ORIGINAL RESEARCH

Real-World Associations of Renin–Angiotensin–Aldosterone System Inhibitor Dose, Hyperkalemia, and Adverse Clinical Outcomes in a Cohort of Patients With New-Onset Chronic Kidney Disease or Heart Failure in the United Kingdom

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Background—Dosing of renin–angiotensin–aldosterone system inhibitors (RAASi) may be modified to manage associated hyperkalemia risk; however, this approach could adversely affect cardiorenal outcomes. This study investigated real-world associations of RAASi dose, hyperkalemia, and adverse clinical outcomes in a large cohort of UK cardiorenal patients.

Methods and Results—This observational study included RAASi-prescribed patients with new-onset chronic kidney disease (n=100 572) or heart failure (n=13 113) first recorded between January 2006 and December 2015 in Clinical Practice Research Datalink and linked Hospital Episode Statistics databases. Odds ratios associating hyperkalemia and RAASi dose modification were estimated using logistic generalized estimating equations with normal (<5.0 mmol/L) serum potassium level as the reference category. Patients with serum potassium ≥5.0 mmol/L had higher risk of RAASi down-titration (adjusted odds ratios, chronic kidney disease: 1.79 [95% CI, 1.64–1.96]; heart failure: 1.33 [95% CI, 1.08–1.62]). Poisson models were used to estimate adjusted incident rate ratios of adverse outcomes based on total RAASi exposure (<50% and ≥50% of the guideline-recommended RAASi dose). Incidence of major adverse cardiac events and mortality was consistently higher in the lower dose group (adjusted incident rate ratios: chronic kidney disease: 5.60 [95% CI, 5.29–5.93] for mortality and 1.60 [95% CI, 1.55–1.66] for nonfatal major adverse cardiac events; heart failure: 7.34 [95% CI, 6.35–8.48] for mortality and 1.85 [95% CI, 1.71–1.99] for major adverse cardiac events).

Conclusions—The results of this real-world analysis highlight the potential negative impact of suboptimal RAASi dosing and the need for strategies that allow patients to be maintained on appropriate therapy, avoiding RAASi dose modification or discontinuation. **(*J Am Heart Assoc*. 2019;8:e012655. DOI: 10.1161/JAHA.119.012655.)**

Key Words: chronic kidney disease • heart failure • hyperkalemia • major adverse cardiac event • renin–angiotensin system

The renin–angiotensin–aldosterone system (RAAS) plays a key role in the regulation of blood volume, blood pressure, and cardiovascular function.[1] Modification of the RAAS through the use of RAAS inhibitors (RAASi), such as angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), and mineralocorticoid receptor antagonists (MRAs), is an important therapeutic option for the treatment of numerous cardiorenal conditions, reducing progression of chronic kidney disease (CKD), improving heart function and reducing cardiovascular morbidity and mortality.[2–8] However, RAASi use is known to reduce potassium (K^+) excretion and increase the risk of hyperkalemia in an already vulnerable population.[9,10]

Hyperkalemia is a potentially life-threatening electrolyte imbalance, defined as a serum/plasma K^+ level above the normal physiological range of 3.5 to 5.0 mmol/L,[11] that can induce electrophysiological disturbances, potentially leading to cardiac arrhythmias, cardiac arrest, and sudden death.[12–14]

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Accompanying Data S1, Tables S1 through S9 and Figures S1 through S3 are available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.119.012655

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Clinical Perspective

What Is New?

- This study aimed to estimate real-world associations of renin–angiotensin–aldosterone system inhibitor (RAASi) dose, hyperkalemia, and adverse clinical outcomes in a large cohort of UK patients with new-onset chronic kidney disease or heart failure.
- Underprescribing of RAASi relative to guideline-recommended dosing was ubiquitous among the study population and increased following hyperkalemia events.
- The incidence of major adverse cardiac events and mortality was consistently higher in patients who were underprescribed RAASi (ie, receiving <50% of the recommended dose over the majority of their follow-up).

What Are the Clinical Implications?

- Results of this study emphasize the potential negative impact of suboptimal RAASi dosing and, consequently, the need for strategies that allow patients to be maintained on appropriate therapy, avoiding RAASi dose modification or discontinuation.
- We propose that European Society of Cardiology–recommended RAASi doses for patients with heart failure may be generalizable to chronic kidney disease patients in the absence of chronic kidney disease–specific recommendations.

The long-term management of serum K^+ often requires down-titration or discontinuation of RAASi, an approach supported by UK clinical practice guidelines: the National Institute for Health and Care Excellence (NICE) recommends not offering RAASi to CKD patients whose pretreatment serum K^+ is >5.0 mmol/L and discontinuing them in patients whose serum K^+ reaches ≥6.0 mmol/L,[6] whereas guidelines from the UK Renal Association advocate cautious use or avoidance of drugs that impair K^+ elimination (including RAASi) and recommend discontinuation following a hyperkalemia episode.[15] In routine clinical practice, underdosing of RAASi has been found to be common among both heart failure (HF)[16–19] and CKD[19] patients, with RAASi down-titration or discontinuation following 22% to 47% of hyperkalemia events in cardiorenal patients.[19,20] RAASi down-titration or discontinuation in these patients has been shown to be associated with adverse clinical outcomes, including death.[16,18,19]

The link between RAASi use and hyperkalemia, and evidence of poor outcomes associated with suboptimal RAASi dosing have both been reported previously.[16–18,20] However, the relationships of RAASi dose, hyperkalemia, and clinical outcomes in cardiorenal patients have not been fully described. Nevertheless, outcomes in RAASi-treated patients are of high potential interest to cardiologists, nephrologists, general practitioners, and the general medical community, given the widespread applications of RAASi in cardiorenal medicine. Our study aimed to address this evidence gap by estimating real-world associations of RAASi dose, hyperkalemia, and adverse clinical outcomes in a large cohort of UK patients with new-onset CKD or HF. More specifically, the study addressed 2 objectives: to investigate the associations between the incidence of hyperkalemia and changes to RAASi dose (down-titration or discontinuation) and to assess real-world RAASi dosing and its association with adverse clinical outcomes.

Methods

Because of the sensitive nature of the data collected for this study, requests to access the data set by qualified researchers trained in human subject confidentiality protocols may be sent to the Clinical Practice Research Datalink (CPRD) at enquiries@cprd.com.

Study Population

Adults (aged ≥18 years) with new-onset HF or nondialysis CKD stage ≥3 who were prescribed RAASi treatment between January 1, 2006, and December 31, 2015, were included in the study. RAASi considered included specific ACEIs, ARBs, and MRAs for which dosage was recommended by the European Society of Cardiology (ESC) 2016 guidelines for the treatment of HF[3]; recommended dosage was applied to both HF and CKD patients, given the lack of specific guidelines on RAASi dosing in CKD. For HF patients, no information of left ventricular ejection fraction was available.

Patient data were obtained from the CPRD—a source of longitudinal, coded, anonymized electronic health records from a UK-wide network of >1100 primary care practices[21] considered to be broadly representative of patients within the United Kingdom. The database includes information on >10 million currently registered patients, with linked secondary care data from Hospital Episode Statistics (HES) available for a subset of patients from participating practices in England.[21,22]

Each patient's follow-up period was defined as time from the date of their first RAASi prescription following the initial CKD or HF record (or first CKD or HF record date for those not on RAASi) during the study period until death, loss to follow-up, or end of the study, whichever occurred first. CKD was defined as (1) a READ code for CKD stage ≥3, (2) an *International Classification of Diseases, Tenth Revision* (*ICD-10*) code for CKD stage ≥3 obtained from HES data linked to the CPRD, or (3) an estimated glomerular filtration rate <60 mL/min per 1.73 m^2. HF was defined as (1) a READ code for HF or (2) an *ICD-10* code for HF obtained from HES data linked to the CPRD. The nature of the first event recorded during the study period (CKD or HF)

determined patient classification to the respective cohorts. Patients were excluded from the study if they had a history of CKD or HF recorded within the 5 years before the study period (ie, between January 1, 2001, and December 31, 2005) or if information on treatment dose received was inadequate. In addition, CKD patients were excluded if their first CKD event during the study period was dialysis or a kidney transplant. Patient characteristics were described at baseline, that is, at the time of each patient's first RAASi prescription after their CKD or HF event. Rather than relying solely on measurements taken on the baseline date, a look-forward period of 12 months was used for baseline patient characteristics; the measurement taken closest to the baseline date within a 12-month window after that date was used as the baseline value.

The study was approved by the UK Independent Scientific Advisory Committee for Medicines and Healthcare Products Regulatory Agency database research on December 15, 2016 (study protocol 16_223R). Informed consent from individual patients was not required.

Statistical Analysis

All statistical analyses were performed using R v3.4.2,[14] with the exception of the multinomial logistic regression model for discontinuation and down-titration of RAASi, which was performed in SAS v9.4.

RAASi down-titration was defined as a reduction in RAASi dose between consecutive prescriptions with a gap of <90 days between the end of one prescription (expected end based on prescribing date, dosing strategy, and number of tablets) and start of the next. Treatment discontinuation was defined by the cessation of RAASi prescriptions or a >90-day interval between consecutive prescriptions for the same therapy. A multinomial multivariable logistic regression model was used to estimate adjusted odds ratios (ORs) of RAASi down-titration and discontinuation, comparing patients with and without hyperkalemia (serum K^+ ≥5.0 versus <5.0 mmol/L). Serum K^+ thresholds of ≥5.5 mmol/L and ≥6.0 mmol/L were investigated in sensitivity analyses.

When estimating associations between RAASi dose and death (all-cause mortality) and nonfatal MACE (a composite of arrhythmia, HF, myocardial infarction, and stroke[23]), patient follow-up was separated into quarterly time windows, and only those windows spent on RAASi treatment were included in the analysis. Mean RAASi dose within each quarter was calculated as the mean dose across all therapies within each quarter, weighted by the proportion of time within each quarter that a patient was on each therapy (calculated as specified in Data S1 and Figure S1). Crude event rates were calculated per 1000 patient-years of exposure time stratified by dose. Cumulative incidence curves were fitted using Cox models adjusted using baseline characteristics, stratified by patients who spent the majority of their follow-up (defined at ≥75% of quarters) on <50% or ≥50% of ESC guideline-recommended RAASi dose.[3]

Adjusted incident rate ratios (IRRs) were used to further explore associations between adverse outcomes and RAASi dose within time-updated intervals, comparing patients on <50% and ≥50% of ESC guideline-recommended RAASi dose. IRRs were derived from Poisson regression models estimated by generalized estimating equations to align with a prior publication by Furuland et al,[24] which described the development of risk equations to predict the risk of adverse clinical outcomes using time-varying serum K^+ levels in CKD patients from the CPRD. Additional covariates were included to control for patient characteristics and clinical histories (eg age, sex, smoking status, clinical history, medication use, and laboratory values). Variable reduction, which minimizes the number of covariates included in a statistical model while maintaining power, was initially performed by the LASSO (least absolute shrinkage and selection operator) method, with final variable selection being informed by clinical interpretability and the quasi information criterion.

Multiple imputation[25,26] and last observation carried forward were used to accommodate missing clinical measurements. Five imputed data sets were produced, and model coefficients and their standard errors (SEs) were pooled across data sets based on Rubin Rules,[27] to capture the variance of the coefficients both within and between the imputed data sets. Multiple imputation was performed on all clinical variables with all candidate covariates and outcome variables from the analysis models, using the chained equations method, as implemented in the R package "mice."[28] A schematic of the multiple imputation process is presented in Figures S2 and S3. The performance of missing data entry using multiple imputation was verified by performing a sensitivity analysis using a 3-month (data not shown) as opposed to 12-month (Table S1) look-forward period for baseline patient characteristics. Although the percentage of missing baseline data was considerably higher with the shorter look-forward period, the model results changed very little (data not shown), suggesting that imputation methods were appropriate and the proportion of missing data did not substantially affect the results of the analysis.

Further details surrounding the modeling methodology are outlined in Data S1, and detailed outputs of the model are listed in Tables S2 through S7.

P.M. and D.A. had full access to all the data in the study and take responsibility for its integrity and the data analysis.

Results

Baseline Patient Disposition

Data for 191 964 CKD patients and 21 334 HF patients were identified: of these, 14 132 CKD and 996 HF patients were

excluded because no ESC-recommended[3] dose was available for their received treatments; a further 6252 CKD and 1162 HF patients were excluded because of missing or unusable RAASi dose information. Patients who did not receive any RAASi therapy over the follow-up period (71 008 CKD and 6063 HF patients, respectively, hereby referred to as *non-RAASi*) were included in some analyses for comparative purposes. This resulted in final RAASi cohort sizes of 100 572 CKD and 13 113 HF patients (Figure 1). More details on patient attrition (Table S8) and missing data are provided in Data S1, and baseline patient characteristics of the HF and CKD cohorts stratified by ESC-recommended dose are listed in Table 1. In addition, baseline characteristics were compared between the RAASi cohort and the patients who were excluded from the study because of receiving a medication for which a recommended dose was not specified in the ESC guidelines or because of missing or unusable RAASi dose information; this comparison is provided in Table S9.

