SGLT2 inhibitors reduce discontinuation of ACE inhibitors and angiotensin receptor blockers: a joint analysis of the CREDENCE and DAPA-CKD trials

Journal:	*Kidney International*
Manuscript ID	Draft
Article Type:	Clinical Investigation
Date Submitted by the Author:	n/a
Complete List of Authors:	Fletcher, Robert; The George Institute for Global Health, Heart Failure Program Jongs, Niels; University Medical Centre Groningen, 5. Department Clinical Pharmacy and Pharmacology Chertow, Glenn; Stanford University School of Medicine, Medicine/Nephrology; Stanford University School of Medicine McMurray, John; University of Glasgow, BHF Cardiovascular Research Center Arnott, Clare; The George Institute for Global Health, UNSW Sydney; University of New South Wales Jardine, Meg ; University of Sydney, NHMRC Clinical Trials Centre Mahaffey, Kenneth; Stanford Center for Clinical Research, Department of Medicine, Stanford University School of Medicine Perkovic, Vlado; The George Institute for Global Health, Heart Failure Program; University of New South Wales, Faculty of Medicine and Health Rockenschaub, Patrick; Charité Universitätsmedizin Berlin, Charité Lab for Artificial Intelligence in Medicine; Berlin Institute of Health at Charite, QUEST Center for Transforming Biomedical Research Rossing, Peter; Steno Diabetes Centre, ; University of Aarhus, Correa-Rotter, Ricardo; Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Department of Nephrology and Mineral Metabolism Toto, Robert; University Texas Southwestern Medical Center, Division of Nephrology Vaduganathan, Muthiah; Brigham and Women's Hospital Heart and Vascular Center, Wheeler, David; University College London, Centre for Nephrology Heerspink, Hiddo J.; University Medical Center Groningen, Neuen, Brendon; The George Institute for Global Health, Heart Failure Program; Royal North Shore Hospital
Subject Area:	Clinical Nephrology
Keywords:	chronic kidney disease, ACE Inhibitors, renin angiotensin system

SGLT2 inhibitors reduce discontinuation of ACE inhibitors and angiotensin receptor blockers: a joint analysis of the CREDENCE and DAPA-CKD trials

Robert A. Fletcher MSc[1], Niels Jongs PhD[2], Glenn M. Chertow MD[3], John J. V. McMurray MD[4], Clare Arnott PhD[1,5,6], Meg J. Jardine PhD[1,7], Kenneth W. Mahaffey MD[8], Vlado Perkovic PhD[1,9], Patrick Rockenschaub PhD[10,11], Peter Rossing MD[12,13], Ricardo Correa-Rotter MD[14], Robert D. Toto MD[15], Muthiah Vaduganathan MD MPH[16], David C. Wheeler MD[1,17], Hiddo J. L. Heerspink PhD[1,2], Brendon L. Neuen PhD[1,18]

[1]The George Institute for Global Health, UNSW, Sydney, New South Wales, Australia

[2]Department of Clinical Pharmacy and Pharmacology, University of Groningen, University Medical Center Groningen, Groningen, Netherlands

[3]Departments of Medicine, Epidemiology and Population Health, and Health Policy, Stanford University School of Medicine, Stanford, CA, USA

[4]Institute of Cardiovascular and Medical Sciences, University of Glasgow, Glasgow, UK

[5]Department of Cardiology, Royal Prince Alfred Hospital, Sydney, New South Wales, Australia

[6]Sydney Medical School, University of Sydney, Sydney, New South Wales, Australia

[7]NHMRC Clinical Trials Centre, University of Sydney, New South Wales, Australia

[8]Department of Medicine, Stanford Center for Clinical Research, Stanford University School of Medicine, Stanford, CA, USA

[9]Faculty of Medicine and Health, UNSW, Sydney, New South Wales, Australia

[10]Charité Lab for Artificial Intelligence in Medicine, Charité Universitätsmedizin Berlin, Berlin, Germany

[11]QUEST Center for Transforming Biomedical Research, Berlin Institute of Health (BIH), Berlin, Germany

[12]Complications Research, Steno Diabetes Center Copenhagen, Copenhagen, Denmark

[13]Department of Clinical Medicine, University of Copenhagen, Copenhagen, Denmark

[14]National Medical Science and Nutrition Institute Salvador Zubirán, Mexico City, Mexico

[15]Department of Internal Medicine, UT Southwestern Medical Center, Dallas, TX, USA

[16]Cardiovascular Division, Brigham and Women's Hospital, Boston, MA, USA

[17]Department of Renal Medicine, University College London, London, UK

[18]Royal North Shore Hospital, Sydney, New South Wales, Australia

Running title: SGLT2 inhibitors reduce discontinuation of RAS blockade

Abstract word count: 221

Manuscript word count: 2418

Main manuscript: 2 tables and 3 figures

Supplementary appendix: 1 table and 1 figure

Corresponding author:

Brendon L Neuen MBBS (Hons) MSc PhD

The George Institute for Global Health

Level 5, 1 King Street

Newtown NSW 2042, Australia

Tel: +61 2 8052 4300

Email: bneuen@georgeinstitute.org.au

ABSTRACT

Strategies to enable persistent use of renin-angiotensin-system (RAS) blockade to improve outcomes in chronic kidney disease (CKD) have long been sought-after. The effect of sodium-glucose cotransporter 2 (SGLT2) inhibitors on discontinuation of RAS blockade has yet to be evaluated. We conducted a joint analysis of individual participant data from CREDENCE and DAPA-CKD, two randomised, double-blind, placebo-controlled, event-driven trials of SGLT2 inhibitors in patients with CKD. The main outcome was time to incident temporary or permanent discontinuation of RAS blockade, defined as interruption of an angiotensin converting enzyme inhibitor or angiotensin receptor blocker for at least 4 weeks or complete cessation during the double-blind on-treatment period. Cox regression analyses were performed to estimate treatment effects from each trial. Hazard ratios and corresponding 95% CIs were pooled with fixed-effects meta-analysis to obtain summary treatment effects, overall and across key subgroups. During a median follow-up of 2.2 years across both trials, 743 of 8533 (8.7%) participants discontinued RAS blockade. SGLT2 inhibitors reduced discontinuation of RAS blockade by 15% (HR 0.85, 95% CI 0.74–0.99) with consistent effects across trials (P-heterogeneity=0.95). The reduction in RAS blockade discontinuation was more pronounced among patients with baseline urinary albumin:creatinine ratio ≥1000 mg/g (pooled HR 0.78, 95% CI 0.64–0.95; P-heterogeneity=0.003). In patients with albuminuric CKD with and without type 2 diabetes, SGLT2 inhibitors facilitate use of RAS blockade.

