Supplemental Material: **Ambulatory Treatments for RAAS Inhibitor-Related Hyperkalemia and the 1–Year Risk of Recurrence**

Supplemental Table 1. REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) statement checklist.[15]

	Item No	STROBE items	RECORD items	Reported
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract. (b) Provide in the abstract an informative and balanced summary of what was done and what was found.	(1.1) The type of data used should be specified in the title or abstract. When possible, the name of the databases used should be included. (1.2) If applicable, the geographic region and time frame within which the study took place should be reported in the title or abstract. (1.3) If linkage between databases was conducted for the study, this should be clearly stated in the title or abstract.	Abstract
Introduction				
Background/ rationale	2	Explain the scientific background and rationale for the investigation being reported.		Introduction
Objectives	3	State specific objectives, including any prespecified hypotheses.		Introduction
Methods				
Study design	4	Present key elements of study design early in the paper.		Methods
Setting	5	Describe the setting, locations, and relevant dates, including periods of		Methods

		recruitment, exposure, follow-up, and data collection.		
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up. (b) For matched studies, give matching criteria and number of exposed and unexposed.	(6.1) The methods of study population selection (such as codes or algorithms used to identify subjects) should be listed in detail. If this is not possible, an explanation should be provided. (6.2) Any validation studies of the codes or algorithms used to select the population should be referenced. If validation was conducted for this study and not published elsewhere, detailed methods and results should be provided. (6.3) If the study involved linkage of databases, consider use of a flow diagram or other graphical display to demonstrate the data linkage process, including the number of individuals with linked data at each stage.	Methods & Figure 1
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable.	(7.1) A complete list of codes and algorithms used to classify exposures, outcomes, confounders, and effect modifiers should be provided. If these cannot be reported, an explanation should be provided.	Methods, Table S2, Table S3
Data sources/ measurement	8	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe		Methods

		comparability of assessment methods if there is more than one group.		
Bias	9	Describe any efforts to address potential sources of bias.		Methods
Study size	10	Explain how the study size was arrived at.		Methods & Figure 1
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why.		Methods
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding. (b) Describe any methods used to examine subgroups and interactions. (c) Explain how missing data were addressed. (d) If applicable, explain how loss to follow-up was addressed. (e) Describe any sensitivity analyses.		Methods
Data access and cleaning methods		N/A	(12.1) Authors should describe the extent to which the investigators had access to the	Methods

			database population used to create the study population. (12.2) Authors should provide information on the data cleaning methods used in the study.	
Linkage		N/A	(12.3) State whether the study included person-level, institutional-level, or other data linkage across two or more databases. The methods of linkage and methods of linkage quality evaluation should be provided.	Methods
Results				
Participants	13	(a) Report numbers of individuals at each stage of study--e.g. numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analyzed. (b) Give reasons for non-participation at each stage. (c) Consider use of a flow diagram.	(13.1) Describe in detail the selection of the persons included in the study (i.e., study population selection), including filtering based on data quality, data availability, and linkage. The selection of included persons can be described in the text and/or by means of the study flow diagram.	Results & Figure 1
Descriptive data	14	(a) Give characteristics of study participants (e.g. demographic, clinical, social) and information on exposures and potential		Results & Table 1

		confounders. (b) Indicate number of participants with missing data for each variable of interest. (c) Summarize follow-up time (e.g. average and total amount).	
Outcome data	15	Report numbers of outcome events or summary measures over time.	Results, Table 2, Figure 2
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (e.g. 95% confidence interval). Make clear which confounders were adjusted for and why they were included. (b) Report category boundaries when continuous variables were categorized. (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period.	Results, Table 1, Table 2, Figure 2
Other analyses	17	Report other analyses done (e.g. analyses of subgroups and interactions, and sensitivity analyses).	Results, Figure S1, Tables S4-6

Key results	18	Summarize key results with reference to study objectives.		Discussion
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias.	(19.1) Discuss the implications of using data that were not created or collected to answer the specific research question(s). Include discussion of misclassification bias, unmeasured confounding, missing data, and changing eligibility over time, as they pertain to the study being reported.	Discussion
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence.		Discussion
Generalizability	21	Discuss the generalizability (external validity) of the study results.		Discussion
Other information				
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based.		Funding
Accessibility of protocol, raw data, and		N/A	(22.1) Authors should provide information on how to access any supplemental information such as the study protocol, raw	

programming code	data, or programming code.