RAASi Doses Prescribed During Follow-Up

Frequency of individual RAASi use and the number of prescriptions >50% of the ESC guideline-recommended dose for both cohorts are shown in Table 2. ACEIs were the most commonly prescribed RAASi type among both CKD (76.4%) and HF (73.5%) patients. ARBs were more frequently prescribed in CKD than HF patients (32.1% versus 25.1%), whereas the reverse was observed for MRAs (9.6% versus 43.0%). Across all RAASi, ramipril was most frequently prescribed (48.7% of CKD patients and 60.0% of HF patients). Nearly all MRA prescriptions (91.2% and 90.5% for the CKD and HF cohorts, respectively) included doses >50% of the guideline-recommended dose, compared with just over a third of ARB prescriptions (39.8% and 35.1% for the CKD and HF cohorts, respectively). The mean duration of a discontinuation was 867.02 days (SD: 790.01) for the CKD cohort and 690.33 days (SD: 655.55) for the HF cohort.

Associations Between Hyperkalemia and RAASi Titration

Due to the potential causal association between RAASi use and acute kidney injury,[29] prescriptions issued after any renal failure event were excluded from the discontinuation and down-titration analysis. RAASi down-titrations and discontinuations were more common for patients with hyperkalemia compared with those without, and there appeared to be a linear correlation between increasing hyperkalemia severity (ie, higher K^+ threshold used to define hyperkalemia) and the odds of down-titration or discontinuation (Figure 2). At a K^+ threshold of 5.0 mmol/L, 3.5% (95% CI, 3.3–3.7%) of prescriptions in the CKD cohort were down-titrated and 3.7% (95% CI, 3.5–3.9%) were discontinued for patients with serum K^+ above threshold compared with 1.8% (95% CI, 1.8–1.9%) and 2.6% (95% CI, 2.6–2.7%), respectively, for those below threshold. Similar results were observed in the HF cohort, in which 3.7% (95% CI, 3.2–4.2%) of prescriptions were down-titrated and 3.6% (95% CI, 3.0–4.1%) were discontinued for patients with serum K^+ ≥5.0 mmol/L compared with 2.9% (95% CI, 2.7–3.2%) and 2.8% (95% CI, 2.6–3.1%), respectively, for those with serum K^+ <5.0 mmol/L. The percentage of discontinued and down-

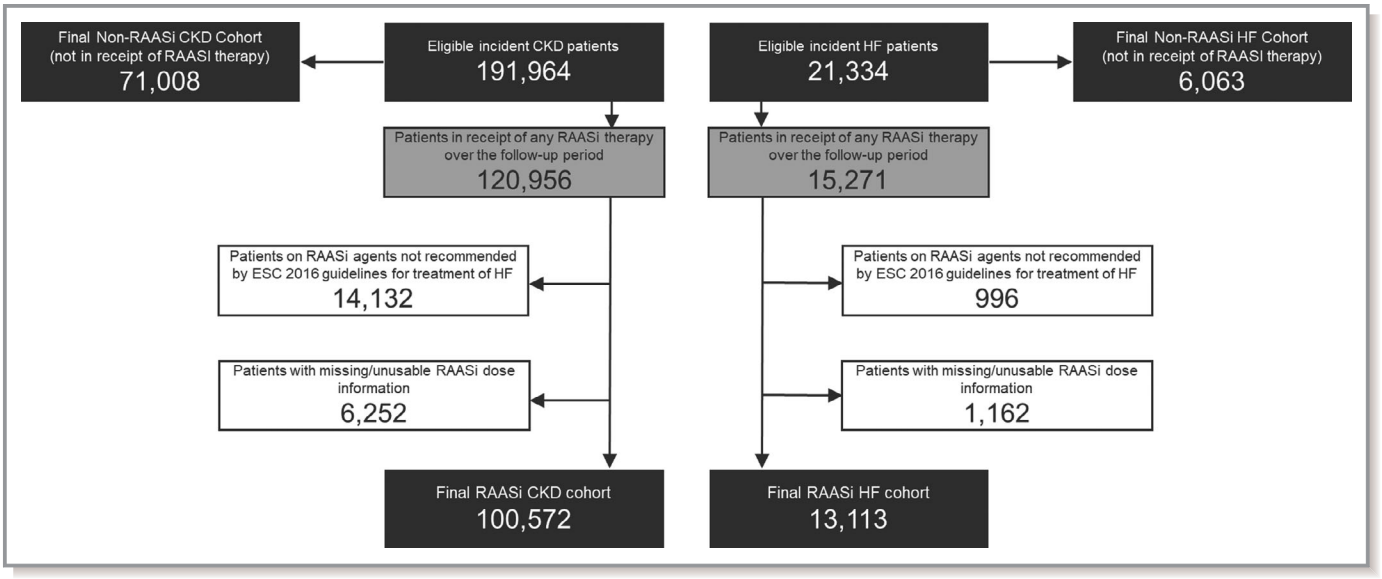

Figure 1. Study participation flow diagram. CKD indicates chronic kidney disease; ESC, European Society of Cardiology; HF, heart failure; RAASi, renin–angiotensin–aldosterone system inhibitors.

Table 1. Baseline Patient Demographics, Clinical Characteristics, and Clinical Histories of the CKD and HF Cohorts Stratified by the RAASi Dose Achieved During the Majority of Patients' Follow-Up Period

Variable	CKD Cohort				HF Cohort			
	RAASi Dose Achieved During the Majority (≥75%) of Follow-Up				RAASi Dose Achieved During the Majority (≥75%) of Follow-Up			
	Non-RAASi (n=71 008)	<50% of ESC-Recommended Dose (n=27 935)*	≥50% of ESC-Recommended Dose (n=26 596)*	*P* Value (ANOVA/χ^2)	Non-RAASi (n=6063)	<50% of ESC-Recommended Dose (n=4568)*	≥50% of ESC-Recommended Dose (n=2758)*	*P* Value (ANOVA/χ^2)
Baseline† patient demographics and clinical characteristics								
Age, y, mean (SD)	71.77 (14.20)	74.84 (10.79)	71.43 (10.36)	<0.01‡	74.97 (15.83)	75.5 (12.48)	68.93 (12.74)	<0.01‡
Female	46 320 (65.22)	16 492 (59.04)	14 776 (55.56)	<0.01‡	3007 (49.59)	2015 (44.11)	906 (32.85)	<0.01‡
Current smoker	10 599 (14.92)	3681 (13.18)	3705 (13.93)	<0.01‡	702 (11.58)	807 (17.67)	582 (21.10)	<0.01‡
BMI, kg/m^2, mean (SD)	27.02 (5.59)	28.28 (5.69)	29.80 (5.88)	<0.01‡	26.49 (6.90)	27.49 (6.42)	29.73 (6.66)	<0.01‡
SBP, mm Hg, mean (SD)	134.33 (18.36)	138.58 (19.92)	143.45 (19.90)	<0.01‡	128.17 (20.75)	125.91 (20.70)	132.98 (21.92)	<0.01‡
eGFR, mL/min/1.73 m^2, mean (SD)	51.43 (8.47)	51.23 (10.45)	51.98 (8.65)	<0.01‡	63.38 (19.52)	64.7 (17.74)	67.75 (15.40)	<0.01‡
Serum potassium, mEq/L, mean (SD)	4.44 (0.53)	4.49 (0.52)	4.49 (0.51)	<0.01‡	4.28 (0.60)	4.42 (0.55)	4.42 (0.51)	<0.01‡
Serum phosphorus, mEq/L, mean (SD)	1.14 (1.00)	1.15 (1.59)	1.11 (0.20)	0.18	1.17 (0.26)	1.16 (0.23)	1.15 (0.21)	0.46
Clinical history within 5 y before initial CKD/HF diagnosis								
Diabetes mellitus	5234 (7.37)	4410 (15.79)	5843 (21.97)	<0.01‡	715 (11.79)	637 (13.94)	524 (19.00)	<0.01‡
MI	872 (1.23)	1467 (5.25)	1090 (4.10)	<0.01‡	234 (3.86)	532 (11.65)	388 (14.07)	<0.01‡
PVD	1059 (1.49)	749 (2.68)	771 (2.90)	<0.01‡	121 (2.00)	159 (3.48)	83 (3.01)	<0.01‡
Stroke	3835 (5.40)	1817 (6.50)	1426 (5.36)	<0.01‡	352 (5.80)	329 (7.20)	135 (4.89)	0.01‡
Arrhythmia	4315 (6.08)	2663 (9.53)	2020 (7.60)	<0.01‡	830 (13.69)	1144 (25.04)	651 (23.60)	<0.01‡
CPD	6199 (8.73)	2818 (10.09)	2526 (9.50)	<0.01‡	562 (9.27)	721 (15.78)	398 (14.43)	<0.01‡
Metastatic tumor	1640 (2.31)	599 (2.14)	508 (1.91)	<0.01‡	89 (1.47)	93 (2.04)	50 (1.81)	0.08
Rheumatic disease	2307 (3.25)	942 (3.37)	732 (2.75)	<0.01‡	126 (2.08)	135 (2.96)	68 (2.47)	0.02‡
Peptic ulcer	568 (0.80)	239 (0.86)	211 (0.79)	0.64	55 (0.91)	54 (1.18)	23 (0.83)	0.24
Cancer	7074 (9.96)	2513 (9.00)	2068 (7.78)	<0.01‡	516 (8.51)	527 (11.54)	220 (7.98)	<0.01‡
Baseline† medication usage								
β-Blockers	11 332 (15.96)	8737 (31.28)	8864 (33.33)	<0.01‡	999 (16.47)	2636 (57.71)	1877 (68.06)	<0.01‡
Statins	19 163 (26.98)	15 562 (55.71)	15 734 (59.16)	<0.01‡	1040 (17.15)	2354 (51.53)	1731 (62.76)	<0.01‡
Bronchodilators	7329 (10.32)	3377 (12.09)	2608 (9.81)	<0.01‡	727 (11.99)	960 (21.02)	474 (17.19)	<0.01‡
Diuretics	16 736 (23.57)	12 911 (46.22)	13 998 (52.63)	<0.01‡	2001 (33.00)	3691 (80.80)	2117 (76.76)	<0.01‡
NSAIDs	9589 (13.50)	2441 (8.74)	2535 (9.53)	<0.01‡	283 (4.67)	217 (4.75)	131 (4.75)	0.97

Continued

Table 1. Continued

Variable	CKD Cohort				HF Cohort			
	RAASi Dose Achieved During the Majority (≥75%) of Follow-Up				RAASi Dose Achieved During the Majority (≥75%) of Follow-Up			
	Non-RAASi (n=71 008)	<50% of ESC-Recommended Dose (n=27 935)*	≥50% of ESC-Recommended Dose (n=26 596)*	*P* Value (ANOVA/χ^2)	Non-RAASi (n=6063)	<50% of ESC-Recommended Dose (n=4568)*	≥50% of ESC-Recommended Dose (n=2758)*	*P* Value (ANOVA/χ^2)
Calcium channel blockers	11 778 (16.58)	7775 (27.83)	10 547 (39.66)	<0.01‡	627 (10.34)	522 (11.43)	589 (21.36)	<0.01‡
OADs	2869 (4.04)	3226 (11.55)	4186 (15.74)	<0.01‡	226 (3.73)	450 (9.85)	392 (14.21)	<0.01‡
Insulin	765 (1.08)	795 (2.85)	1088 (4.09)	<0.01‡	61 (1.01)	109 (2.39)	93 (3.37)	<0.01‡

Data are shown as n (%) except as noted. ANOVA and χ^2 test were used to evaluate differences between HbA1c groups for continuous and categorical variables, respectively. BMI indicates body mass index; CKD, chronic kidney disease; CPD, cardiopulmonary disease; eGFR, estimated glomerular filtration rate; ESC, European Society of Cardiology; HF, heart failure; MI, myocardial infarction; OADs, oral antidiabetics; PVD, peripheral vascular disease; RAASi, renin–angiotensin–aldosterone system inhibitors; SBP, systolic blood pressure.
*The numbers of patients at <50% and ≥50% of the recommended dose do not add up to the total cohort size because patients who spent most of their time on 0% dose and those who do not have a clear majority of time spent at a given dose level are not shown in the table but are included in the total cohort.
†Baseline for RAASi patients is time of each patient's first RAASi prescription after their CKD or HF event and for non-RAASi patients is time of first CKD or HF event.
‡*P*<0.05.

titrated prescriptions increased with increasing K^+ threshold used to define hyperkalemia (Figure 2).

After adjusting for covariates, a positive, statistically significant association was found between hyperkalemia and RAASi down-titration (Figure 3). Adjusted ORs for down-titration comparing patients with serum K^+ ≥5.0 mmol/L and those with K^+ levels below this threshold (reference category) were 1.79 (95% CI, 1.64–1.96) in the CKD cohort and 1.33 (95% CI, 1.08–1.62) in the HF cohort, increasing to 4.32 (95% CI, 3.50–5.32) and 3.19 (95% CI, 1.86–5.47) in the CKD and HF cohorts, respectively, at the more severe hyperkalemia threshold of 6.0 mmol/L.