KEYWORDS

SGLT2 inhibitors, RAS blockade, chronic kidney disease, meta-analysis

INTRODUCTION

Renin-angiotensin system (RAS) blockade, including angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs), are foundational therapies for slowing progression of chronic kidney disease (CKD). However, the use of ACE inhibitors and ARBs in routine clinical practice has remained suboptimal for more than two decades after landmark randomised trials established their role in slowing CKD progression[1-6]. A major factor contributing to the significant gap in use of ACE inhibitors and ARBs across multiple settings is that these agents are often discontinued due to hyperkalemia, acute kidney injury, and during hospitalizations – and frequently not restarted owing to therapeutic inertia, or concerns regarding potential adverse effects[7,8]. Thus, strategies to enable the persistent use of RAS blockade are a key therapeutic priority in patients with CKD.

Sodium glucose cotransporter 2 (SGLT2) inhibitors have been shown to reduce the risks of kidney failure, cardiovascular events, and mortality in patients with CKD, with or without type 2 diabetes, and are now considered foundational therapy for CKD alongside RAS blockade[9-11]. This class of agents has been shown to have several ancillary benefits, including reducing the risk of serious hyperkalemia, acute kidney injury, and all-cause hospitalization in people with diabetes, CKD, or heart failure[11-19]. As all of these are potential reasons for discontinuation of RAS blockade, we hypothesized that SGLT2 inhibitors could reduce the frequency with which ACE inhibitors or ARBs are withdrawn in patients with CKD. We therefore undertook a joint analysis of CREDENCE and DAPA-CKD: two randomised, double-blind, placebo-controlled, event-driven trials in individuals with CKD, to assess whether SGTL2 inhibitors reduce discontinuation of ACE inhibitors and ARBs.

METHODS

Study Design

This post-hoc analysis used data from two randomised, double-blind, placebo-controlled, multicentre clinical trials of SGLT2 inhibitors in patients with CKD: the CREDENCE trial

(ClinicalTrials.gov identifier: NCT02065791) and the DAPA-CKD trial (NCT03036150). Detailed methods and main findings from these studies have been previously published[9,10].

Participants

CREDENCE enrolled individuals aged ≥30 years with type 2 diabetes and eGFR 30 to 90 mL/min/1.73m^2 and urine albumin:creatinine ratio (UACR) 300 to 5000 mg/g. DAPA-CKD enrolled adults with or without type 2 diabetes, eGFR of 25 to 75 mL/min/1.73m^2, and UACR of 200 to 5000 mg/g. CREDENCE excluded patients with CKD due to aetiologies other than type 2 diabetes. DAPA-CKD excluded patients with type 1 diabetes, polycystic kidney disease, lupus nephritis, anti-neutrophil cytoplasmic antibody-associated vasculitis, and those requiring immunosuppression for kidney disease within six months of enrolment. All participants provided written informed consent, and ethics approval was obtained at all participating centres. In CREDENCE, all participants were required to be receiving the maximum labelled or tolerated dose of an ACE inhibitor or ARB for at least four weeks prior to randomisation. In DAPA-CKD, the same was required, unless contraindicated, resulting in 3% of participants not receiving RAS blockade at baseline. Dual use of an ACE inhibitor and ARB was an exclusion criterion for both trials, although a very small number of participants in both trials commenced dual RAS blockade during the run-in period. Mineralocorticoid receptor antagonists were contraindicated in CREDENCE at baseline due to early concerns about the risk of hyperkalemia with SGLT2 inhibitors but were permitted in DAPA-CKD.

Randomised Treatment

Participants in CREDENCE were randomised 1:1 to canagliflozin 100mg or matching placebo. Participants in DAPA-CKD were randomised 1:1 to dapagliflozin 10mg or matching placebo.

Outcome Definition

The outcome in this study was time to incident temporary or permanent discontinuation of RAS blockade. Using concomitant medication usage data during the trial, we defined temporary discontinuation as interruption of an ACE inhibitor or ARB of at least 4 weeks. We defined permanent discontinuation as the date an individual discontinued their ACE inhibitor or ARB and reported no subsequent use during the double-blind on-treatment period. Patients were censored at the point of death or at the point of reaching the end of the double-blind on-treatment period without discontinuing RAS blockade, whichever occurred first. The end of the double-blind on-treatment period was chosen as the date of censoring owing to the infrequent recording of concomitant medication usage after this date.

Statistical Analysis

All trial participants with a recorded use of either an ACE inhibitor or an ARB at baseline were included in analyses. Baseline characteristics of participants who discontinued RAS blockade and participants who did not discontinue were compared in the pooled CREDENCE/DAPA-CKD population and within each trial. Continuous variables were reported as mean and SD. Categorical variables were reported as frequency and percentage.

We used Cox proportional hazards regression to assess the effect of SGLT2 inhibitors on time to incident temporary or permanent discontinuation of RAS blockade in the intention-to-treat population, separately in each trial. We included stratification terms for category of eGFR at screening (30 to <45 mL, 45 to <60 mL, or 60 to <90 mL/min/1.73m^2) in models in CREDENCE and terms for the diagnosis of type 2 diabetes (yes or no) and the urinary albumin-to-creatinine ratio (≤1000 mg/g or >1000 mg/g) in models in DAPA-CKD. Treatment effects from each study expressed as hazard ratios (HRs) with corresponding 95% confidence intervals (CIs), were pooled using inverse-variance weighting with fixed effects meta-analysis.

We assessed the effect of SGLT2 inhibitors on time to incident temporary or permanent discontinuation of RAS blockade across *a-priori* defined baseline subgroups: eGFR <45 mL/min/1.73m^2 and ≥45 mL/min/1.73m^2; UACR <1000 mg/g and ≥1000 mg/g; serum potassium <5 mmol/L and ≥5 mmol/L. We determined the heterogeneity in treatment effect estimates across subgroups with P-heterogeneity values obtained from random-effects meta-regression using restricted maximum likelihood.