Supplemental Table 2. Databases and code definitions for inclusion, exclusions and outcomes

Variable	Database	Type	Details	Codes
Potassium (mEq/L)	Ontario Laboratory Information System (OLIS)	Inclusion/Exclusion/Outcome	Inclusion: Evidence of first potassium measurement ≥5.3 mEq/L in accrual period. Exclusion: No evidence of a second potassium measurement one year after index date. Outcome: Second potassium test ≥5.3 mEq/L within one year of the index date.	Observation code= 2823-3
Renin-angiotensin-aldosterone system (RAAS) inhibitor	Ontario Drug Database (ODB)	Inclusion		Drug Identification Number (DIN):
Potassium-wasting diuretic	ODB	Inclusion		DIN:
Age	Registered Persons Database (RPDB)	Exclusion		BDATE
Chronic dialysis	Canadian Organ Replacement Register (CORR)	Exclusion		Recipient_Treatment database Treatment_Code≠ 171, 181
Kidney transplantation	CORR	Exclusion		Recipient_Treatment database Treatment_Code= 171, 181
Serum creatinine	OLIS	Exclusion	No evidence of a serum creatinine measurement within two years prior to the index date.	Observation code= 14682-9
Death	RPDB	Exclusion/Outcome		DTH

Hospitalization	Canadian Institute for Health Information (CIHI) Discharge Abstract Database (DAD)	Exclusion	Hospital admission within 30 days of potassium laboratory measurement or index date	ADMDATE
Adverse cardiovascular events:				
Stroke and transient ischemic attack	DAD CIHI National Ambulatory Care Reporting System (NACRS)	Outcome		International Classification of Diseases Tenth Revision (ICD-10): I62, I630, I631, I632, I633, I634, I635, I638, I639, I64, H341, I600, I601, I602, I603, I604, I605, I606, I607, I609, I61, G450, G451, G452, G453, G458, G459, H340
Myocardial infarction	CIHI DAD CIHI NACRS	Outcome		ICD-10: I21, I22
Congestive heart failure	CIHI DAD Ontario Health Insurance Plan (OHIP)	Outcome		ICD 10: I099, I420, I425, I426, I427, I428, I429, I43, I500, I501, I509, I255, J81 Canadian Classification of Health Interventions (CCI): 1HP53, 1HP55, 1HZ53GRFR, 1HZ53LAFR, 1HZ53SYFR OHIP fee code: R701, R702, Z429 OHIP diagnosis code: 428
Coronary artery bypass	CIHI DAD	Outcome		CCI: 1IJ76

	OHIP		OHIP fee code: R742, R743, E654, E645, E652, E646
Percutaneous coronary intervention	CIHI-DAD	Outcome	CCI: 1IJ50, 1IJ57GQ, 1IJ54GQAZ
	OHIP		OHIP fee code: Z434, G262, G298

Supplemental Table 3. List of drug names used to define renin-angiotensin-aldosterone system inhibitor and diuretic exposure groups

Renin-Angiotensin-Aldosterone System Inhibitors (RAASi)				**Diuretics**	
Angiotensin-Converting Enzyme (ACE) Inhibitors	**Angiotensin II Receptor Blockers (ARBs)**	**Mineralocorticoid Receptor (MR) Antagonists**	**Epithelial Sodium Channel (ENaC) Inhibitors**	**Loop Diuretics**	**Thiazide Diuretics**
Benazepril	Candesartan	Eplerenone	Amiloride	Bumetanide	Chlorthalidone
Captopril	Eprosartan	Spironolactone	Triamterene	Ethacrynic Acid	Hydrochlorothiazide
Cilazapril	Irbesartan			Furosemide	Indapamide
Enalapril	Losartan				Metolazone
Fosinopril	Olmesartan				
Lisinopril	Telmisartan				
Perindopril	Valsartan				
Quinapril					
Ramipril					
Trandolapril					

Supplemental Table 4. Recurrent hyperkalemia, cardiovascular events, and all-cause mortality within one year by outpatient hyperkalemia intervention (hyperkalemia definition K^+ ≥5.8 mEq/L).