The pattern of estimated associations between RAASi discontinuation and hyperkalemia was similar, although the associations were weaker than for down-titration, and in the HF cohort, CIs around the ORs at different K^+ levels overlapped

Table 2. Guideline-Recommended Doses of RAASi During Follow-Up

Drug	Guideline-Recommended Daily Dose (mg)	CKD Cohort, n (%)			HF Cohort, n (%)		
		Prescriptions	Prescriptions ≥50% Guideline-Recommended Dose	Patients	Prescriptions	Prescriptions ≥50% Guideline-Recommended Dose	Patients
ACEIs	…	2 558 015 (66.81)	1 628 928 (63.68)	76 788 (76.35)	245 524 (54.39)	150 468 (61.28)	9636 (73.48%)
Ramipril	10	1 518 468 (39.66)	1 001 162 (65.93)	48 960 (48.68)	195 053 (43.21)	120 869 (61.97)	7874 (60.05%)
Lisinopril	20	827 171 (21.60)	515 919 (62.37)	24 820 (24.68)	40 869 (9.05)	25 339 (62.00)	1643 (12.53%)
Enalapril maleate	40	198 480 (5.18)	104 383 (52.59)	5461 (5.43)	9160 (2.03)	4048 (44.19)	362 (2.76%)
Captopril	150	13 896 (0.36)	7464 (53.71)	469 (0.47)	442 (0.10)	212 (47.96)	26 (0.20%)
ARBs	…	1 089 808 (28.46)	433 446 (39.77)	32 297 (32.11)	90 935 (20.15)	31 914 (35.10)	3291 (25.10%)
Candesartan cilexetil	32	517 665 (13.52)	181 537 (35.07)	16 526 (16.43)	55 597 (12.32)	19 285 (34.69)	1990 (15.18%)
Losartan K^+	150	473 597 (12.37)	205 895 (43.47)	16 448 (16.35)	27 633 (6.12)	9788 (35.42)	1315 (10.03%)
Valsartan	320	98 546 (2.57)	46 014 (46.69)	3120 (3.10)	7705 (1.71)	2841 (36.87)	271 (2.07%)
MRAs	…	181 199 (4.73)	165 280 (91.21)	9687 (9.63)	114 933 (25.46)	104 021 (90.51)	5640 (43.01%)
Spironolactone	50	168 822 (4.41)	153 765 (91.08)	9252 (9.20)	99 159 (21.97)	88 965 (89.72)	5126 (39.09%)
Eplerenone	50	12 377 (0.32)	11 515 (93.04)	666 (0.66)	15 774 (3.49)	15 056 (95.45)	779 (5.94%)
Total	…	3 829 022	2 227 654 (58.18)	100 572	451 392	286 403 (63.45)	13 113

ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; CKD, chronic kidney disease; HF, heart failure; MRA, mineralocorticoid receptor antagonist; RAASi, renin–angiotensin–aldosterone system inhibitors.

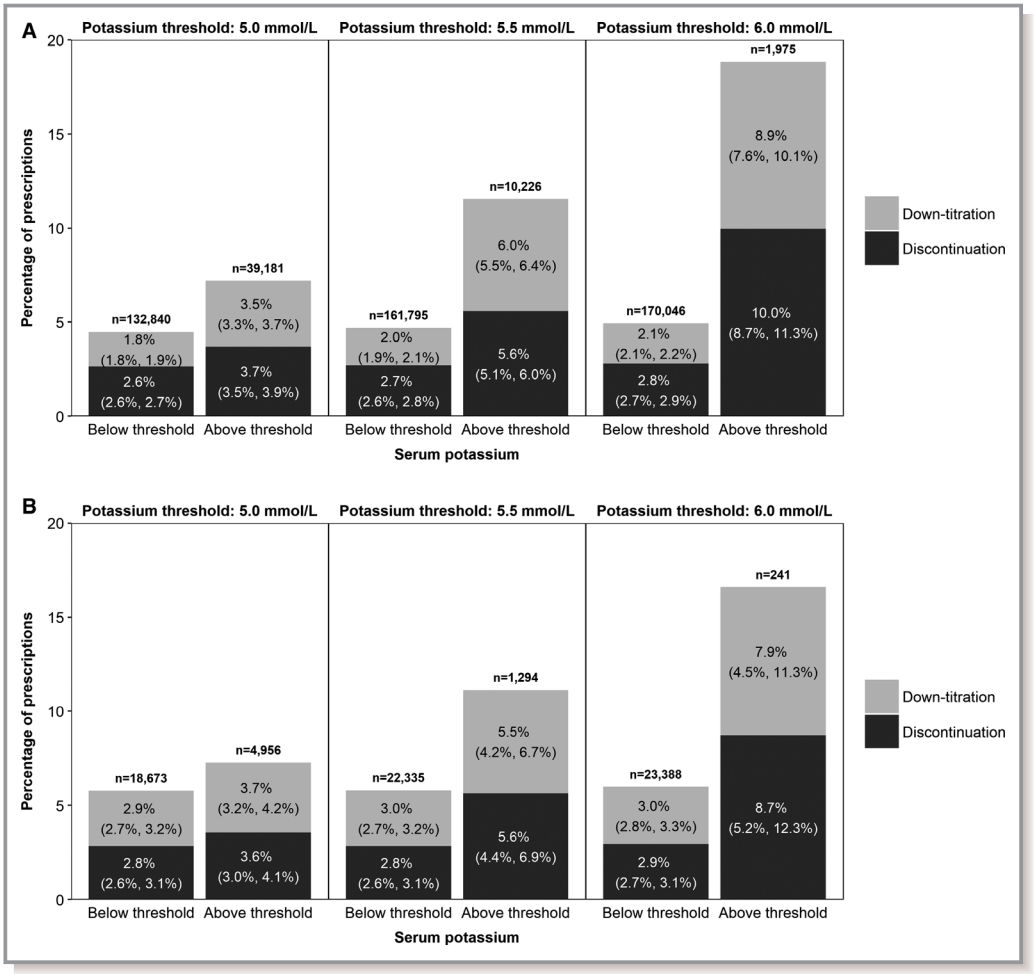

Figure 2. Dose modification of renin–angiotensin–aldosterone system inhibitor prescriptions ending within 7 days of a serum potassium (K^+) measurement, stratified by serum K^+ threshold for CKD patients (**A**) and HF patients (**B**). Percentages of prescriptions that were maintained or up-titrated are not shown; prescription numbers include all prescriptions, regardless of dose. The percentage of down-titrated or discontinued prescriptions is shown on the bars, alongside the 95% CI (in brackets).

(Figure 3). Comparing patients with serum K^+ ≥5.0 mmol/L with those below the threshold, adjusted ORs for discontinuation were 1.27 (95% CI, 1.17–1.38) in the CKD cohort and 1.13 (95% CI, 0.92–1.40) in the HF cohort. When a K^+ threshold of ≥6.0 mmol/L was considered, adjusted ORs for discontinuation increased to 2.90 (95% CI, 2.33–3.60) and 2.74 (95% CI, 1.53–4.89) in the CKD and HF cohorts, respectively.

Associations Between RAASi Dosing and Adverse Clinical Outcomes

The patterns of Cox-adjusted cumulative incidence of mortality from baseline were similar between CKD and HF cohorts: mortality was consistently lower in patients who spent most of their follow-up on ≥50% of the ESC guideline-recommended dose compared with those mostly receiving <50% of the recommended dose, whereas patients who did not receive any RAASi therapy over the follow-up period had a slightly lower incidence of mortality than patients on <50% dose (Figure 4). In both CKD and HF cohorts, cumulative incidence of nonfatal major adverse cardiac events (MACE) was lowest in non-RAASi patients and highest in patients taking <50% of the guideline-recommended dose.

Event rates for all-cause mortality and MACE in the CKD and HF cohorts stratified by the dose received within the interval where the event occurred are summarized in Table 3. In the CKD cohort, mortality occurred at a rate of 57.7 (95% CI, 56.6–58.9) deaths per 1000 patient-years for patients on <50% of guideline-recommended dose compared with 7.2 (95% CI, 6.8–7.6) deaths per 1000 patient-years for those prescribed ≥50% of the dose (Table 3). The corresponding rates of MACE were 130.4 (95% CI, 128.7–132.1) and 73.0 (95% CI, 71.8–74.2) events per 1000 patient-years, respectively. Similar patterns were observed in the HF cohort but

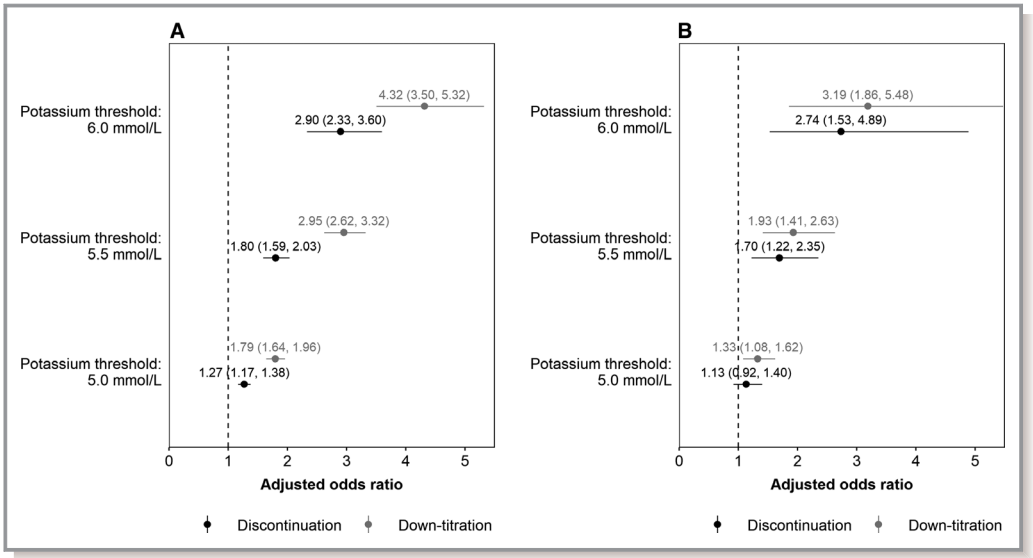

Figure 3. Adjusted odds ratios (and 95% CIs) for dose modification of renin–angiotensin–aldosterone system inhibitors, stratified by serum potassium (K^+) threshold for CKD patients (**A**) and HF patients (**B**). An odds ratio of 1 (dotted line) indicates the odds of discontinuation or down-titration under the defined threshold.

with even more pronounced differences between patients on <50% and ≥50% of guideline-recommended RAASi dose: mortality rates were 141.7 (95% CI, 136.4–147.3) compared with 12.5 (95% CI, 10.9–14.4) deaths per 1000 patient-years, respectively, and MACE rates were 290.4 (95% CI, 282.6–298.3) versus 148.5 (95% CI, 142.7–154.5) events per 1000 patient-years, respectively.

After adjusting for covariates, statistically significant inverse associations were estimated between mean RAASi dose and the incidence of mortality and MACE (Table 3). In the CKD cohort, adjusted IRRs comparing patients on <50% of the recommended dose with those on >50% were 5.6 (95% CI, 5.3–5.9) for mortality and 1.6 (95% CI, 1.6–1.7) for MACE. In the HF cohort, larger adjusted IRRs of 7.3 (95% CI, 6.3–8.5) for mortality and 1.8 (95% CI, 1.7–2.0) for MACE were estimated.

Discussion

This study investigated the associations between (1) hyperkalemia (a potential adverse effect of RAASi treatment) and dosing of RAASi in CKD and HF patients in the United Kingdom and (2) suboptimal RAASi dosing and adverse clinical outcomes, including all-cause mortality and nonfatal MACE.

RAASi dosing during the study follow-up period was frequently suboptimal when compared with the ESC guidelines,[3] with 41.8% of prescriptions for CKD patients and 36.5% for HF patients including less than half of the guideline-recommended dose. This was a particular concern for ARBs and ACEIs, whereas prescribers appeared to be more adherent to the ESC guidelines regarding MRA doses.

RAASi dose down-titrations and discontinuations during the study follow-up period were rare, although the odds of discontinuation and down-titration were higher in patients with hyperkalemia than those without. This became more prominent as the K^+ threshold used to define hyperkalemia increased.