We considered violation of proportional hazards in Cox models via visual inspection of Kaplan-Meier survival curves and formal post-estimation tests of scaled Schoenfeld residuals. We performed all analyses in R version 4.2.1.

RESULTS

The study population comprised a total 8533 participants: 4392 from CREDENCE and 4141 from DAPA-CKD. 9 participants (0.2%; 3 randomised to canagliflozin, 6 randomised to placebo) in CREDENCE and 163 participants (3.8%; 72 randomised to dapagliflozin, 91 randomised to placebo) in DAPA-CKD were not included in analyses as they either had no record of ACE inhibitor or ARB use at baseline, or had recorded dual use of both an ACE inhibitor and an ARB at baseline.

Selected baseline characteristics of patients included within analyses, in each trial and in the pooled population stratified by treatment arm, are presented in **Table 1**. There was no compelling evidence of covariate imbalance. Baseline characteristics of participants in the pooled population stratified by discontinuation/non-discontinuation of RAS blockade during follow-up are presented in **Table 2,** and displayed for each trial in **Table S1**. Across both trials, participants who discontinued RAS blockade had lower eGFR (mean [SD], 44.9 [14.7] mL/min/1.73m^2 versus 50.4 [15.7] mL/min/1.73m^2) and higher serum potassium (mean [SD, 4.7 [0.6] mmol/L versus 4.5 [0.5] mmol/L; **Table 2**), and were more likely to have a UACR >1000 mg/g (n [%], 397 [53.4%] versus 3651 [46.9%]; **Table 2**). In DAPA-CKD, participants

who discontinued RAS blockade were more likely to have diabetes (n [%], 278 [73.9%] versus 2500 [66.4%]) and cardiovascular disease (n [%], 171 [45.5%] versus 1380 [36.7%]), and higher glycated haemoglobin (HbA1c; mean [SD], 7.3% [1.8] versus 7.0% [1.7]; **Table S1**).

During a median follow-up of 2.2 years in both trials, 743 participants temporarily or permanently discontinued RAS blockade: 367 (8.3%; 172 randomised to canagliflozin, 195 randomised to placebo) from CREDENCE and 376 (8.7%; 177 randomised to dapagliflozin, 199 randomised to placebo) from DAPA-CKD. Across both trials, the rate of discontinuation of RAS blockade was 4.0 events per 100 person years (95% CI 3.5–4.4) in patients randomised to SGLT2 inhibitors, and 4.6 events per 100 person years (95% CI 4.2–5.1) in patients randomised to placebo. Kaplan-Meier curves for discontinuation of RAS blockade are shown in **Figure 1**. Overall, SGLT2 inhibitors reduced the risk of temporary or permanent discontinuation of RAS blockade by 15% (HR 0.85, 95% CI 0.74–0.99; **Figure 2**). The effect was consistent across both trials (HR for CREDENCE 0.85, 95% CI 0.69–1.04; HR for DAPA-CKD 0.86, 95% CI 0.70–1.05; P-heterogeneity=0.95; **Figure 2**). Violation of proportional hazards was not observed by formal post-estimation tests of scaled Schoenfeld residuals (P=0.85 for CREDENCE, P=0.18 for DAPA-CKD).

The effect of SGLT2 inhibitors on discontinuation of RAS blockade across baseline-defined subgroups of eGFR, UACR, and serum potassium is displayed in **Figure 3**. Rates of discontinuation of RAS blockade were substantially higher in participants with eGFR <45 mL/min/1.73m^2, UACR ≥1000 mg/g, and serum potassium ≥5 mmol/L. The reduction in discontinuation of RAS blockade with SGLT2 inhibitors was consistent in those with baseline eGFR <45 mL/min/1.73m^2 (HR 0.80, 95% CI 0.66–0.97) as in those with eGFR ≥45 mL/min/1.73m^2 (HR 0.91, 95% CI 0.73–1.14), P-heterogeneity=0.15. Treatment effects were also consistent for patients with baseline serum potassium <5 mmol/L (HR 0.86, 95% CI 0.72–1.03) as in those with serum potassium ≥5 mmol/L (HR 0.83, 95% CI 0.64–1.08), P-

heterogeneity=0.78. The magnitude of benefit with respect to discontinuation of RAS blockade was more pronounced in those with baseline UACR ≥1000 mg/g (pooled HR 0.78, 95% CI 0.64–0.95) compared with those with baseline UACR <1000 mg/g (pooled HR 0.95, 95% CI 0.77–1.17), P-heterogeneity=0.003. Individual trial results for each baseline-defined subgroup are presented in **Figure S1**.

DISCUSSION

In this joint analysis of the CREDENCE and DAPA-CKD trials, SGLT2 inhibitors reduced the risk of temporary or permanent discontinuation of RAS blockade by 15%, with consistent effects across trials. We observed risk reductions with SGLT2 inhibitors that were consistent irrespective of baseline eGFR or baseline serum potassium, and more pronounced in those with baseline UACR ≥1000 mg/g. Because the rate of discontinuation was considerably higher in these patients, absolute benefits are also likely to be larger. These findings indicate that SGLT2 inhibitors may have ancillary benefits in facilitating use of ACE inhibitors or ARBs in patients with CKD, the traditional foundation for attenuating CKD progression.

Despite proven benefits in slowing CKD progression, RAS blockade remains significantly underused in at-risk patients. In the United States, use of ACE inhibitors and ARBs in CKD has plateaued over the last decade, with fewer than half of patients with CKD receiving these medications[6]. Data indicate similar trends in low- and middle-income countries[5]. Reasons for the underuse of RAS blockade in CKD are complex and incompletely understood, but highlight potential gaps in identification and recognition of CKD, barriers to care, and guideline adherence.

