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ORIGINAL ARTICLE

Adverse clinical outcomes associated with RAAS inhibitor discontinuation: analysis of over 400 000 patients from the UK Clinical Practice Research Datalink (CPRD)

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ABSTRACT

Background. Users of guideline-recommended renin–angiotensin–aldosterone system (RAAS) inhibitors may experience disruptions to their treatment, e.g. due to hyperkalaemia, hypotension or acute kidney injury. The risks associated with treatment disruption have not been comprehensively assessed; therefore, we evaluated the risk of adverse clinical outcomes in RAAS inhibitor users experiencing treatment disruptions in a large population-wide database.

Methods. This exploratory, retrospective analysis utilized data from the UK's Clinical Practice Research Datalink, linked to Hospital Episodes Statistics and the Office for National Statistics databases. Adults (≥18 years) with first RAAS inhibitor use (defined as angiotensin-converting enzyme inhibitors or angiotensin receptor blockers) between 1 January 2009 and 31 December 2014 were eligible for inclusion. Time to the first occurrence of adverse clinical outcomes [all-cause mortality, all-cause hospitalization, cardiac arrhythmia, heart failure hospitalization, cardiac arrest, advancement in chronic kidney disease (CKD) stage and acute kidney injury] was compared between RAAS inhibitor users with and without interruptions or cessations to treatment during follow-up. Associations between baseline characteristics and adverse clinical outcomes were also assessed.

Results. Among 434 027 RAAS inhibitor users, the risk of the first occurrence of all clinical outcomes, except advancement in CKD stage, was 8–75% lower in patients without interruptions or cessations versus patients with interruptions/cessations. Baseline characteristics independently associated with increased risk of clinical outcomes included increasing age, smoking, CKD, diabetes and heart failure.

Conclusions. These findings highlight the need for effective management of factors associated with RAAS inhibitor interruptions or cessations in patients for whom guideline-recommended RAAS inhibitor treatment is indicated.

Keywords: cardiovascular, CKD, epidemiology, hyperkalaemia, renin–angiotensin system

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INTRODUCTION

Renin–angiotensin–aldosterone system (RAAS) inhibitors are indicated for a variety of cardiorenal conditions, including hypertension, chronic kidney disease (CKD) and heart failure [1–4]. Many current treatment guidelines recommend the up-titration of RAAS inhibitors to maximum tolerated doses, as used in clinical trials, in order for patients to derive maximum clinical benefit from treatment [3, 5].

RAAS inhibitor therapy has proven efficacy in reducing clinical events; however, it is associated with an increased risk of hyperkalaemia. This potentially life-threatening electrolyte disorder can lead to cardiac arrhythmias, cardiac arrest and sudden death [6–10]. To reduce the risk of these adverse clinical outcomes, physicians frequently reduce the dose or discontinue RAAS inhibitor therapy in patients with or thought to be at risk of hyperkalaemia [11]. Indeed, this practice is recommended by several clinical treatment guidelines [4, 5].

Other reasons for modification of RAAS inhibitor therapy include hypotension or acute kidney injury [12]. Additionally, during the novel coronavirus disease 2019 (COVID-19) pandemic, some suggestions were made to withdraw RAAS inhibitor therapy amid fears that these agents might increase the risk of patients developing severe COVID-19 [13]. These concerns, potentially amplified by social media, may have encouraged some patients to discontinue their RAAS inhibitor therapy [14]; however, the strong consensus from major guidelines is that patients should continue using these medications as prescribed [14–17].

Recent studies have shown associations between both suboptimal dosing and interruptions to RAAS inhibitor therapy and a variety of adverse clinical events, including mortality and major adverse cardiovascular events (MACEs) [10, 11, 18–20]. However, there are limited data on the impact of RAAS inhibitor interruptions or discontinuations on clinical events relevant for patients with CKD, such as those related to loss of renal function. Additional data are required to comprehensively assess the risks associated with interrupting or discontinuing RAAS inhibitor therapy in patients with a clear indication for treatment.