Over 10 years, cumulative incidence of death was consistently highest in both CKD and HF patients receiving <50% of the ESC guideline-recommended dose, followed by those receiving no RAASi, and was lowest for patients who spent most of their follow-up on ≥50% of the ESC-recommended dose. The cumulative incidence of nonfatal MACE, however, showed a different pattern from mortality in that it was lowest in both CKD and HF patients receiving no RAASi, followed by patients receiving ≥50% of the recommended dose and highest in patients receiving <50% of the recommended dose. A possible explanation for this finding is that the use of RAASi reduces the severity of MACE events, so the majority of MACE in non-RAASi patients would be fatal, and this study considered only nonfatal MACE. RAASi use has been associated with lower severity of some MACE events, including myocardial infarction[30] and stroke,[31,32] although the evidence for the latter appears inconclusive.[33] The hypothesis that patients not in receipt of RAASi are more likely to experience severe, fatal MACE is plausible given the excess mortality risk observed in these patients in the present study. However, it is also possible that the non-RAASi cohort includes a mixture of patients (1) who are well-managed on other medications; (2) who have HF with preserved ejection fraction, which has no approved therapy that has been demonstrated to reduce mortality and thus may have no firm indication for RAASi treatment; and (3) who are at high risk of hyperkalemia-related complications so that RAASi is contraindicated. The potential heterogeneity of this group warrants caution when

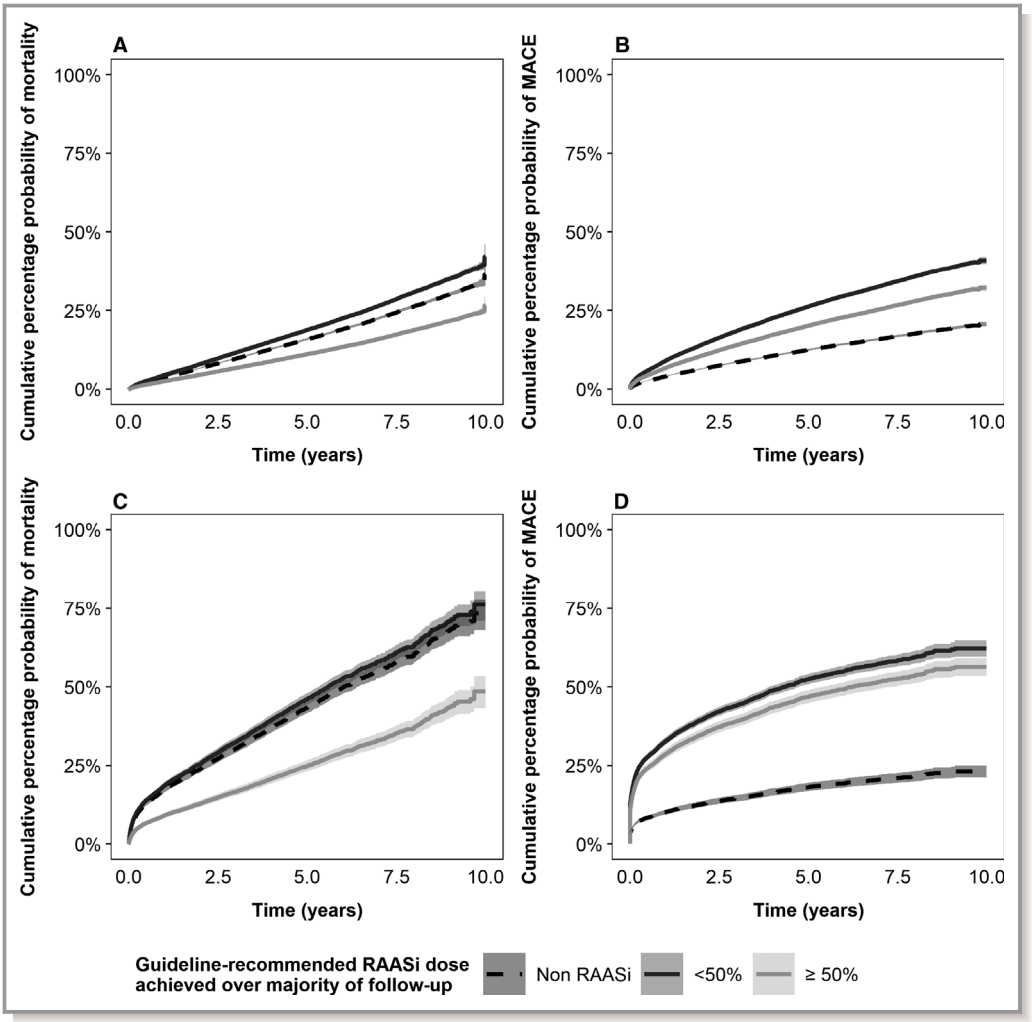

Figure 4. Cox models (and 95% CIs) of cumulative incidence of mortality for CKD patients (**A**), major adverse cardiac events (MACE) for CKD disease patients (**B**), mortality for HF patients (**C**), and MACE for HF patients (**D**). Each graph compares 3 patient groups: (1) those who did not receive any RAASi therapy during the follow-up and patients who spent the majority of their follow-up on either (2) <50% or (3) ≥50% of the European Society of Cardiology guideline-recommended dose. RAASi indicates renin–angiotensin–aldosterone system inhibitors.

interpreting the results observed in these patients. Independent of RAASi dose received, recent history of MACE significantly increased the incidence of mortality in both the CKD and HF cohorts (Tables S4 and S5, respectively).

Among patients receiving RAASi, doses >50% of the ESC guideline-recommended dose were associated with a consistently lower cumulative incidence of mortality and MACE compared with doses <50%, supporting the beneficial effects of adherence to prescribing guidelines concerning dosing. Indeed, in the CKD cohort, suboptimal RAASi dosing within a given quarter was associated with significantly higher odds of death and MACE occurring within the same quarter, although the association was more pronounced for death than MACE (IRR: 5.60 and 1.60, respectively). HF patients receiving suboptimal RAASi dosing in a given quarter were at 7.34 times higher risk of imminent death than those receiving ≥50% of the recommended dose, but the relationship was, again, less prominent for MACE (IRR: 1.85). This result may indicate that RAASi activation is a more important driver of mortality in HF patients than in CKD patients.

We aimed to expand on previous studies, which have investigated either associations between K^+ levels and RAASi dosing or RAASi dosing and patient outcomes,[16–18,20] providing a fuller picture of the real-world links among hyperkalemia, RAASi dose, and adverse clinical outcomes. Earlier studies typically featured relatively small patient samples, short follow-up periods, and lack of adjustment for patient and disease characteristics that could confound the relationship of RAASi dose, serum K^+, and patient outcomes. In contrast, this study included a large cohort of UK patients with new-onset CKD or

Table 3. Incidence of Mortality and MACE Stratified by RAASi Dose Within the Interval When These Events Occurred

Cohort	Outcome	RAASi Dose (of ESC Guideline-Recommended)	Event Count	Rate Per 1000 Patient-Years (95% CI)	Adjusted IRR (95% CI)
CKD	Mortality	<50%	10 506	57.73 (56.63–58.85)	5.59 (5.28–5.92)
		≥50%	1377	7.17 (6.80–7.56)	Reference
	MACE	<50%	23 726	130.38 (128.72–132.05)	1.61 (1.56–1.66)
		≥50%	14 004	72.95 (71.75–74.17)	Reference
HF	Mortality	<50%	2601	141.74 (136.35–147.30)	7.33 (6.34–8.47)
		≥50%	206	12.53 (10.87–14.36)	Reference
	MACE	<50%	5328	290.35 (282.61–298.26)	1.86 (1.72–2.00)
		≥50%	2442	148.49 (142.66–154.50)	Reference

CKD, chronic kidney disease; ESC, European Society of Cardiology; HF, heart failure; IRR, incident rate ratio; MACE, major adverse cardiac event; RAASi, renin–angiotensin–aldosterone system inhibitor.

HF, provided up to 10 years of follow-up, and attempted to minimize bias by adjusting for differences in patient clinical and demographic characteristics.

Limitations of the current study arise mainly from its retrospective design. Primarily, the study was able to determine only associations rather than causality between hyperkalemia and changes to RAASi dosing and between RAASi dosing and adverse clinical outcomes. To focus more clearly on discontinuation or down-titration of RAASi associated with hyperkalemia, we excluded from the analysis any RAASi prescriptions issued after a renal failure event, which included both acute kidney injury (that may potentially be caused or exacerbated by RAASi use[29]) and end-stage renal disease. Many covariates available within the CPRD are not routinely collected in National Health Service primary care, which leads to few patients having a complete set of covariates, reflecting the time and organizational constraints imposed on primary care in England. The proportion of missing data is consistent with other publications utilizing the CPRD database[34–36] and therefore can be considered to reflect the patterns of testing in routine primary care. Missing data were filled in using multiple imputation methods that preserve its inherent variability and uncertainty and that are frequently used in research based on clinical databases.[37,38] This approach was favored over including only patients who had a complete set of covariates in the analysis, which would produce a greatly reduced data set and result in bias within the analyses.

Despite the employment of analytical and statistical measures to control for clinically relevant covariates, it is possible that additional factors that were not assessed in this study could have contributed to the observed associations, particularly when considering MACE and mortality, which are likely to arise from multiple causes that may not always be possible to define clearly. Furthermore, there are no published guidelines regarding RAASi dosing in patients with CKD, so recommended therapies and doses were assumed to be the same as those for HF patients. Finally, although the CPRD linked to HES data includes information on primary and secondary care provided to a large and diverse sample of patients, the use of these linked databases as the sole data source renders the study reliant on the accuracy and completeness of CPRD and HES data entry and restricts the population to the UK setting.

Despite the aforementioned limitations, this study provides important real-world data on the characteristics of CKD and HF patients treated with RAASi in the United Kingdom and on the associations of RAASi dose, hyperkalemia, and adverse clinical outcomes. Underprescribing of RAASi was ubiquitous among the study population and increased following hyperkalemia events. The results highlight the potential negative impact of suboptimal RAASi dosing, indicate the generalizability of ESC-recommended RAASi doses in HF to CKD patients, and emphasize the need for strategies that allow patients to be maintained on appropriate therapy, avoiding RAASi dose modification or discontinuation.

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Supplemental Material

Data S1.

Supplementary Methods

Calculation of mean RAASi doses

Each patient's follow-up time was divided into quarters, each consisting of 91.3125 days, and only patient-quarters spent on RAASi were included in the analysis, while intervals of discontinuation were omitted. Mean RAASi dose within each quarter (expressed as percentage of the ESC guideline-recommended dose) was calculated as the mean dose (also expressed as percentage of the ESC guideline-recommended dose for each therapy) across all therapies within each quarter, weighted by proportion of the quarter that the patient was on each therapy. Where a therapy was discontinued during a quarter, a dose of 0 was assumed for that therapy from the date of discontinuation to the end of the interval and included in the quarterly average. Specifically, we compared a patient's dosage within each quarter to the ESC 2016 guidelines [1], as well as partly using each patient's history of RAASi therapy. If a patient had never been prescribed an MRA, it was assumed that MRA treatment was not required. Once a patient was prescribed an MRA, MRA treatment was assumed to be required from then on and treatment discontinuations were considered as described in the manuscript for all other RAASi therapies. The following summarises ESC guidelines on RAASi treatment, as used for the purpose of this analysis:

- ACE inhibitors are recommended in all symptomatic patients with HF with reduced left-ventricular ejection fraction (LVEF), unless contraindicated or not tolerated

- ARBs are recommended only as an alternative in patients intolerant of ACE inhibitors
- MRAs are recommended in all patients symptomatic despite treatment with an ACE inhibitor, who have heart failure with reduced LVEF and their LVEF is ≤35%

In the absence of LVEF data, total target dose prior to initiation of MRA therapy was assumed to be 100% of an ACEi/ARB dose only (i.e. MRA was assumed not to be required). For all periods after initiation on MRA therapy, total target dose was assumed to be 100% of an ACEi/ARB dose + 100% of an MRA dose (i.e. MRA was assumed to be required from this point onwards). An example calculation of the total RAASi dose as a percentage of the guideline-recommended dose is presented in Figure S1. Note, that despite the ESC guidelines recommending ARBs as an alternative to ACE inhibitors in case of intolerance, patients receiving ACE inhibitors and ARBs concomitantly were not excluded from the analyses.

Missing data: Multiple imputation methods

Final estimates of adjusted incidence rate ratios (IRRs) and hazard ratios (HRs) were derived from five multiply imputed datasets, as illustrated in Figure S2. The model coefficients and their standard errors from each of the five imputed datasets were pooled to produce the final set of estimates using Rubin Rules, as described by Carpenter et al[2]. All missing baseline values of clinical variables (where patients did not have a measurement taken at index) were estimated using multiple imputation, with the last observation carried forward (LOCF) method then being applied for time periods between clinical measurements. The application of multiple imputation to

impute missing values in datasets derived from large clinical databases has been explored in other studies and has been shown to provide valid results[3, 4].
Multiple imputation was performed by the method of Chained Equations[5] as implemented in R package mice[6] (Figure S3).

For this study, k=5 completed datasets were produced after performing i=50 iterations for the HF and CKD cohorts (this was sufficient to ensure convergence of the imputations).

The default method used by 'mice' for step (4) in the above algorithm is predictive mean matching (PMM); however, for this study linear regression predictions were used directly due to the low percentage of complete data for some variables. The multiple imputation models included the full set of candidate covariates from the analysis models that were subsequently fitted to the imputed datasets, plus each patient's total follow-up time and their observed number of events (deaths, major adverse cardiovascular events [MACE] and RAASi discontinuation) over the study follow-up period.

All clinical variables except serum potassium and estimated glomerular filtration rate (eGFR) were log transformed prior to fitting imputation models to enforce normality of their distributions. For these variables, a retransformation bias-correction factor was applied to the imputations after they were back-transformed to their original scale.