Maintaining persistent use of RAS blockade remains a commonly encountered challenge in clinical practice. Due to therapeutic inertia and/or perceived safety concerns, ACE inhibitors and ARBs are often not restarted after temporary cessation, typically due to acute kidney injury, hyperkalaemia and/or hospitalization[7,8]. Potassium binders have long been touted as

a tool to enable persistent use of RAS blockade by reducing hyperkalaemia, but concerns about rare gastrointestinal side effects of sodium polystyrene sulfonate, limited access to newer potassium binders, and uncertain effects on clinical outcomes persist[20]. In contrast, SGLT2 inhibitors have direct benefits on clinical outcomes and are well tolerated, with serious adverse events occurring less commonly compared to placebo in CREDENCE and DAPA-CKD[9,10]. The apparent greater benefit in reducing discontinuation of RAS blockade in those with ≥1000 mg/g of albuminuria are highly clinically relevant, as it is these patients who are at highest risk of CKD progression.

Historically there has also been uncertainty about the merits of discontinuing versus continuing RAS blockade in people with advanced CKD, which has recently been addressed by the STOP ACEi trial[21]. While there was no difference in rate of decline in eGFR between those who continued versus discontinued RAS blockade in this trial, there was a numerically increased incidence of kidney replacement therapy and cardiovascular events in those who discontinued RAS blockade. These results are supported by traditional cohort studies and studies using target-trial emulation techniques, which also observed increased risks of cardiovascular events after RAS blockade was discontinued[7,22,23]. Therefore, strategies to enable persistent use of RAS blockade, even in advanced CKD, are highly desired.

Common events leading to discontinuation of RAS blockade include hospitalisation, hyperkalemia, acute kidney injury, and progression to advanced CKD, the risks of which of have all been shown to decrease with SGLT2 inhibitors. SGLT2 inhibitors reduce the risk of time to first serum potassium >6 mmol/L by approximately 15-20% in people with type 2 diabetes at high cardiovascular risk and/or with CKD, and almost 40% in those with heart failure[12-14]. Large, collaborative meta-analyses also demonstrate that SGLT2 inhibitors reduce the risk of acute kidney injury by almost 25%, with consistent benefits in those with and without diabetes[15]. Finally, in patients with CKD, SGLT2 inhibitors significantly reduced the risk of all-cause hospitalisation, with similar reductions observed in patients with diabetes

at high cardiovascular risk and patients with heart failure[11,16-19]. Together with data from the EMPEROR-Reduced trial, where empagliflozin reduced risk of discontinuation of mineralocorticoid receptor antagonists by 22% in patients with heart failure with reduced ejection fraction[24], combined evidence suggests that SGLT2 inhibitors may enhance tolerability of guideline directed medical therapy in both heart failure and CKD.

The CREDENCE and DAPA-CKD trials were international multicentre randomised trials with rigorous recording of concomitant medications throughout the trial, which permitted accurate determination of time to temporary or permanent discontinuation of RAS blockade. The use of individual participant data ensured that consistency in methodology and outcome definitions could be used, and time-to-event analyses could be conducted. The large sample size of the two combined trials and relatively long follow-up duration increased the precision of effect estimates and allowed the examination of the consistency of effects across clinically relevant subgroups. Furthermore, the requirement that all participants were using an ACE inhibitor or ARB for at least four weeks prior to randomisation (unless contraindicated in DAPA-CKD) allowed for the vast majority of the intention-to-treat population to be used for randomised analyses.

These analyses have limitations that need to be considered in the interpretation of these findings. This was a post hoc analysis, and neither trial was specifically designed to assess the effect of SGLT2 inhibitors on discontinuation of RAS blockade. Second, it was not possible to ascertain the exact reason for RAS blockade discontinuation, as only the timing of medication usage during the trial was available. This required that a proxy definition for discontinuation was used. Third, these results were generated from well-designed trials involving experienced investigators who were encouraged to continue guideline-directed background care wherever possible. It is therefore possible that the effect of SGLT2 inhibitors on RAS blockade discontinuation may be even more pronounced in real-world settings where this occurs much more frequently than in clinical trials[25,26].

In people with albuminuric CKD with and without type 2 diabetes, SGLT2 inhibitors facilitated use of RAS blockade.

ACKNOWLEDGEMENTS

The authors thank all investigators, patients, and research teams for their contribution to the reported clinical trials. The authors received no financial support for the research, authorship, and/or publication of this article and agreed on the decision to submit for publication.

AUTHOR CONTRIBUTIONS

Mr Fletcher and Dr Neuen had full access to the CREDENCE data. Dr Jongs and Dr Heerspink had full access to the DAPA-CKD data. All take responsibility for the integrity of the data and the accuracy of the data analysis.

Concept and design: Fletcher, Neuen.

Acquisition, analysis, or interpretation of data: Fletcher, Jongs, Chertow, McMurray, Arnott, Mahaffey, Perkovic, Rockenschaub, Rossing, Correa-Rotter, Toto, Vaduganathan, Wheeler, Heerspink, Neuen.

Critical revision of the manuscript for important intellectual content: Fletcher, Jongs, Chertow, McMurray, Arnott, Mahaffey, Perkovic, Rockenschaub, Rossing, Correa-Rotter, Toto, Vaduganathan, Wheeler, Heerspink, Neuen.

Drafting of the manuscript: Fletcher, Neuen.

Statistical analysis: Fletcher, Jongs, Rockenschaub.

Obtained funding: NA

Administrative, technical, or material support: Jongs, Arnott, Heerspink, Neuen.

Supervision: Rockenschaub, Arnott, Heerspink, Neuen.