In a previous investigation, the rates of hyperkalaemia and treatment interruptions or cessations were assessed in a large, real-world population of patients receiving RAAS inhibitor therapy ($n = 434\,027$) [21]. Overall, 154 120 (35.5%) patients had a history of hyperkalaemia. Among all users, 319 659 (73.7%) experienced an interruption or cessation of treatment, and approximately one-third had experienced interruption or cessation of therapy within 1 year of RAAS inhibitor initiation. After 1 year, ∼50% of patients with a history of severe hyperkalaemia (defined as serum potassium >6.0 mmol/L), and ∼20% of all other patients, had experienced an interruption or a cessation. The risk of interruptions or cessations was highest for patients who experienced severe hyperkalaemia, as well as those with advanced CKD and non-White ethnicity [21]. The presence of comorbidities, including heart failure, diabetes and advanced CKD, were also associated with increased risk of interruptions in RAAS inhibitor therapy [21].

Here, we present findings from an exploratory component of the initial analysis by Wetmore *et al.* [21]. The aim was to assess the association between RAAS inhibitor interruptions or cessations and clinical outcomes in the same patient cohort as previously described [21].

MATERIALS AND METHODS

Study design and patient population

This was an additional, pre-specified analysis conducted as part of a retrospective cohort analysis of RAAS inhibitor users. The design and primary outcomes of the study have been reported previously [21]. In brief, the study utilized data from the UK's Clinical Practice Research Datalink (CPRD), linked to Hospital Episodes Statistics (HES) and the Office for National Statistics databases. Eligible patients were adults aged ≥18 years who had first received RAAS inhibitor treatment [defined as angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs)] between 1 January 2009 and 31 December 2014, and for whom at least 1 year of data before the date of first RAAS inhibitor prescription were available. Mineralocorticoid receptor antagonists were prescribed infrequently and were not included in the definition of RAAS inhibitors in this analysis. Key exclusion criteria included active cancer [indicated by at least one relevant Read code in CPRD or International Classification of Diseases, Tenth Revision (ICD-10) code in HES] during the 1 year prior to first RAAS inhibitor use and dehydration (indicated by relevant ICD-10 or Read codes) in the 7 days prior to first RAAS inhibitor use. The study period was between 1 January 2009 and 31 December 2015. Patients were followed up from the day after their first RAAS inhibitor use (index date) until the earliest event: transfer out of the practice, loss to follow-up, death or end of the study period (31 December 2015).

The study was conducted in accordance with the International Society for Pharmacoepidemiology Guidelines for Good Pharmacoepidemiology Practices and the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance Guide on Methodological Standards in Pharmacoepidemiology. Approval for the study was obtained from the Institutional Review Board of Hennepin Healthcare; specific approval for database research was obtained from the Independent Scientific Advisory Committee for Medicines and Healthcare Products Regulatory Agency in the UK.

Outcomes

Associations between treatment interruptions or cessations and time to the first occurrence of clinical outcomes of interest were assessed in users of RAAS inhibitors during the study follow-up. As in previous analyses [21], treatment interruptions were defined as a period with no active RAAS inhibitor prescription followed by the appearance, at any future point during the study period, of a new prescription. Treatment cessations were defined as permanent discontinuation, i.e. the point after which no RAAS inhibitor prescriptions appeared during the study period. Prescriptions that lapsed within 90 days of the end of the study period were classified as interruptions.

Outcomes analyses included patients with pre-existing conditions, such as heart failure or CKD, prior to the index date. The occurrence of clinical outcomes was determined based on the presence of single diagnosis, procedure, drug or laboratory value codes [including ICD-10 and Read codes (a partial list of codes is presented in Supplementary data, Table S1)], or combinations of codes and/or conditions that could be applied to identify a specific outcome of interest. Specific clinical outcomes were ascertained as follows.

Time to all-cause mortality. Patient record in CPRD indicating a transfer out of practice due to death or a HES record indicating

death. Deaths were confirmed using linked data from the Office of National Statistics.

Time to first all-cause hospitalization. First patient record in the HES database indicating an admission to the hospital.

Time to first heart failure hospitalization. Presence of a relevant ICD-10 code in the HES database.