Sample size and patient attrition

The study cohort was derived from all patients on the Clinical Practice Research Datalink (CPRD) (making use of linked Hospital Episode Statistics [HES] data) aged ≥18 years between 1 January 2006 and 31 December 2015. Patients not in receipt of renin-angiotensin-aldosterone system inhibitor (RAASi) therapies, defined as a composite of specific angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs) and mineralocorticoid receptor antagonists (MRAs) for which a recommended dose is provided by the European Society of Cardiology (ESC) 2016 Guidelines[1], at any point over the duration of the follow-up period were included in some analyses for comparative purposes. Patients who received ESC-recommended RAASi therapy but had no adequate information on treatment dose available were also excluded. Guideline-recommended therapies included 4 ACE-Is (ramipril, lisinopril, enalapril maleate, captopril), 3 ARBs (candesartan cilexetil, losartan potassium and valsartan) and 2 MRAs (spironolactone and eplerenone). Specific inclusion and exclusion criteria for chronic kidney disease (CKD) and heart failure (HF) patients are listed in the manuscript. Table S8 provides details of sample size and patient attrition.

Table S1. Proportion of missing data at baseline for continuous variables in the CKD and HF cohorts.

Variable	CKD cohort			HF cohort		
	RAASi dose achieved during the majority (≥75%) of follow-up			RAASi dose achieved during the majority (≥75%) of follow-up		
	Non-RAASi (n=71,008)	<50% of ESC-recommended dose (n=27,935)†	≥50% of ESC-recommended dose (n=26,596)†	Non-RAASi (n=6,063)	<50% of ESC-recommended dose (n=4,568)†	≥50% of ESC-recommended dose (n=2,758)†
Baseline* patient demographics and clinical characteristics						
BMI (kg/m^2)	44,857 (63.16%)	13,504 (48.34%)	11,164 (41.98%)	5,361 (88.41%)	2,515 (55.06%)	1,056 (38.29%)
SBP (mmHg)	20,105 (28.31%)	1,812 (6.49%)	850 (3.20%)	4,262 (70.28%)	609 (13.33%)	123 (4.46%)
DBP (mmHg)	20,105 (28.31%)	1,812 (6.49%)	850 (3.20%)	4,262 (70.28%)	609 (13.33%)	123 (4.46%)
eGFR (mL/min/1.73m2)	25,681 (36.16%)	11,398 (40.80%)	9,746 (36.64%)	5,558 (91.66%)	2,946 (64.49%)	1,666 (60.41%)
Serum potassium (mEq/L)	11,427 (16.09%)	2,478 (8.87%)	1,796 (6.75%)	4,625 (76.27%)	909 (19.90%)	310 (11.24%)
Serum phosphorus (mEq/L)	54,739 (77.08%)	22,127 (79.21%)	21,583 (81.15%)	5,744 (94.72%)	3,869 (84.70%)	2,330 (84.48%)
Total Cholesterol (mmol/L)	34,271 (48.26%)	8,964 (32.09%)	6,302 (23.70%)	5,347 (88.18%)	2,383 (52.17%)	896 (32.49%)
WBC	22,206 (31.27%)	9,234 (33.06%)	9,323 (35.05%)	4,818 (79.45%)	1,744 (38.18%)	961 (34.84%)

BMI: body mass index; CKD: chronic kidney disease; DBP: diastolic blood pressure; eGFR: estimated glomerular filtration rate; HF: heart failure; RAASi: renin-angiotensin-aldosterone system inhibitors; SBP: systolic blood pressure; WBC: white blood cell count.

*Baseline for RAASi patients is time of each patient's first RAASi prescription after their first CKD/HF event, for non-RAASi patients is time of first CKD/HF event. †The numbers of patients receiving <50% and ≥50% of the recommended dose do not add up to the total cohort size because patients who spent most of their time on 0% dose and those who do not have a clear majority of time spent at a given dose level are not shown in the Table but are included in the total cohort

Table S2. Model output for dose modification of RAASi, stratified by serum K+ threshold for CKD cohort.

Explanatory variable	Outcome	OR	95% lower CI	95% upper CI	P-value
Incidence of down-titration or discontinuation: Hyperkalaemia threshold: 5.0 mmol/L					
Serum potassium: ≥5.0 mmol/L	Down-titration	1.7941	1.6449	1.9568	<.0001
Serum potassium: ≥5.0 mmol/L	Discontinuation	1.2707	1.1710	1.3790	<.0001
Drug type: ARB	Down-titration	0.8142	0.6857	0.9667	0.0189
Drug type: ARB	Discontinuation	1.0566	0.9324	1.1974	0.3874
Drug type: MRA	Down-titration	1.1947	1.0887	1.3110	0.0002
Drug type: MRA	Discontinuation	0.6329	0.5772	0.6940	<.0001
Age (years)	Down-titration	1.0074	1.0031	1.0118	0.0009
Age (years)	Discontinuation	1.0042	1.0003	1.0082	0.0332
Gender at baseline: Male	Down-titration	1.1268	1.0370	1.2245	0.0049
Gender at baseline: Male	Discontinuation	1.0573	0.9822	1.1381	0.1381
Time from baseline (years)	Down-titration	0.9954	0.9790	1.0121	0.5895
Time from baseline (years)	Discontinuation	1.0036	0.9886	1.0189	0.643
Time-updated eGFR: < 15 mL/min/1.73m^2	Down-titration	0.5506	0.2911	1.0415	0.0666
Time-updated eGFR: < 15 mL/min/1.73m^2	Discontinuation	1.6700	1.1067	2.5199	0.0146
Time-updated eGFR: 30 to <45 mL/min/1.73m^2	Down-titration	0.5268	0.4402	0.6304	<.0001
Time-updated eGFR: 30 to <45 mL/min/1.73m^2	Discontinuation	0.5178	0.4433	0.6049	<.0001
Time-updated eGFR: 45 to <60 mL/min/1.73m^2	Down-titration	0.5213	0.4488	0.6055	<.0001
Time-updated eGFR: 45 to <60 mL/min/1.73m^2	Discontinuation	0.4976	0.4362	0.5676	<.0001
Time-updated eGFR: ≥ 60 mL/min/1.73m^2	Down-titration	0.7130	0.6101	0.8332	<.0001
Time-updated eGFR: ≥ 60 mL/min/1.73m^2	Discontinuation	0.6516	0.5672	0.7486	<.0001
Time-updated blood pressure: Low	Down-titration	1.9265	1.7171	2.1614	<.0001
Time-updated blood pressure: Low	Discontinuation	1.2531	1.1217	1.3998	<.0001
Time-updated blood pressure: Normal	Down-titration	1.3356	1.2190	1.4634	<.0001
Time-updated blood pressure: Normal	Discontinuation	1.3454	1.2442	1.4549	<.0001
Time-updated blood pressure: Pre-High	Down-titration	5.6593	3.8225	8.3787	<.0001
Time-updated blood pressure: Pre-High	Discontinuation	1.9398	1.1596	3.2450	0.0116
Concomitant diuretics: Yes	Down-titration	0.7996	0.1101	5.8051	0.8251
Concomitant diuretics: Yes	Discontinuation	0.5597	0.0748	4.1901	0.572
Concomitant NSAIDS: Yes	Down-titration	0.0007	0.0004	0.0014	<.0001
Concomitant NSAIDS: Yes	Discontinuation	2.4010	0.2704	21.3177	0.4318
Concomitant Betablockers: Yes	Down-titration	1.8414	0.5549	6.1106	0.3184
Concomitant Betablockers: Yes	Discontinuation	0.9140	0.2134	3.9158	0.9037
Concomitant RAASi: Yes	Down-titration	1.4096	1.2434	1.5980	<.0001
Concomitant RAASi: Yes	Discontinuation	3.0102	2.7026	3.3528	<.0001
Incidence of down-titration or discontinuation: Hyperkalaemia threshold: 5.5 mmol/L					
Serum potassium: ≥5.5 mmol/L	Down-titration	2.9523	2.6222	3.3240	<.0001
Serum potassium: ≥5.5 mmol/L	Discontinuation	1.8004	1.5937	2.0338	<.0001
Drug type: ARB	Down-titration	0.8082	0.6808	0.9593	0.0149
Drug type: ARB	Discontinuation	1.0540	0.9301	1.1944	0.41
Drug type: MRA	Down-titration	1.1910	1.0851	1.3072	0.0002
Drug type: MRA	Discontinuation	0.6332	0.5775	0.6943	<.0001
Age (years)	Down-titration	1.0077	1.0034	1.0121	0.0005
Age (years)	Discontinuation	1.0044	1.0005	1.0084	0.0266
Gender at baseline: Male	Down-titration	1.1277	1.0376	1.2257	0.0047
Gender at baseline: Male	Discontinuation	1.0559	0.9809	1.1367	0.1485
Time from baseline (years)	Down-titration	0.9961	0.9795	1.0130	0.6481
Time from baseline (years)	Discontinuation	1.0037	0.9887	1.0190	0.6358
Time-updated eGFR: < 15 mL/min/1.73m^2	Down-titration	0.5002	0.2622	0.9542	0.0355
Time-updated eGFR: < 15 mL/min/1.73m^2	Discontinuation	1.5831	1.0383	2.4138	0.0328
Time-updated eGFR: 30 to <45 mL/min/1.73m^2	Down-titration	0.5438	0.4535	0.6522	<.0001
Time-updated eGFR: 30 to <45 mL/min/1.73m^2	Discontinuation	0.5325	0.4555	0.6226	<.0001
Time-updated eGFR: 45 to <60 mL/min/1.73m^2	Down-titration	0.5409	0.4642	0.6303	<.0001
Time-updated eGFR: 45 to <60 mL/min/1.73m^2	Discontinuation	0.5114	0.4478	0.5841	<.0001
Time-updated eGFR: ≥ 60 mL/min/1.73m^2	Down-titration	0.7370	0.6293	0.8631	0.0002

Time-updated eGFR: ≥ 60 mL/min/1.73m^2	Discontinuation	0.6656	0.5788	0.7655	<.0001
Time-updated blood pressure: Low	Down-titration	1.9278	1.7180	2.1633	<.0001
Time-updated blood pressure: Low	Discontinuation	1.2557	1.1239	1.4030	<.0001
Time-updated blood pressure: Normal	Down-titration	1.3324	1.2159	1.4601	<.0001
Time-updated blood pressure: Normal	Discontinuation	1.3466	1.2453	1.4562	<.0001
Time-updated blood pressure: Pre-High	Down-titration	5.4882	3.6607	8.2279	<.0001
Time-updated blood pressure: Pre-High	Discontinuation	1.9224	1.1524	3.2071	0.0123
Concomitant diuretics: Yes	Down-titration	0.7749	0.1056	5.6878	0.802
Concomitant diuretics: Yes	Discontinuation	0.5306	0.0687	4.0987	0.5434
Concomitant NSAIDS: Yes	Down-titration	0.0007	0.0004	0.0013	<.0001
Concomitant NSAIDS: Yes	Discontinuation	2.3570	0.2798	19.8521	0.4303
Concomitant Betablockers: Yes	Down-titration	2.0334	0.6458	6.4025	0.2253
Concomitant Betablockers: Yes	Discontinuation	0.9589	0.2238	4.1087	0.9549
Concomitant RAASi: Yes	Down-titration	1.3978	1.2325	1.5852	<.0001
Concomitant RAASi: Yes	Discontinuation	2.9892	2.6832	3.3301	<.0001
Incidence of down-titration or discontinuation: Hyperkalaemia threshold: 6.0 mmol/L					
Serum potassium: ≥6.0 mmol/L	Down-titration	4.3185	3.5042	5.3219	<.0001
Serum potassium: ≥6.0 mmol/L	Discontinuation	2.8982	2.3343	3.5984	<.0001
Drug type: ARB	Down-titration	0.8069	0.6802	0.9573	0.0139
Drug type: ARB	Discontinuation	1.0536	0.9297	1.1939	0.4135
Drug type: MRA	Down-titration	1.1816	1.0766	1.2969	0.0004
Drug type: MRA	Discontinuation	0.6316	0.5760	0.6925	<.0001
Age (years)	Down-titration	1.0075	1.0032	1.0119	0.0007
Age (years)	Discontinuation	1.0042	1.0003	1.0082	0.0323
Gender at baseline: Male	Down-titration	1.1405	1.0494	1.2396	0.002
Gender at baseline: Male	Discontinuation	1.0591	0.9838	1.1401	0.1268
Time from baseline (years)	Down-titration	0.9989	0.9824	1.0157	0.8956
Time from baseline (years)	Discontinuation	1.0048	0.9898	1.0201	0.5324
Time-updated eGFR: < 15 mL/min/1.73m^2	Down-titration	0.4903	0.2546	0.9441	0.033
Time-updated eGFR: < 15 mL/min/1.73m^2	Discontinuation	1.5142	0.9844	2.3292	0.059
Time-updated eGFR: 30 to <45 mL/min/1.73m^2	Down-titration	0.4866	0.4067	0.5821	<.0001
Time-updated eGFR: 30 to <45 mL/min/1.73m^2	Discontinuation	0.5103	0.4372	0.5957	<.0001
Time-updated eGFR: 45 to <60 mL/min/1.73m^2	Down-titration	0.4981	0.4284	0.5791	<.0001
Time-updated eGFR: 45 to <60 mL/min/1.73m^2	Discontinuation	0.4956	0.4346	0.5652	<.0001
Time-updated eGFR: ≥ 60 mL/min/1.73m^2	Down-titration	0.7037	0.6013	0.8235	<.0001
Time-updated eGFR: ≥ 60 mL/min/1.73m^2	Discontinuation	0.6534	0.5686	0.7510	<.0001
Time-updated blood pressure: Low	Down-titration	1.9071	1.6995	2.1401	<.0001
Time-updated blood pressure: Low	Discontinuation	1.2453	1.1143	1.3917	0.0001
Time-updated blood pressure: Normal	Down-titration	1.3213	1.2062	1.4474	<.0001
Time-updated blood pressure: Normal	Discontinuation	1.3408	1.2400	1.4499	<.0001
Time-updated blood pressure: Pre-High	Down-titration	5.7110	3.8741	8.4189	<.0001
Time-updated blood pressure: Pre-High	Discontinuation	1.9494	1.1681	3.2532	0.0107
Concomitant diuretics: Yes	Down-titration	0.8136	0.1133	5.8443	0.8375
Concomitant diuretics: Yes	Discontinuation	0.5725	0.0766	4.2787	0.5868
Concomitant NSAIDS: Yes	Down-titration	0.0006	0.0004	0.0012	<.0001
Concomitant NSAIDS: Yes	Discontinuation	2.1920	0.2835	16.9465	0.452
Concomitant Betablockers: Yes	Down-titration	2.0168	0.6213	6.5461	0.2428
Concomitant Betablockers: Yes	Discontinuation	0.9622	0.2256	4.1037	0.9585
Concomitant RAASi: Yes	Down-titration	1.4384	1.2698	1.6293	<.0001
Concomitant RAASi: Yes	Discontinuation	3.0177	2.7104	3.3599	<.0001