DISCLOSURE STATEMENTS

RAF is supported by a PhD studentship from the Health Data Research UK-The Alan Turing Institute Wellcome Trust Programme in Health Data Science. This funding had no role in the production of this manuscript. **NJ** reports travel grants from AstraZeneca. **GC** has received fees from AstraZeneca for the DAPA-CKD trial steering committee, research grants from NIDDK, NIAID, and CSL Behring; he is on the board of directors for Satellite Healthcare, has received fees for advisory boards for Cricket, DiaMedica, and Reata. He holds stock options for Ardelyx, CloudCath, Durect, DxNow, Outset, Renibus, and Unicycive; has received fees from Akebia, Gilead, Sanifit and Vertex for trial steering committees; and has received fees for DSMB service from Bayer, Gilead, Mineralys, Palladio and ReCor. **JJVM** has received funding to his institution from Amgen and Cytokinetics for his participation in the Steering Committee for the ATOMIC-HF, COSMIC-HF, and GALACTIC-HF trials and meetings and other activities related to these trials; has received payments through Glasgow University from work on clinical trials, consulting and other activities from Alnylam, Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol Myers Squibb, Cardurion, Dal-Cor, GlaxoSmithKline, Ionis, KBP Biosciences, Novartis, Pfizer, and Theracos; has received personal lecture fees from the Corpus, Abbott, Hikma, Sun Pharmaceuticals, Medscape/Heart.Org, Radcliffe Cardiology, Servier Director, and Global Clinical Trial Partners (GCTP). **CA** is supported by an NHMRC/MRFF Priority Fellowship and a NSW Health EMC Grant. **MJ** is supported by a Medical Research Future Fund Next Generation Clinical Researchers Program Career Development Fellowship; is responsible for research projects that have received unrestricted funding from Baxter, Amgen, Eli Lilly, and Merck Sharpe Dohme; serves on a Steering Committee sponsored by CSL; has served on advisory boards sponsored by Akebia, Baxter, Boehringer Ingelheim, and Vifor; and has spoken at scientific meetings sponsored by Janssen; with any consultancy, honoraria, or travel support paid to her institution. **KM** has received research support from Afferent, Amgen, Apple Inc, AstraZeneca, Cardiva Medical Inc, Daiichi, Ferring, Google (Verily), Johnson & Johnson, Luitpold, Medtronic, Merck, National Institutes of Health, Novartis, Sanofi, St. Jude, and Tenax, and has served as a consultant (speaker fees for continuing medical education

events only) for Abbott, Ablynx, AstraZeneca, Baim Institute, Boehringer Ingelheim, Bristol-Myers Squibb, Elsevier, GlaxoSmithKline, Johnson & Johnson, MedErgy, Medscape, Mitsubishi Tanabe, Myokardia, NIH, Novartis, Novo Nordisk, Portola, Radiometer, Regeneron, Springer Publishing, and University of California, San Francisco. **VP** serves as a Board Director for St.Vincent's Health Australia, George Clinical and several Medical Research Institutes. He has received honoraria for Steering Committee roles, scientific presentations and/or advisory board attendance from Abbvie, Amgen, Astra Zeneca, Bayer, Baxter, Boehringer Ingelheim, Chinook, Durect, Eli Lilly, Gilead, GSK, Janssen, Merck, Mitsubishi Tanabe, Mundipharma, Novartis, Novo Nordisk, Otsuka, Pharmalink, Pfizer, Reata, Travere, Relypsa, Roche, Sanofi, Servier and Tricida. **PR** is supported by the Alexander von Humboldt Foundation. **PR(2)** declares receiving consultancy and/or speaking fees (to his institution) from Astellas, AstraZeneca, Bayer, Boehringer Ingelheim, Eli Lilly, Gilead, MSD, Novo Nordisk, Sanofi and Vifor Pharma, and research grants from AstraZeneca, Bayer and Novo Nordisk. **RCR** has received consulting and/or speaker and/or advisory board fees from AstraZeneca, Chinook Therapeutics, Novo Nordisk, Boehringer, Bayer, GSK, Janssen, Amgen, and Sanofi. **RDT** reports grant support from NIH and is a consultant to and has received honoraria from AstraZeneca, Bayer, Boehringer Ingelheim, Otsuka, Reata, and Relypsa. **MV** has received research grant support or served on advisory boards for American Regent, Amgen, AstraZeneca, Bayer AG, Baxter Healthcare, Boehringer Ingelheim, Cytokinetics, Lexicon Pharmaceuticals, Novartis, Pharmacosmos, Relypsa, Roche Diagnostics, Sanofi, and Tricog Health, speaker engagements with AstraZeneca, Novartis, and Roche Diagnostics, and participates on clinical trial committees for studies sponsored by Galmed, Novartis, Bayer AG, Occlutech, and Impulse Dynamics. **DCW** has received honoraria and/or consultancy fees from Amgen, AstraZeneca, Boehringer Ingelheim, Bayer, GlaxoSmithKline, Gilead, Janssen, Napp, Mundipharma, Medscape, Merck Sharp and Dohme, Reata, Takeda, Tricida, Vifor Fresenius and Zydus. **HJLH** is consultant for AstraZeneca, Bayer, Boehringer Ingelheim, Chinook, CSL Behring, Dimerix, Eli-Lilly, Gilead, Janssen, Merck, Novo Nordisk, ProKidney, Travere Therapeutics

and Vifor Fresenius. He has received research support from AstraZeneca, Boehringer Ingelheim, Janssen, and Novo Nordisk. **BLN** has received fees for advisory boards, steering committee roles, scientific presentations, and travel support from AstraZeneca, Bayer, Boehringer Ingelheim, Cambridge Healthcare Research, Medscape, and Janssen, with all honoraria paid to his institution.