	RECURRENT HYPERKALEMIA			CARDIOVASCULAR EVENTS			ALL-CAUSE MORTALITY		
Intervention	**No. Events (%)**	**Unadjusted HR (95% CI)**	**Adjusted HR[a] (95% CI)**	**No. Events (%)**	**Unadjusted HR (95% CI)**	**Adjusted HR[a] (95% CI)**	**No. Events (%)**	**Unadjusted HR (95% CI)**	**Adjusted HR[a] (95% CI)**
No Intervention (N=4,060)	695 (17)	Reference	Reference	974 (24)	Reference	Reference	432 (11)	Reference	Reference
RAASi Discontinuation (N=1,211)	158 (13)	0.74 (0.63-0.88)	0.75 (0.63-0.90)	279 (23)	0.96 (0.84-1.10)	1.07 (0.93-1.23)	125 (10)	0.97 (0.80-1.18)	1.22 (0.99-1.50)
RAASi Dose Decrease (N=284)	56 (20)	1.17 (0.89-1.54)	1.01 (0.76-1.35)	114 (40)	1.93 (1.58-2.35)	1.33 (1.07-1.65)	34 (12)	1.14 (0.80-1.62)	0.93 (0.66-1.33)
New Diuretic Rx (N=44)	9 (20)	1.26 (0.64-2.49)	1.42 (0.71-2.84)	8 (18)	0.73 (0.37-4.46)	1.49 (0.72-3.07)	≤5	0.87 (0.32-2.37)	1.85 (0.69-4.98)
Diuretic Dose Increase (N=99)	25 (25)	1.56 (1.04-2.33)	1.36 (0.90-2.04)	50 (50)	2.62 (1.97-3.50)	1.55 (1.15-2.09)	23 (23)	2.34 (1.54-3.55)	1.88 (1.23-2.88)
New SPS Rx (N=78)	19 (24)	1.44 (0.93-2.25)	1.10 (0.70-1.73)	26 (33)	1.47 (1.00-2.16)	1.11 (0.76-1.61)	10 (13)	1.21 (0.65-2.25)	1.21 (0.64-2.28)

Abbreviations: CI, confidence interval; HR, hazard ratio; K^+, potassium; RAASi, renin-angiotensin-aldosterone system inhibitor; Rx, prescription; SPS, sodium polystyrene sulfonate.

[a] Models adjusted for: demographics (age, sex, income quintile, rural locale, residence in a long-term care facility), pre-existing comorbid illnesses (coronary artery disease, myocardial infarction, coronary artery bypass graft, congestive heart failure, atrial fibrillation/flutter, stroke, peripheral vascular disease, venous thromboembolism, hypertension, diabetes mellitus, chronic liver disease, and major cancer; within previous five years), baseline eGFR category (<30, 30-60, and >60 mL/min/1.73m^2), baseline serum potassium, medication use (non-steroidal anti-inflammatory drugs [NSAIDs], beta-blockers, statins, and antiplatelet agents; within previous 120 days), and health service utilization (number of hospitalizations and emergency room visits, any nephrology or cardiology visits; within previous one year).

[b] In accordance with ICES privacy policies, cell sizes less than or equal to five cannot be reported.

Supplemental Table 5. Recurrent hyperkalemia, cardiovascular events, and all-cause mortality within one year by outpatient hyperkalemia intervention (hyperkalemia definition K^+ ≥5.3 mEq/L) including censoring at intervention discontinuation.

	RECURRENT HYPERKALEMIA			CARDIOVASCULAR EVENTS			ALL-CAUSE MORTALITY		
Intervention	**No. Events (%)**	**Unadjusted HR (95% CI)**	**Adjusted HR[a] (95% CI)**	**No. Events (%)**	**Unadjusted HR (95% CI)**	**Adjusted HR[a] (95% CI)**	**No. Events (%)**	**Unadjusted HR (95% CI)**	**Adjusted HR[a] (95% CI)**
No Intervention (N=38,254)	13413 (35)	Reference	Reference	8041 (21)	Reference	Reference	3339 (9)	Reference	Reference
RAASi Discontinuation (N=8,417)	2275 (27)	0.80 (0.76-0.83)	0.80 (0.77-0.84)	1470 (17)	0.87 (0.83-0.92)	0.95 (0.90-1.01)	557 (7)	0.82 (0.75-0.89)	1.06 (0.97-1.17)
RAASi Dose Decrease (N=1,675)	508 (30)	1.08 (0.99-1.18)	0.94 (0.85-1.03)	500 (30)	1.92 (1.75-2.11)	1.37 (1.24-1.51)	145 (9)	1.25 (1.06-1.48)	1.03 (0.87-1.22)
New Diuretic Rx (N=308)	57 (19)	0.79 (0.60-1.02)	0.83 (0.64-1.09)	35 (11)	0.79 (0.57-1.10)	0.98 (0.69-1.38)	12 (4)	0.69 (0.39-1.21)	1.10 (0.62-1.93)
Diuretic Dose Increase (N=748)	228 (30)	1.15 (1.01-1.32)	0.97 (0.85-1.12)	304 (41)	3.02 (2.68-3.40)	1.67 (1.47-1.89)	104 (14)	2.13 (1.75-2.60)	1.28 (1.05-1.57)
New SPS Rx (N=169)	24 (14)	2.23 (1.49-3.35)	1.43 (0.95-2.15)	16 (9)	1.91 (1.18-3.09)	1.29 (0.83-2.02)	≤5[b]	0.39 (0.06-2.67)	0.39 (0.06-2.77)