CI: confidence interval; eGFR: estimated glomerular filtration rate; HF: heart failure; MACE: major adverse cardiac event; OR: odds ratio; RAASi: renin-angiotensin-aldosterone system inhibitor; SE: standard error.
A one-unit change in explanatory variables increase the log odds of down-titration or discontinuation by the value of the corresponding estimate.

Table S3. Model output for dose modification of RAASi, stratified by serum K+ threshold for HF cohort.

Explanatory variable	Outcome	OR	95% lower CI	95% upper CI	P-value
Incidence of down-titration or discontinuation: Hyperkalaemia threshold: 5.0 mmol/L					
Serum potassium: ≥5.0 mmol/L	Down-titration	1.3250	1.0832	1.6207	0.0062
Serum potassium: ≥5.0 mmol/L	Discontinuation	1.1341	0.9163	1.4036	0.2479
Drug type: ARB	Down-titration	0.3855	0.3053	0.4869	<.0001
Drug type: ARB	Discontinuation	1.1037	0.9043	1.3472	0.3322
Drug type: MRA	Down-titration	1.1521	0.9369	1.4168	0.1795
Drug type: MRA	Discontinuation	0.7204	0.5507	0.9423	0.0167
Age (years)	Down-titration	1.0088	1.0012	1.0166	0.022
Age (years)	Discontinuation	1.0126	1.0045	1.0207	0.0025
Gender at baseline: Male	Down-titration	1.4118	1.1667	1.7085	0.0004
Gender at baseline: Male	Discontinuation	1.0280	0.8473	1.2471	0.7794
Time from baseline (years)	Down-titration	0.8974	0.8501	0.9472	<.0001
Time from baseline (years)	Discontinuation	0.9251	0.8754	0.9777	0.0059
Time-updated eGFR: < 15 mL/min/1.73m^2	Down-titration	3.1522	1.0667	9.3146	0.0378
Time-updated eGFR: < 15 mL/min/1.73m^2	Discontinuation	5.0576	1.7513	14.6063	0.0027
Time-updated eGFR: 30 to <45 mL/min/1.73m^2	Down-titration	0.8873	0.5015	1.5698	0.6811
Time-updated eGFR: 30 to <45 mL/min/1.73m^2	Discontinuation	0.5572	0.3565	0.8708	0.0103
Time-updated eGFR: 45 to <60 mL/min/1.73m^2	Down-titration	1.0342	0.5775	1.8521	0.9101
Time-updated eGFR: 45 to <60 mL/min/1.73m^2	Discontinuation	0.5726	0.3604	0.9098	0.0183
Time-updated eGFR: ≥ 60 mL/min/1.73m^2	Down-titration	1.0901	0.6087	1.9523	0.7716
Time-updated eGFR: ≥ 60 mL/min/1.73m^2	Discontinuation	0.5606	0.3377	0.9304	0.0252
Time-updated blood pressure: Low	Down-titration	1.5510	1.2625	1.9054	<.0001
Time-updated blood pressure: Low	Discontinuation	1.0048	0.8123	1.2429	0.9649
Time-updated blood pressure: Normal	Down-titration	1.0369	0.8278	1.2988	0.7529
Time-updated blood pressure: Normal	Discontinuation	1.0169	0.8216	1.2587	0.8773
Time-updated blood pressure: Pre-High	Down-titration	3.3364	1.9145	5.8146	<.0001
Time-updated blood pressure: Pre-High	Discontinuation	1.5633	0.7125	3.4300	0.2651
Concomitant diuretics: Yes	Down-titration	1.2880	0.9917	1.6729	0.0579
Concomitant diuretics: Yes	Discontinuation	0.7465	0.5715	0.9751	0.0319
Concomitant NSAIDS: Yes	Down-titration	1.0712	0.7411	1.5485	0.7145
Concomitant NSAIDS: Yes	Discontinuation	1.0520	0.7122	1.5539	0.7989
Concomitant Betablockers: Yes	Down-titration	1.0592	0.8817	1.2725	0.5391
Concomitant Betablockers: Yes	Discontinuation	0.8557	0.7117	1.0288	0.0975
Concomitant RAASi: Yes	Down-titration	1.1522	0.9464	1.4028	0.1582
Concomitant RAASi: Yes	Discontinuation	1.4110	1.1405	1.7457	0.0015
Incidence of down-titration or discontinuation: Hyperkalaemia threshold: 5.5 mmol/L					
Serum potassium: ≥5.5 mmol/L	Down-titration	1.9278	1.4125	2.6312	<.0001
Serum potassium: ≥5.5 mmol/L	Discontinuation	1.6960	1.2233	2.3514	0.0015
Drug type: ARB	Down-titration	0.3852	0.3049	0.4866	<.0001
Drug type: ARB	Discontinuation	1.1011	0.9021	1.3440	0.3435
Drug type: MRA	Down-titration	1.1563	0.9399	1.4224	0.1697
Drug type: MRA	Discontinuation	0.7223	0.5521	0.9450	0.0176
Age (years)	Down-titration	1.0089	1.0013	1.0167	0.0217
Age (years)	Discontinuation	1.0124	1.0041	1.0207	0.003
Gender at baseline: Male	Down-titration	1.4130	1.1676	1.7099	0.0004
Gender at baseline: Male	Discontinuation	1.0273	0.8469	1.2460	0.785
Time from baseline (years)	Down-titration	0.8980	0.8509	0.9477	<.0001
Time from baseline (years)	Discontinuation	0.9249	0.8750	0.9776	0.0057
Time-updated eGFR: < 15 mL/min/1.73m^2	Down-titration	3.0508	1.0614	8.7693	0.0384
Time-updated eGFR: < 15 mL/min/1.73m^2	Discontinuation	4.8235	1.6507	14.0949	0.004
Time-updated eGFR: 30 to <45 mL/min/1.73m^2	Down-titration	0.8962	0.5024	1.5987	0.7105
Time-updated eGFR: 30 to <45 mL/min/1.73m^2	Discontinuation	0.5737	0.3679	0.8946	0.0142
Time-updated eGFR: 45 to <60 mL/min/1.73m^2	Down-titration	1.0519	0.5829	1.8983	0.8664
Time-updated eGFR: 45 to <60 mL/min/1.73m^2	Discontinuation	0.5899	0.3718	0.9359	0.025
Time-updated eGFR: ≥ 60 mL/min/1.73m^2	Down-titration	1.0873	0.6025	1.9622	0.7811

Time-updated eGFR: ≥ 60 mL/min/1.73m^2	Discontinuation	0.5623	0.3386	0.9336	0.026
Time-updated blood pressure: Low	Down-titration	1.5583	1.2682	1.9148	<.0001
Time-updated blood pressure: Low	Discontinuation	1.0144	0.8196	1.2555	0.8954
Time-updated blood pressure: Normal	Down-titration	1.0371	0.8278	1.2993	0.7518
Time-updated blood pressure: Normal	Discontinuation	1.0209	0.8247	1.2638	0.8494
Time-updated blood pressure: Pre-High	Down-titration	3.3923	1.9480	5.9072	<.0001
Time-updated blood pressure: Pre-High	Discontinuation	1.5987	0.7304	3.4995	0.2404
Concomitant diuretics: Yes	Down-titration	1.2783	0.9845	1.6596	0.0653
Concomitant diuretics: Yes	Discontinuation	0.7436	0.5691	0.9715	0.0298
Concomitant NSAIDS: Yes	Down-titration	1.0726	0.7438	1.5469	0.7076
Concomitant NSAIDS: Yes	Discontinuation	1.0549	0.7149	1.5565	0.788
Concomitant Betablockers: Yes	Down-titration	1.0648	0.8863	1.2792	0.5023
Concomitant Betablockers: Yes	Discontinuation	0.8575	0.7134	1.0308	0.1017
Concomitant RAASi: Yes	Down-titration	1.1530	0.9476	1.4030	0.1549
Concomitant RAASi: Yes	Discontinuation	1.3972	1.1280	1.7307	0.0022
Incidence of down-titration or discontinuation: Hyperkalaemia threshold: 6.0 mmol/L					
Serum potassium: ≥6.0 mmol/L	Down-titration	3.1912	1.8593	5.4771	<.0001
Serum potassium: ≥6.0 mmol/L	Discontinuation	2.7357	1.5312	4.8879	0.0007
Drug type: ARB	Down-titration	0.3867	0.3060	0.4887	<.0001
Drug type: ARB	Discontinuation	1.1063	0.9062	1.3506	0.3213
Drug type: MRA	Down-titration	1.1589	0.9423	1.4254	0.1624
Drug type: MRA	Discontinuation	0.7240	0.5535	0.9471	0.0185
Age (years)	Down-titration	1.0090	1.0016	1.0166	0.0186
Age (years)	Discontinuation	1.0125	1.0044	1.0206	0.0026
Gender at baseline: Male	Down-titration	1.4152	1.1700	1.7119	0.0003
Gender at baseline: Male	Discontinuation	1.0263	0.8461	1.2449	0.7915
Time from baseline (years)	Down-titration	0.9001	0.8531	0.9498	0.0001
Time from baseline (years)	Discontinuation	0.9270	0.8772	0.9797	0.0072
Time-updated eGFR: < 15 mL/min/1.73m^2	Down-titration	3.2333	1.1458	9.1242	0.0266
Time-updated eGFR: < 15 mL/min/1.73m^2	Discontinuation	5.2200	1.8454	14.7653	0.0018
Time-updated eGFR: 30 to <45 mL/min/1.73m^2	Down-titration	0.8770	0.4941	1.5569	0.6541
Time-updated eGFR: 30 to <45 mL/min/1.73m^2	Discontinuation	0.5754	0.3677	0.9005	0.0156
Time-updated eGFR: 45 to <60 mL/min/1.73m^2	Down-titration	1.0346	0.5757	1.8594	0.9095
Time-updated eGFR: 45 to <60 mL/min/1.73m^2	Discontinuation	0.5935	0.3733	0.9434	0.0274
Time-updated eGFR: ≥ 60 mL/min/1.73m^2	Down-titration	1.0819	0.6021	1.9440	0.7923
Time-updated eGFR: ≥ 60 mL/min/1.73m^2	Discontinuation	0.5699	0.3431	0.9466	0.0299
Time-updated blood pressure: Low	Down-titration	1.5597	1.2693	1.9165	<.0001
Time-updated blood pressure: Low	Discontinuation	1.0134	0.8191	1.2538	0.9026
Time-updated blood pressure: Normal	Down-titration	1.0394	0.8296	1.3021	0.7373
Time-updated blood pressure: Normal	Discontinuation	1.0248	0.8278	1.2686	0.8223
Time-updated blood pressure: Pre-High	Down-titration	3.4264	1.9584	5.9947	<.0001
Time-updated blood pressure: Pre-High	Discontinuation	1.6048	0.7317	3.5197	0.2378
Concomitant diuretics: Yes	Down-titration	1.2697	0.9782	1.6482	0.0728
Concomitant diuretics: Yes	Discontinuation	0.7413	0.5675	0.9684	0.0282
Concomitant NSAIDS: Yes	Down-titration	1.0753	0.7450	1.5519	0.6979
Concomitant NSAIDS: Yes	Discontinuation	1.0576	0.7167	1.5606	0.7779
Concomitant Betablockers: Yes	Down-titration	1.0685	0.8896	1.2835	0.4787
Concomitant Betablockers: Yes	Discontinuation	0.8605	0.7159	1.0344	0.1097
Concomitant RAASi: Yes	Down-titration	1.1654	0.9578	1.4181	0.126
Concomitant RAASi: Yes	Discontinuation	1.4055	1.1356	1.7396	0.0018

CI: confidence interval; eGFR: estimated glomerular filtration rate; HF: heart failure; MACE: major adverse cardiac event; OR: odds ratio; RAASi: renin-angiotensin-aldosterone system inhibitor; SE: standard error.
A one-unit change in explanatory variables increase the log odds of down-titration or discontinuation by the value of the corresponding estimate.