REFERENCES

1. Lewis EJ, Hunsicker LG, Clarke WR, Berl T, Pohl MA, Lewis JB, et al. Renoprotective Effect of the Angiotensin-Receptor Antagonist Irbesartan in Patients with Nephropathy Due to Type 2 Diabetes. New England Journal of Medicine. 2001;345(12):851-60.
2. Lewis EJ, Hunsicker LG, Bain RP, Rohde RD. The Effect of Angiotensin-Converting-Enzyme Inhibition on Diabetic Nephropathy. New England Journal of Medicine. 1993;329(20):1456-62.
3. Brenner BM, Cooper ME, de Zeeuw D, Keane WF, Mitch WE, Parving H-H, et al. Effects of Losartan on Renal and Cardiovascular Outcomes in Patients with Type 2 Diabetes and Nephropathy. New England Journal of Medicine. 2001;345(12):861-9.
4. Hou FF, Zhang X, Zhang GH, Xie D, Chen PY, Zhang WR, et al. Efficacy and Safety of Benazepril for Advanced Chronic Renal Insufficiency. New England Journal of Medicine. 2006;354(2):131-40.
5. Prasad N, Yadav AK, Kundu M, Sethi J, Jaryal A, Sircar D, et al. Prescription Practices in Patients With Mild to Moderate CKD in India. Kidney Int Rep. 2021;6(9):2455-62.
6. Murphy DP, Drawz PE, Foley RN. Trends in Angiotensin-Converting Enzyme Inhibitor and Angiotensin II Receptor Blocker Use among Those with Impaired Kidney Function in the United States. Journal of the American Society of Nephrology. 2019;30(7):1314-21.
7. Leon SJ, Whitlock R, Rigatto C, Komenda P, Bohm C, Sucha E, et al. Hyperkalemia-Related Discontinuation of Renin-Angiotensin-Aldosterone System Inhibitors and Clinical Outcomes in CKD: A Population-Based Cohort Study. American Journal of Kidney Diseases. 2022;80(2):164-73.e1.
8. Tomson C, Tomlinson LA. Stopping RAS Inhibitors to Minimize AKI: More Harm than Good? Clinical Journal of the American Society of Nephrology. 2019;14(4).
9. Perkovic V, Jardine MJ, Neal B, Bompoint S, Heerspink HJL, Charytan DM, et al. Canagliflozin and Renal Outcomes in Type 2 Diabetes and Nephropathy. New England Journal of Medicine. 2019;380(24):2295-306.
10. Heerspink HJL, Stefánsson BV, Correa-Rotter R, Chertow GM, Greene T, Hou F-F, et al. Dapagliflozin in Patients with Chronic Kidney Disease. New England Journal of Medicine. 2020;383(15):1436-46.
11. Group TE-KC. Empagliflozin in Patients with Chronic Kidney Disease. New England Journal of Medicine. 2022;388(2):117-27.
12. Ferreira JP, Zannad F, Butler J, Filipattos G, Ritter I, Schüler E, et al. Empagliflozin and serum potassium in heart failure: an analysis from EMPEROR-Pooled European Heart Journal. 2022;43(31):2984-93.
13. Neuen BL, Oshima M, Agarwal R, Arnott C, Cherney DZ, Edwards R, et al. Sodium-Glucose Cotransporter 2 Inhibitors and Risk of Hyperkalemia in People With Type 2 Diabetes: A Meta-Analysis of Individual Participant Data From Randomized, Controlled Trials. Circulation. 2022;145(19):1460-70.
14. Neuen BL, Oshima M, Perkovic V, Agarwal R, Arnott C, Bakris G, et al. Effects of canagliflozin on serum potassium in people with diabetes and chronic kidney disease: the CREDENCE trial. European Heart Journal. 2021;42(48):4891-901.
15. Baigent C, Emberson J, Haynes R, Herrington WG, Judge P, Landray MJ, et al. Impact of diabetes on the effects of sodium glucose co-transporter-2 inhibitors on kidney outcomes: collaborative meta-analysis of large placebo-controlled trials. The Lancet. 2022;400(10365):1788-801.
16. Feng KY, Li J, Ianus J, de Zeeuw D, Fulcher GR, Pfeifer M, et al. Reasons for hospitalizations in patients with type 2 diabetes in the CANVAS programme: A secondary analysis. Diabetes Obes Metab. 2021;23(12):2707-15.

17. Schechter M, Jongs N, Chertow GM, Mosenzon O, McMurray JJV, Correa-Rotter R, et al. Effects of Dapagliflozin on Hospitalizations in Patients With Chronic Kidney Disease : A Post Hoc Analysis of DAPA-CKD. Ann Intern Med. 2023;176(1):59-66.
18. Schechter M, Wiviott SD, Raz I, Goodrich EL, Rozenberg A, Yanuv I, et al. Effects of dapagliflozin on hospitalisations in people with type 2 diabetes: post-hoc analyses of the DECLARE-TIMI 58 trial. The Lancet Diabetes & Endocrinology.
19. Vaduganathan M, Claggett BL, Jhund P, Miao ZM, Boer RAd, Lam CSP, et al. Dapagliflozin and All-Cause Hospitalizations in Patients With Heart Failure With Preserved Ejection Fraction. Journal of the American College of Cardiology. 2023;81(10):1004-6.
20. Noel JA, Bota SE, Petrcich W, Garg AX, Carrero JJ, Harel Z, et al. Risk of Hospitalization for Serious Adverse Gastrointestinal Events Associated With Sodium Polystyrene Sulfonate Use in Patients of Advanced Age. JAMA Internal Medicine. 2019;179(8):1025-33.
21. Bhandari S, Mehta S, Khwaja A, Cleland JGF, Ives N, Brettell E, et al. Renin–Angiotensin System Inhibition in Advanced Chronic Kidney Disease. New England Journal of Medicine. 2022;387(22):2021-32.
22. Fu EL, Evans M, Clase CM, Tomlinson LA, van Diepen M, Dekker FW, et al. Stopping Renin-Angiotensin System Inhibitors in Patients with Advanced CKD and Risk of Adverse Outcomes: A Nationwide Study. Journal of the American Society of Nephrology. 2021;32(2):424-35.
23. Qiao Y, Shin J-I, Chen TK, Inker LA, Coresh J, Alexander GC, et al. Association Between Renin-Angiotensin System Blockade Discontinuation and All-Cause Mortality Among Persons With Low Estimated Glomerular Filtration Rate. JAMA Internal Medicine. 2020;180(5):718-26.
24. Ferreira JP, Zannad F, Pocock SJ, Anker SD, Butler J, Filippatos G, et al. Interplay of Mineralocorticoid Receptor Antagonists and Empagliflozin in Heart Failure: EMPEROR-Reduced. Journal of the American College of Cardiology. 2021;77(11):1397-407.
25. Janse RJ, Fu EL, Clase CM, Tomlinson L, Lindholm B, van Diepen M, et al. Stopping versus continuing renin–angiotensin–system inhibitors after acute kidney injury and adverse clinical outcomes: an observational study from routine care data. Clinical Kidney Journal. 2022;15(6):1109-19.
26. Humphrey TJL, James G, Wittbrodt ET, Zarzuela D, Hiemstra TF. Adverse clinical outcomes associated with RAAS inhibitor discontinuation: analysis of over 400 000 patients from the UK Clinical Practice Research Datalink (CPRD). Clinical Kidney Journal. 2021;14(10):2203-12.