For the RAASi discontinuation group, patients were censored upon restart of a RAASi. For all other interventions, patients were censored if there were no refills of the intervention medication within the prescription period plus an additional 50% of time. Abbreviations: CI, confidence interval; HR, hazard ratio; K^+, potassium; RAASi, renin-angiotensin-aldosterone system inhibitor; Rx, prescription; SPS, sodium polystyrene sulfonate.

[a] Models adjusted for: demographics (age, sex, income quintile, rural locale, residence in a long-term care facility), pre-existing comorbid illnesses (coronary artery disease, myocardial infarction, coronary artery bypass graft, congestive heart failure, atrial fibrillation/flutter, stroke, peripheral vascular disease, venous thromboembolism, hypertension, diabetes mellitus, chronic liver disease, and major cancer; within previous five years), baseline eGFR category (<30, 30-60, and >60 mL/min/1.73m^2), baseline serum potassium, medication use (non-steroidal anti-inflammatory drugs [NSAIDs], beta-blockers, statins, and antiplatelet agents; within previous 120 days), and health service utilization (number of hospitalizations and emergency room visits, any nephrology or cardiology visits; within previous one year).

[b] In accordance with ICES privacy policies, cell sizes less than or equal to five cannot be reported.

Supplemental Table 6. Recurrent hyperkalemia, cardiovascular events, and all-cause mortality within one year by outpatient hyperkalemia intervention (hyperkalemia definition K^+ ≥5.8 mEq/L) including censoring at intervention discontinuation.

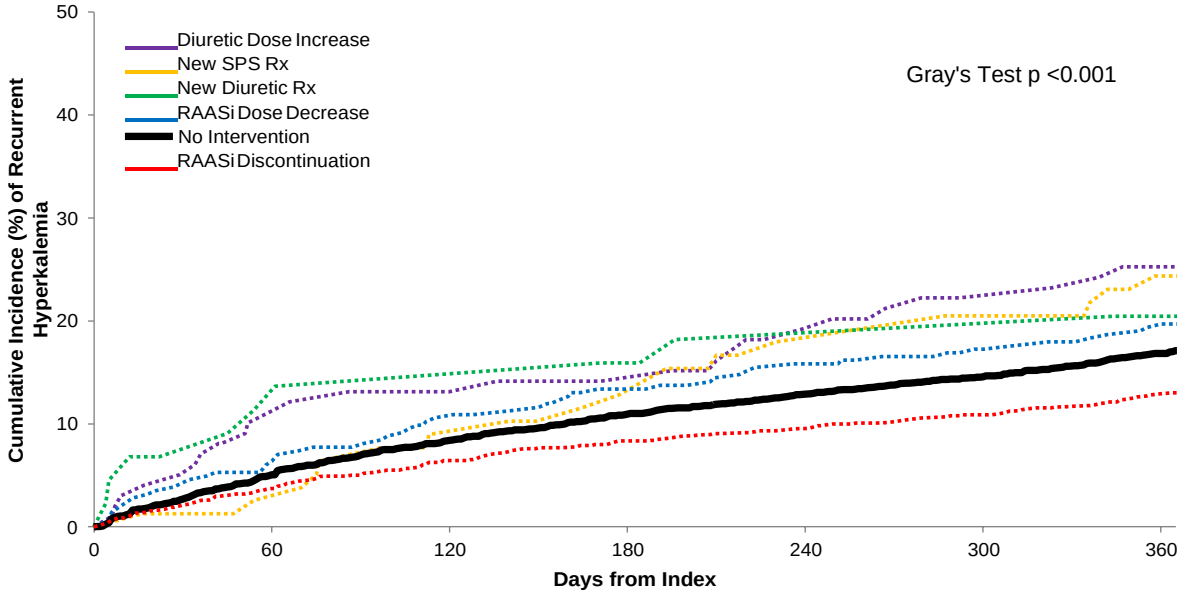
	RECURRENT HYPERKALEMIA			CARDIOVASCULAR EVENTS			ALL-CAUSE MORTALITY		
Intervention	**No. Events (%)**	**Unadjusted HR (95% CI)**	**Adjusted HR[a] (95% CI)**	**No. Events (%)**	**Unadjusted HR (95% CI)**	**Adjusted HR[a] (95% CI)**	**No. Events (%)**	**Unadjusted HR (95% CI)**	**Adjusted HR[a] (95% CI)**
No Intervention (N=4,060)	695 (17)	Reference	Reference	974 (24)	Reference	Reference	432 (11)	Reference	Reference
RAASi Discontinuation (N=1,211)	142 (12)	0.72 (0.60-0.86)	0.73 (0.60-0.88)	259 (21)	0.94 (0.82-1.08)	1.05 (0.91-1.22)	112 (9)	0.96 (0.78-1.18)	1.20 (0.97-1.49)
RAASi Dose Decrease (N=284)	48 (17)	1.22 (0.91-1.63)	1.04 (0.77-1.41)	102 (36)	2.07 (1.68-2.55)	1.44 (1.15-1.81)	32 (11)	1.36 (0.95-1.94)	1.12 (0.78-1.61)
New Diuretic Rx (N=44)	≤5[b]	0.67 (0.21-2.19)	0.75 (0.23-2.47)	≤5[b]	0.88 (0.40-1.93)	1.96 (0.92-4.21)	6 (14)	0.73 (0.18-2.93)	1.56 (0.39-6.30)
Diuretic Dose Increase (N=99)	21 (21)	1.71 (1.11-2.64)	1.45 (0.94-2.26)	41 (41)	2.67 (1.96-3.64)	1.58 (1.16-2.14)	17 (17)	2.29 (1.42-3.71)	1.78 (1.09-2.91)
New SPS Rx (N=78)	≤5[b]	1.60 (0.74-3.45)	1.16 (0.53-2.52)	8 (10)	1.60 (0.84-3.07)	0.99 (0.57-1.72)	≤5[b]	0.59 (0.09-3.94)	0.74 (0.10-5.28)