Table S4. Model output for adverse outcomes stratified by RAASi dose within interval outcome occurred for the CKD cohort.

Explanatory variable	IRR	95% lower CI	95% upper CI	P-value
Incidence of death				
Mean RAASi dose in interval: <50%	5.6013	5.2878	5.9333	<0.0001
Time-updated BMI (kg/m2)	0.9847	0.9806	0.9889	<0.0001
Time-updated blood pressure: Low	2.0211	1.6524	2.4722	<0.0001
Time-updated blood pressure: Pre-high	0.6307	0.6013	0.6616	<0.0001
Time-updated blood pressure: High	0.5256	0.4992	0.5533	<0.0001
Time-updated serum potassium (mmol/L)	0.9763	0.9379	1.0163	0.2418
Time-updated phosphorous (mmol/L)	1.0039	0.9964	1.0114	0.3115
Time-updated eGFR (mL/min/1.73m2)	0.9849	0.9831	0.9866	<0.0001
Time-updated cholesterol (mmol/L)	0.7701	0.7539	0.7867	<0.0001
Time-updated WBC (x109/L)	1.0949	1.0879	1.1019	<0.0001
Time-updated OADs usage: Yes	0.6545	0.6052	0.7079	<0.0001
Time-updated CCB usage: Yes	0.7337	0.6999	0.7691	<0.0001
Time-updated diuretic usage: Yes	0.8486	0.8131	0.8858	<0.0001
Time-updated beta blockers usage: Yes	0.7006	0.6692	0.7333	<0.0001
Time-updated statins usage: Yes	0.3484	0.3328	0.3647	<0.0001
History of HF prior to interval: Yes	1.8325	1.7172	1.9555	<0.0001
History of MACE prior to interval: Yes	1.7810	1.7026	1.8630	<0.0001
History of PVD prior to interval: Yes	1.5806	1.4627	1.7080	<0.0001
History of dementia prior to interval: Yes	1.7772	1.6545	1.9090	<0.0001
History of diabetes (without chronic) prior to interval: Yes	1.7260	1.6275	1.8304	<0.0001
History of cancer prior to interval: Yes	1.9352	1.8512	2.0230	<0.0001
History of metatumour prior to interval: Yes	1.8557	1.7191	2.0032	<0.0001
Age (years)	1.0588	1.0560	1.0617	<0.0001
Smoker at baseline: Yes	1.4518	1.3722	1.5361	<0.0001
Time since baseline (days)	0.9999	0.9999	0.9999	<0.0001
Incidence of MACE				
Mean RAASi dose in interval: <50%	1.6039	1.5528	1.6568	<0.0001
Time-updated BMI (kg/m^2)	0.9984	0.9953	1.0015	0.2986
Time-updated blood pressure: Low	1.2004	1.0083	1.4292	0.0401
Time-updated blood pressure: Pre-high	0.8816	0.8482	0.9162	<0.0001
Time-updated blood pressure: High	0.9547	0.9159	0.9951	0.0285
Time-updated serum potassium (mmol/L)	0.8977	0.8726	0.9235	<0.0001
Time updated cholesterol (mmol/L)	0.9924	0.9771	1.0079	0.3327
Time-updated WBC (x10^9/L)	1.0307	1.0246	1.0370	<0.0001
Time-updated diuretic use: Yes	1.1718	1.1309	1.2141	<0.0001
Time-updated beta blockers use: Yes	2.0226	1.9486	2.0994	<0.0001
Time-updated statins usage: Yes	1.2579	1.2101	1.3076	<0.0001
Time-updated bronchodilators usage: Yes	1.2741	1.2212	1.3293	<0.0001
History of HF prior to interval: Yes	12.4495	11.6996	13.2475	<0.0001
History of MACE prior to interval: Yes (one quarter lagged)	0.5394	0.5068	0.5742	<0.0001
Age (years)	1.0328	1.0307	1.0349	<0.0001
Gender at baseline (Male)	1.1619	1.1215	1.2038	<0.0001
Time since baseline (days)	0.9998	0.9998	0.9998	<0.0001

BMI: body mass index; CI: confidence interval; eGFR: estimated glomerular filtration rate; HF: heart failure; IRR: incident rate ratios; MACE: major adverse cardiac event; RAASi: renin-angiotensin-aldosterone system inhibitor; SE: standard error.
A one-unit change in explanatory variables increased the expected incidence of death or MACE changes by the value of the corresponding estimate.

Table S5. Model output for adverse outcomes stratified by RAASi dose within interval outcome occurred for the HF cohort.

Explanatory variable	IRR	95% lower CI	95% upper CI	P-value
Incidence of death				
Mean RAASi dose in interval: <50%	7.3356	6.3463	8.4792	<0.0001
Time-updated BMI (kg/m^2)	0.9807	0.9732	0.9883	<0.0001
Time-updated blood pressure: Low	2.0305	1.6685	2.4711	<0.0001
Time-updated blood pressure: Pre-high	0.6533	0.6007	0.7106	<0.0001
Time-updated blood pressure: High	0.5727	0.5180	0.6332	<0.0001
Time-updated phosphorous (mmol/L)	1.2850	1.1512	1.4344	<0.0001
Time-updated serum potassium(mmol/L)	0.8546	0.7918	0.9224	0.0001
Time-updated eGFR (mL/min/1.73m^2)	0.9894	0.9870	0.9918	<0.0001
Time-updated cholesterol (mmol/L)	0.8017	0.7695	0.8352	<0.0001
Time-updated WBC (x10^9/L)	1.0793	1.0641	1.0947	<0.0001
Time-updated CCB use: Yes	0.6687	0.5778	0.7740	<0.0001
Time-updated diuretic use: Yes	0.6687	0.6132	0.7292	<0.0001
Time-updated beta blockers use: Yes	0.5238	0.4813	0.5699	<0.0001
Time-updated statins use: Yes	0.4077	0.3726	0.4460	<0.0001
History of MACE prior to interval: Yes	1.2100	1.1129	1.3156	<0.0001
History of PVD prior to interval: Yes	1.4277	1.2285	1.6591	<0.0001
History of dementia prior to interval: Yes	1.3870	1.1860	1.6220	<0.0001
History of diabetes (without chronic) prior to interval: Yes	1.3673	1.2346	1.5143	<0.0001
History of cancer prior to interval: Yes	1.4619	1.3310	1.6057	<0.0001
History of metatumour prior to interval: Yes	1.6344	1.3650	1.9570	<0.0001
Age (years)	1.0376	1.0328	1.0424	<0.0001
Gender at baseline: Male	1.1232	1.0318	1.2226	0.0073
Smoker at baseline: Yes	1.1287	1.0094	1.2621	0.0337
Time since baseline (days)	0.9998	0.9998	0.9999	<0.0001
Incidence of MACE				
Mean RAASi dose in interval: <50%	1.8471	1.7132	1.9914	<0.0001
Time-updated BMI (kg/m2)	0.9920	0.9862	0.9977	0.0061
Time-updated serum potassium (mmol/L)	0.8077	0.7560	0.8629	<0.0001
Time updated eGFR (mL/min/1.73m2)	0.9953	0.9931	0.9975	<0.0001
Age (years)	1.0070	1.0036	1.0103	<0.0001
Time since baseline (days)	0.9994	0.9993	0.9995	<0.0001

BMI: body mass index; CCB: calcium channel blockers; CI: confidence interval; eGFR: estimated glomerular filtration rate; HF: heart failure; IRR: incident rate ratios; MACE: major adverse cardiac event; RAASi: renin-angiotensin-aldosterone system inhibitor; SE: standard error; WBC: white blood cell.

A one-unit change in explanatory variables increased the expected incidence of death or MACE changes by the value of the corresponding estimate.

Table S6. Model output for survival analysis of adverse outcomes stratified by majority RAASi dose over the follow up for CKD cohort.

Explanatory variable	HR	95% lower CI	95% upper CI	P-value
Death				
Mean RAASi dose in interval: <50%	1.2074	1.1737	1.2421	<0.0001
Mean RAASi dose in interval: ≥50%	0.6829	0.6599	0.7068	<0.0001
Baseline age (years)	1.0942	1.0926	1.0957	<0.0001
Gender at baseline: Male	1.3616	1.3292	1.3947	<0.0001
Baseline smoker: Yes	1.7042	1.6475	1.7629	<0.0001
Baseline BMI (kg/m^2)	0.9827	0.9803	0.9852	<0.0001
History of diabetes	1.4735	1.4248	1.5238	<0.0001
MACE				
Mean RAASi dose in interval: <50%	2.2846	2.2175	2.3538	<0.0001
Mean RAASi dose in interval: ≥50%	1.6882	1.6330	1.7453	<0.0001
Baseline age (years)	1.0551	1.0536	1.0565	<0.0001
Gender at baseline: Male	1.3624	1.3282	1.3976	<0.0001
Baseline smoker: Yes	1.1438	1.1002	1.1891	<0.0001
Baseline BMI (kg/m^2)	1.0045	1.0020	1.0070	0.0004
History of diabetes	1.1251	1.0859	1.1657	<0.0001

BMI: body mass index; CI: confidence interval; HR: hazard ratio; MACE: major adverse cardiac event; RAASi: renin-angiotensin-aldosterone system inhibitor; SE: standard error.

A one-unit change in explanatory variables increased the risk of death or MACE by the value of the corresponding hazard ratio.

Table S7. Model output for survival analysis of adverse outcomes stratified by majority achieved RAASi dose over the follow up for HF cohort.

Explanatory variable	HR	95% lower CI	95% upper CI	P-value
Death				
Mean RAASi dose in interval: <50%	1.0856	1.0180	1.1577	0.0122
Mean RAASi dose in interval: ≥50%	0.5021	0.4568	0.5517	<0.0001
Baseline age (years)	1.0618	1.0584	1.0652	<0.0001
Gender at baseline: Male	1.1285	1.0618	1.1994	0.0001
Baseline smoker: Yes	1.6205	1.4903	1.7622	<0.0001
Baseline BMI (kg/m^2)	0.9908	0.9855	0.9962	0.0008
History of diabetes	1.1875	1.0901	1.2935	0.0001
MACE				
Mean RAASi dose in interval: <50%	3.7225	3.4179	4.0542	<0.0001
Mean RAASi dose in interval: ≥50%	3.1694	2.8766	3.4920	<0.0001
Baseline age (years)	1.0175	1.0147	1.0202	<0.0001
Gender at baseline: Male	1.1127	1.0448	1.1850	0.0009
Baseline smoker: Yes	1.0787	0.9930	1.1718	0.0730
Baseline BMI (kg/m^2)	1.0066	1.0016	1.0117	0.0102
History of diabetes	1.0345	0.9510	1.1253	0.4296

BMI: body mass index; CI: confidence interval; HR: hazard ratio; MACE: major adverse cardiac event; RAASi: renin-angiotensin-aldosterone system inhibitor; SE: standard error.
A one-unit change in explanatory variables increased the risk of death or MACE by the value of the corresponding hazard ratio.

Table S8. Summary of sample size and patient attrition.

Population	CKD cohort		HF cohort	
	N	%	N	%
Patients meeting CKD/HF-specific inclusion criteria identified in the CPRD	191,964	100.00%	21,334	100.00%
Patients not in receipt of any RAASi therapy at any point over the follow-up period: **Final analysed Non-RAASi cohort**	**71,008**	**36.99%**	**6,063**	**28.42%**
Prescriptions for RAASi agents not recommended by ESC 2016 guidelines for treatment of HF	-14,132	-7.36%	-996	-4.67%
RAASi prescriptions with missing/unusable dose information	-6,252	-3.26%	-1,162	-5.45%
Final analysed RAASi cohort	**100,572**	**52.39%**	**13,113**	**61.47%**

CPRD: Clinical Practice Research Datalink; CKD: chronic kidney disease; ESC: European Society of Cardiology; HF: heart failure; RAASi: Renin-Angiotensin-Aldosterone System Inhibitors

Table S9. Baseline patient demographics, clinical characteristics and clinical histories of CKD and HF patients included in the analysis (RAASi) and patients excluded due to receiving RAASi agents for which a recommended dose was not specified by the European Society of Cardiology guidelines[1], or due to missing/unusable RAASi dose information.