Table 1. Selected baseline characteristics of participants in CREDENCE and DAPA-CKD overall and by randomised treatment.

Characteristic	CREDENCE (N=4392)*	DAPA-CKD (N=4141)†	Combined (N=8533)	
			SGLT2i (N=4279)	Placebo (N=4254)
Randomised to SGLT2i	2199 (50.1)	2080 (50.2)	..	..
Age, years	63.0 (9.2)	61.8 (12.1)	62.4 (10.7)	62.5 (10.8)
Female	1490 (33.9)	1376 (33.2)	1450 (33.9)	1416 (33.3)
Race				
White	2925 (66.6)	2210 (53.4)	2579 (60.3)	2556 (60.1)
Black	224 (5.1)	182 (4.4)	209 (4.9)	197 (4.6)
Asian	875 (19.9)	1403 (33.9)	1140 (26.6)	1138 (26.8)
Other	368 (8.4)	346 (8.4)	351 (8.2)	363 (8.5)
Systolic blood pressure, mm Hg	140.0 (15.6)	137.1 (17.3)	138.3 (16.5)	138.8 (16.4)
Glycated haemoglobin, %	8.3 (1.3)	7.1 (1.7)	7.7 (1.5)	7.7 (1.5)
Serum potassium, mmol/L	4.5 (0.5)	4.6 (0.6)	4.6 (0.5)	4.5 (0.6)
Serum potassium				
<5 mmol/L	3567 (81.3)	3003 (72.7)	3291 (76.9)	3279 (76.6)
≥5 mmol/L	821 (18.7)	1128 (27.3)	981 (22.9)	968 (22.6)
Estimated glomerular filtration rate, mL/min/1.73m^2	56.2 (18.2)	43.3 (12.4)	50.0 (15.6)	49.8 (15.7)
Estimated glomerular filtration rate				
<45 mL/min/1.73m^2	1363 (31.0)	2407 (58.1)	1898 (44.4)	1872 (44.0)
45 to 60 mL/min/1.73m^2	1330 (30.3)	1333 (32.2)	1313 (30.7)	1350 (31.7)
>60 mL/min/1.73m^2	1698 (38.7)	401 (9.7)	1067 (24.9)	1032 (24.3)
Urine albumin:creatinine ratio				
<300 mg/g	526 (12.0)	429 (10.4)	502 (11.7)	453 (10.6)
300 to 1000 mg/g	1815 (41.3)	1715 (41.4)	1746 (40.8)	1784 (41.9)
>1000 mg/g	2051 (46.7)	1997 (48.2)	2031 (47.5)	2017 (47.4)
Duration of diabetes, years	15.8 (8.6)	14.9 (9.8)	15.3 (9.3)	15.5 (9.1)
Diabetes	4392 (100.0)	2778 (67.1)	3599 (84.1)	3571 (83.5)
Cardiovascular disease	2217 (50.5)	1551 (37.5)	1905 (44.5)	1863 (43.8)
Heart failure	652 (14.8)	454 (11.0)	560 (13.1)	546 (12.8)
Use of mineralocorticoid receptor antagonists‡	..	219 (5.3)	104 (2.4)	115 (2.7)

Data are n (%) and mean (SD). *9 patients from the intention-to-treat population in CREDENCE (N=4401) were excluded as they did not have any recorded RAS blockade at baseline. †163 patients from the intention-to-treat population in DAPA-CKD (N=4304) were excluded as they did not have any recorded RAS blockade at baseline. ‡Data on use of mineralocorticoid receptor antagonists is provided for DAPA-CKD only, owing to the fact that the use of these medications was contraindicated in the CREDENCE trial at baseline due to early concerns about the potential risk of hyperkalemia with SGLT2 inhibitors. Abbreviations: CREDENCE, Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation; DAPA-CKD, Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease; RAS, renin-angiotensin system; SGLT2i, sodium glucose cotransporter 2 inhibitor.

Table 2. Selected baseline characteristics of participants in the pooled CREDENCE and DAPA-CKD population stratified by discontinuation/non-discontinuation of RAS blockade during follow-up.

Characteristic	Pooled CREDENCE/DAPA-CKD Population (N=8533)*	
	Participants who discontinued RAS blockade (n=743)	Participants who did not discontinue RAS blockade (n=7790)
Randomised to SGLT2i	349 (47.0)	3930 (50.4)
Age, years	61.7 (11.2)	62.5 (10.7)
Female	226 (30.4)	2640 (33.9)
Race		
White	367 (49.4)	4768 (61.2)
Black	129 (17.4)	928 (11.9)
Asian	185 (24.9)	1442 (18.5)
Other	62 (8.3)	652 (8.4)
Systolic blood pressure, mm Hg	138.6 (18.4)	138.6 (16.3)
Glycated haemoglobin, %	7.8 (1.6)	7.7 (1.5)
Serum potassium, mmol/L	4.7 (0.6)	4.5 (0.5)
Serum potassium		
<5 mmol/L	518 (69.7)	6052 (77.7)
≥5 mmol/L	223 (30.0)	1726 (22.2)
Estimated glomerular filtration rate, mL/min/1.73m^2	44.9 (14.7)	50.4 (15.7)
Estimated glomerular filtration rate		
<45 mL/min/1.73m^2	430 (57.9)	3340 (42.9)
45 to 60 mL/min/1.73m^2	202 (27.2)	2461 (31.6)
>60 mL/min/1.73m^2	111 (14.9)	1988 (25.5)
Urine albumin:creatinine ratio		
<300 mg/g	66 (8.9)	889 (11.4)
300 to 1000 mg/g	280 (37.7)	3250 (41.7)
>1000 mg/g	397 (53.4)	3651 (46.9)
Duration of diabetes, years	15.5 (9.0)	15.4 (9.2)
Diabetes	645 (86.8)	6525 (83.8)
Cardiovascular disease	358 (48.2)	3410 (43.8)
Heart failure	91 (12.2)	1015 (13.0)
Use of mineralocorticoid receptor antagonists†	22 (3.0)	197 (2.5)

Data are n (%) and mean (SD). *9 patients from the intention-to-treat population in CREDENCE (N=4401) were excluded as they did not have any recorded RAS blockade at baseline. 163 patients from the intention-to-treat population in DAPA-CKD (N=4304) were excluded as they did not have any recorded RAS blockade at baseline. †Data on use of mineralocorticoid receptor antagonists is provided for DAPA-CKD only, owing to the fact that the use of these medications was contraindicated in the CREDENCE trial at baseline due to early concerns about the potential risk of hyperkalemia with SGLT2 inhibitors. Abbreviations: CREDENCE, Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation; DAPA-CKD, Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease; RAS, renin-angiotensin system; SGLT2i, sodium glucose cotransporter 2 inhibitor.

