a Medical Research Council (MRC) and National Institute for Health and Care Research (NIHR) partnership. This is published in full in *Efficacy and Mechanism Evaluation*; Vol. 11, No. 5. See the NIHR Funding and Awards website for further award information.

Efficacy and Mechanism Evaluation

ISSN 2050-4373 (Online)

A list of Journals Library editors can be found on the NIHR Journals Library website

Efficacy and Mechanism Evaluation (EME) was launched in 2014 and is indexed by Europe PMC, DOAJ, Ulrichsweb™ (ProQuest LLC, Ann Arbor, MI, USA) and NCBI Bookshelf.

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The EME programme is funded by the Medical Research Council (MRC) and the National Institute for Health and Care Research (NIHR), with contributions from the Chief Scientist Office (CSO) in Scotland and National Institute for Social Care and Health Research (NISCHR) in Wales and the Health and Social Care Research and Development (HSC R&D), Public Health Agency in Northern Ireland.

This report

The research reported in this issue of the journal was funded by the EME programme as award number 11/30/07. The contractual start date was in February 2014. The final report began editorial review in November 2022 and was accepted for publication in May 2023. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The EME editors and production house have tried to ensure the accuracy of the authors' report and would like to thank the reviewers for their constructive comments on the final report document. However, they do not accept liability for damages or losses arising from material published in this report.

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