Variable	CKD cohort			HF cohort		
	RAASi (n=100,572)	Excluded patients† (n=20,384)	p-value (ANOVA /χ^2)	RAASi (n=13,113)	Excluded patients† (n=2,157)	p-value (ANOVA /χ^2)
Baseline* patient demographics and clinical characteristics, mean (SD)						
Age (years)	73.59 (10.93)	73.21 (11.26)	<0.01‡	72.88 (13.13)	73.55 (13.18)	0.03‡
Female, n (%)	58,277 (57.95%)	11,758 (57.69%)	0.49	5,302 (40.43%)	933 (43.25%)	0.01‡
Current Smoker, n (%)	13,742 (13.66%)	2,739 (13.44%)	0.40	2,469 (18.83%)	391 (18.13%)	0.46
BMI (kg/m^2)	28.91 (5.89)	29.00 (5.89)	0.28	28.47 (6.73)	28.27 (6.65)	0.53
SBP (mmHg)	141.97 (20.79)	140.68 (19.87)	<0.01‡	129.34 (21.78)	129.49 (22.12)	0.82
eGFR (mL/min/1.73m2)	50.85 (10.35)	4.48 (0.53)	<0.01‡	65.14 (17.35)	4.41 (0.55)	<0.01‡
Serum potassium (mEq/L)	4.51 (0.53)	50.70 (8.62)	<0.01‡	4.43 (0.54)	69.2 (15.01)	<0.01‡
Serum phosphorus (mEq/L)	1.14 (1.03)	1.13 (0.22)	0.67	1.15 (0.22)	1.15 (0.22)	0.99
Clinical history within 5 years prior to initial CKD/HF diagnosis, n (%)						
Hx diabetes	18,898 (18.79%)	3,957 (19.41%)	0.04‡	2,122 (16.18%)	347 (16.09%)	0.94
Hx MI	4,571 (4.55%)	834 (4.09%)	<0.01‡	1,543 (11.77%)	226 (10.48%)	0.09
Hx PVD	2,994 (2.98%)	567 (2.78%)	0.14	453 (3.45%)	62 (2.87%)	0.19
Hx stroke	6,410 (6.37%)	1,842 (9.04%)	<0.01‡	871 (6.64%)	195 (9.04%)	<0.01‡
Hx arrhythmia	8,769 (8.72%)	1,751 (8.59%)	0.56	3,192 (24.34%)	517 (23.97%)	0.73
Hx CPD	10,240 (10.18%)	1,962 (9.63%)	0.02*	2,020 (15.40%)	319 (14.79%)	0.48
Hx metastatic tumour	2,209 (2.20%)	447 (2.19%)	1.00	231 (1.76%)	35 (1.62%)	0.71
Hx rheumatic disease	3,381 (3.36%)	689 (3.38%)	0.91	374 (2.85%)	60 (2.78%)	0.91
Hx peptic ulcer	899 (0.89%)	182 (0.89%)	<0.01‡	146 (1.11%)	24 (1.11%)	1.00
Hx cancer	8,721 (8.67%)	1,863 (9.14%)	0.03‡	1,349 (10.29%)	230 (10.66%)	0.62
Baseline* medication usage, n (%)						
Beta blockers	32,044 (31.86%)	5,979 (29.33%)	<0.01‡	7,957 (60.68%)	1,113 (51.60%)	<0.01‡
Statins	56,138 (55.82%)	10,774 (52.86%)	<0.01‡	7,200 (54.91%)	1,027 (47.61%)	<0.01‡
Bronchodilators	11,566 (11.50%)	2,352 (11.54%)	0.89	2,691 (20.52%)	431 (19.98%)	0.58
Diuretics	49,721 (49.44%)	10,084 (49.47%)	0.94	10,449 (79.68%)	1,406 (65.18%)	<0.01‡
NSAIDs	9,439 (9.39%)	2,675 (13.12%)	<0.01‡	643 (4.90%)	167 (7.74%)	<0.01‡
Calcium channel blockers	33,644 (33.45%)	6,938 (34.04%)	0.11	2,082 (15.88%)	459 (21.28%)	<0.01‡
OADs	13,316 (13.24%)	2,554 (12.53%)	<0.01‡	1,515 (11.55%)	217 (10.06%)	0.05‡

Insulin	3,849 (3.83%)	757 (3.71%)	0.45	445 (3.39%)	65 (3.01%)	0.40

BMI: body mass index; CKD: chronic kidney disease; CPD: cardiopulmonary disease; eGFR: estimated glomerular filtration rate; ESC: European Society of Cardiology; HF: heart failure; Hx: History of; MI: myocardial infarction; NSAIDs: non-steroidal anti-inflammatory drugs; OADs: oral antidiabetics; RAASi: renin-angiotensin-aldosterone system inhibitors; SBP: systolic blood pressure; SD: standard deviation. ANOVA and Chi-squared test were used to evaluate differences between HbA1c groups for continuous and categorical variables, respectively. *Baseline for RAASi patients is time of each patient's first RAASi prescription after their first CKD/HF event, for the excluded patients its time of first CKD/HF event. †Patients excluded due to to being in receipt of RAASi agents for which a recommended dose was not specified by European Society of Cardiology guidelines or due to missing/unusable RAASi dose information. ‡ Indicates significance at $p < 0.05$

Figure S1. Illustrative example of data structuring for estimating associations between renin-angiotensin-aldosterone system inhibitor dose and adverse clinical outcomes.

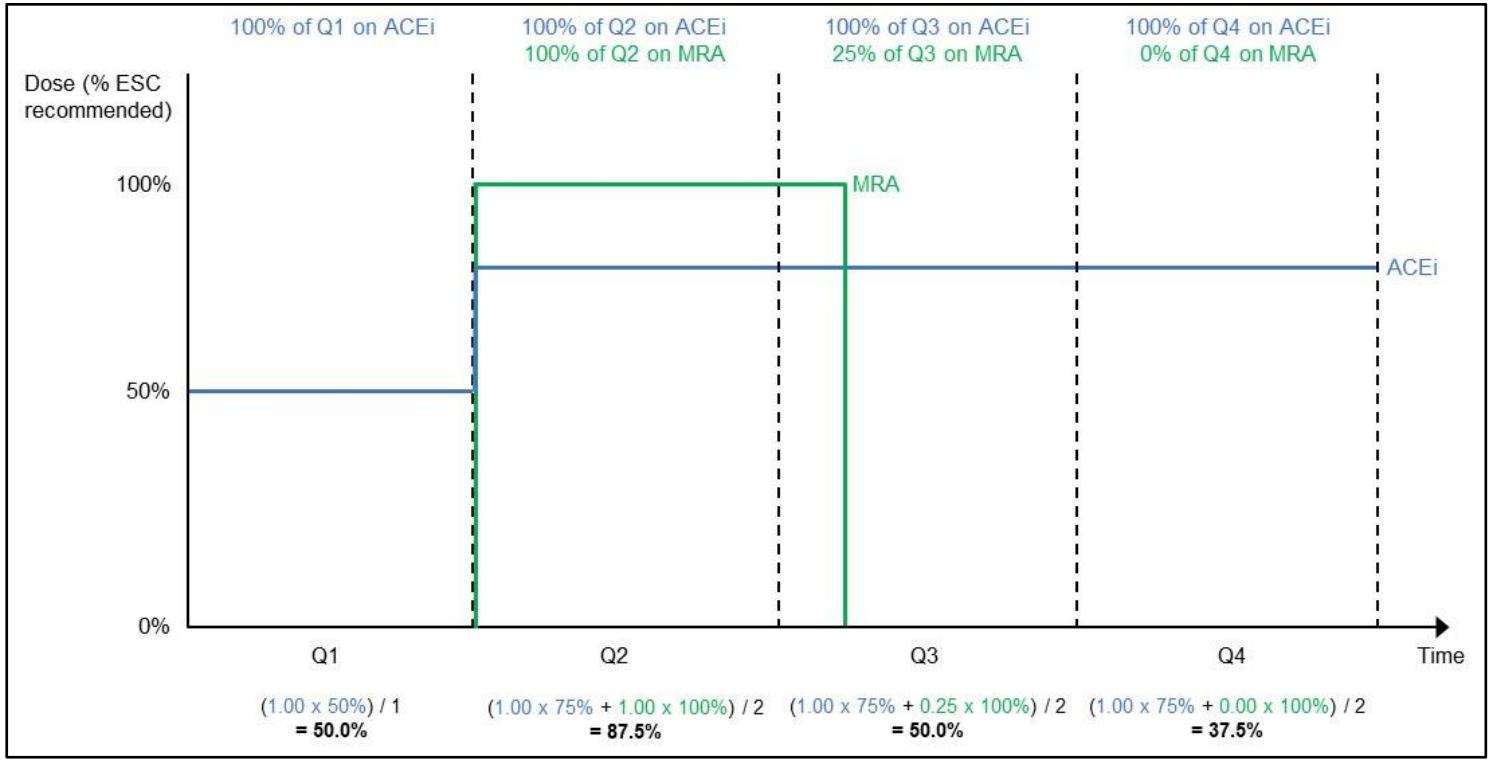


Figure S2. Three stages of the multiple imputation process.

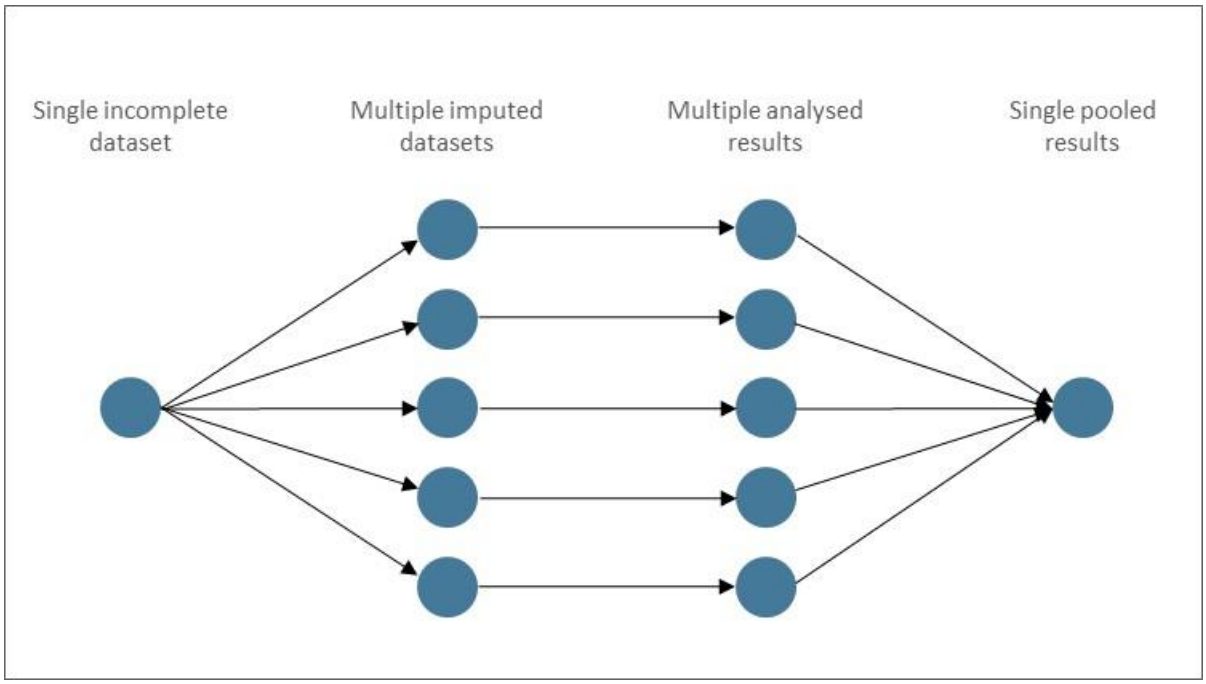
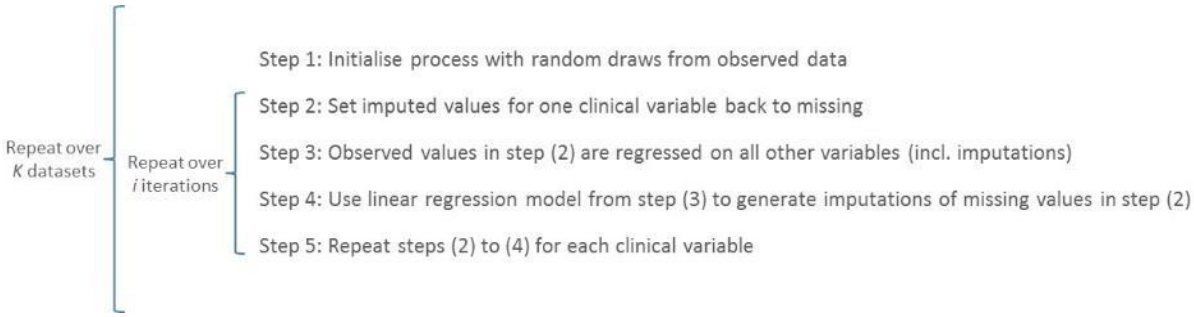


Figure S3. Simple description of the Chained Equations algorithm.



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