For the RAASi discontinuation group, patients were censored upon restart of a RAASi. For all other interventions, patients were censored if there were no refills of the intervention medication within the prescription period plus an additional 50% of time. Abbreviations: CI, confidence interval; HR, hazard ratio; K^+, potassium; RAASi, renin-angiotensin-aldosterone system inhibitor; Rx, prescription; SPS, sodium polystyrene sulfonate.

[a] Models adjusted for: demographics (age, sex, income quintile, rural locale, residence in a long-term care facility), pre-existing comorbid illnesses (coronary artery disease, myocardial infarction, coronary artery bypass graft, congestive heart failure, atrial fibrillation/flutter, stroke, peripheral vascular disease, venous thromboembolism, hypertension, diabetes mellitus, chronic liver disease, and major cancer; within previous five years), baseline eGFR category (<30, 30-60, and >60 mL/min/1.73m^2), baseline serum potassium, medication use (non-steroidal anti-inflammatory drugs [NSAIDs], beta-blockers, statins, and antiplatelet agents; within previous 120 days), and health service utilization (number of hospitalizations and emergency room visits, any nephrology or cardiology visits; within previous one year).

[b] In accordance with ICES privacy policies, cell sizes less than or equal to five cannot be reported.

Supplemental Figure 1: One-year cumulative incidence of recurrent hyperkalemia (serum potassium ≥5.8 mEq/L). The order of the intervention groups are listed from highest to lowest in regard to cumulative incidence of recurrent hyperkalemia over the one-year follow-up period. The numbers listed in the table represent the number of patients in each group remaining at risk in each intervention group at 60-day intervals throughout the one-year follow-up period. RAASi, renin-angiotensin-aldosterone system inhibitor; Rx, prescription; SPS, sodium polystyrene sulfonate.



Diuretic Dose Increase	**99**	**88**	**85**	**79**	**72**	**65**	**61**
New SPS Rx	78	75	69	65	59	58	51
New Diuretic Rx	44	39	38	37	35	35	34
RAASi Dose Decrease	284	265	248	234	222	211	203
No Intervention	4060	3816	3618	3453	3315	3202	3055
RAASi Discontinuation	1211	1150	1098	1058	1030	1001	957

Supplemental Figure 1