Figure 1. Kaplan-Meier curves of incident temporary or permanent discontinuation of RAS blockade in A) CREDENCE, and B) DAPA-CKD. The insets show the same data on an expanded y axis. Abbreviations: CREDENCE, Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation; DAPA-CKD, Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease; RAS, renin-angiotensin system.

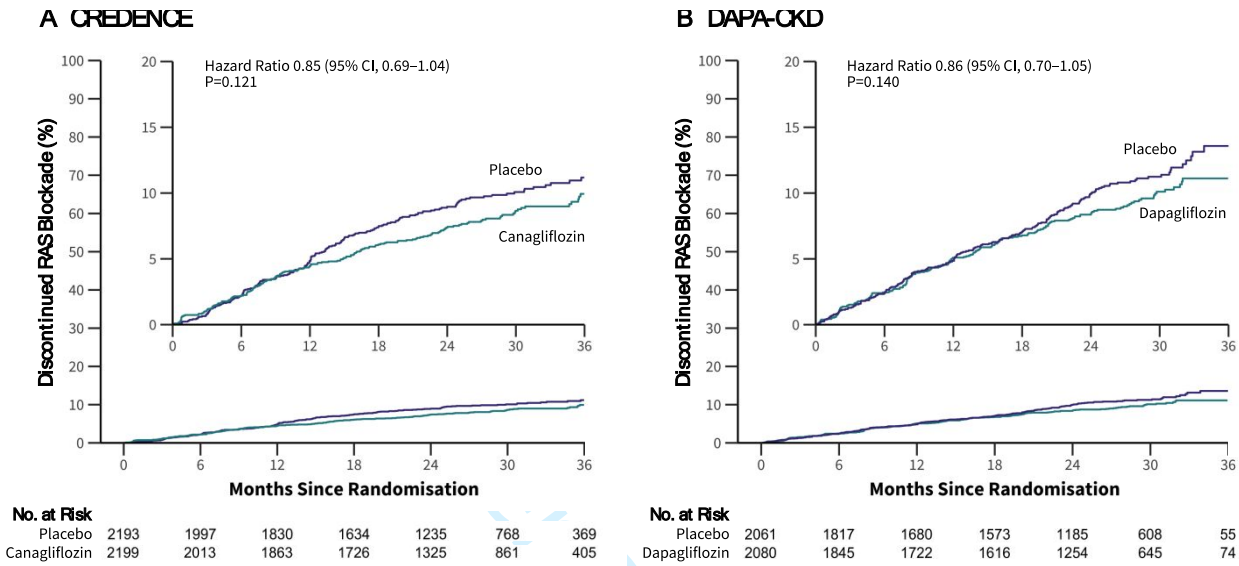

Figure 2. Effects of SGLT2 inhibitors on temporary or permanent discontinuation of RAS blockade. Abbreviations: CREDENCE, Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation; DAPA-CKD, Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease; SGLT2i, sodium glucose cotransporter 2 inhibitor; HR, hazard ratio.

	Events (n/N, %)		Event rate (n/100 person years)			
	SGLT2i	Placebo	SGLT2i	Placebo	HR (95% CI)	P-value
CREDENCE	172/2199 (7.8)	195/2193 (8.9)	3.6	4.3	0.85 (0.69–1.04)	0.121
DAPA-CKD	177/2080 (8.5)	199/2061 (9.7)	4.3	5.0	0.86 (0.70–1.05)	0.140
Overall	**349/4279 (8.2)**	**394/4254 (9.3)**	**4.0**	**4.6**	**0.85 (0.74–0.99)**	**0.032**

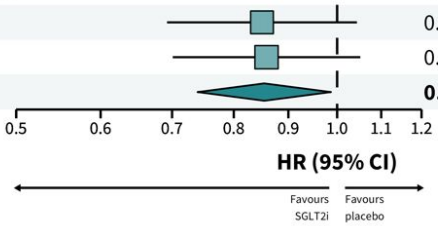

Figure 3. Effects of SGLT2 inhibitors on temporary or permanent discontinuation of RAS blockade by baseline-defined participant subgroups. Abbreviations: CREDENCE, Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation; DAPA-CKD, Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease; SGLT2i, sodium glucose cotransporter 2 inhibitor; HR, hazard ratio.

	Events (n/N, %)		Event rate (n/100 person years)		
	SGLT2i	Placebo	SGLT2i	Placebo	HR (95% CI)
Estimated glomerular filtration rate					
<45 mL/min/1.73m2	198/1898 (10.4%)	232/1872 (12.4%)	5.4	6.7	0.80 (0.66–0.97)
≥45 mL/min/1.73m2	151/2381 (6.3%)	162/2382 (6.8%)	2.9	3.2	0.91 (0.73–1.14)
Heterogeneity across subgroups p = 0.151					
Urine albumin:creatinine ratio					
<1000 mg/g	170/2248 (7.6%)	176/2235 (7.9%)	3.6	3.8	0.95 (0.77–1.17)
≥1000 mg/g	179/2031 (8.8%)	218/2019 (10.8%)	4.4	5.6	0.78 (0.64–0.95)
Heterogeneity across subgroups p = 0.003					
Serum potassium					
<5 mmol/L	244/3293 (7.4%)	275/3281 (8.4%)	3.6	4.1	0.86 (0.72–1.03)
≥5 mmol/L	104/981 (10.6%)	119/968 (12.3%)	5.3	6.4	0.83 (0.64–1.08)
Heterogeneity across subgroups p = 0.780					
Overall	**349/4279 (8.2)**	**394/4254 (9.3)**	**4.0**	**4.6**	**0.85 (0.74–0.99)**