Time to first cardiac arrhythmia. At least one ICD-10 diagnostic code for cardiac arrhythmia in the HES database.

Time to first cardiac arrest. At least one ICD-10 diagnostic code for cardiac arrest in the HES database.

Time to first advancement in CKD stage. Presence of ICD-10 or Read diagnostic codes, and/or estimated glomerular filtration rate (eGFR) showing an advancement in CKD stage from baseline, in the CPRD or HES database. CKD stages were determined according to Kidney Disease: Improving Global Outcomes guideline definitions [2].

Time to first acute kidney injury. At least one relevant Read or ICD-10 code following the index date.

Statistical analysis

Time to clinical outcomes analyses were performed using time-varying Cox proportional hazards models with 'monthly RAAS inhibitor use' (yes/no) used as a time-dependent covariate in each model. Patients were considered as being 'on-treatment' if they refilled their medication within 1.5 times the duration of the prescription length. A maximum of 30 days beyond the end of the last prescription was allowed. For each analysis, patients who did not experience the outcome of interest were censored on 31 December 2015, or at the time of death if this occurred first. For each clinical outcome, an adjusted hazard ratio (HR) with associated 95% confidence intervals (CIs) was calculated using 'off-treatment' as the reference group.

All models were adjusted for demographic characteristics [age, sex, race, smoking status and body mass index (BMI)], the calendar year of the index date and the presence of comorbidities [ischaemic heart disease, arrhythmia, hypertension, cerebrovascular disease, hyperlipidaemia, chronic liver disease, obstructive lung disease, heart failure, diabetes (Type 1 or 2) and CKD]. Variables were included in analyses if at least 80% of patients had an available value for that variable. For variables where missing values were possible, such as laboratory results, smoking and BMI, indicators were created for 'missing' and included in model building (see Supplementary Methods 1). For laboratory data, where a variable had >20% missing data the presence of the laboratory test was included as a binary variable.

Each clinical outcome was assessed separately, and patient data could contribute to each outcome analysis regardless of whether they experienced the other outcomes. Person-time per patient could vary by analysis for each specific outcome; e.g. a patient who experienced heart failure hospitalization would be censored at that time for the heart failure hospitalization analysis but would not be censored at that point for other outcomes. Patients who had already experienced an outcome at baseline (e.g. heart failure hospitalization) were excluded from analyses of that outcome. Patients with CKD had their disease stage assessed at baseline and progression beyond this stage was considered in analyses of advancement in CKD stage. For all analyses, being on or off treatment was determined prior to the occurrence of any event. In instances where a patient experienced a change to their RAAS inhibitor therapy after an event had occurred (e.g. following hospitalization), this would not result in a change to their treatment status in the analysis. Statistical analyses were performed using SAS software (SAS Institute, Cary, NC, USA).

RESULTS

Patients

In total, 434 027 patients met the criteria for inclusion in the study cohort (see Supplementary data, Figure S1). Full characteristics of these patients have been described previously [21] and are summarized in Supplementary data, Table S2. Overall, 35.5% of patients ($n = 154\,257$) were new RAAS inhibitor users, defined as no RAAS inhibitor use for ≥6 months preceding the first RAAS inhibitor treatment on or after the study start date. The majority of RAAS inhibitor users (88%) were ≥50 years of age; 51% were male; and 80% were of White ethnicity. The proportion of patients who were normal weight (BMI <25 kg/m^2), overweight (BMI 25 to <30 kg/m^2) and obese (BMI ≥30 kg/m^2) were 15.1, 26.0 and 29.3%, respectively. In total, 13.5 and 34.8% of patients were current and ex-smokers, respectively. The most common comorbidities among patients in the cohort were hypertension (77.3%), hyperlipidaemia (29.6%) and ischaemic heart disease (23.0%). A total of 7.5, 18.5 and 19.9% of patients had heart failure, diabetes and CKD, respectively, at baseline. The proportion of patients taking ACEIs or ARBs at baseline was 91.3 and 24.4%, respectively, including the 17.1% of patients who were receiving dual ACEI/ARB therapy.

Associations between RAAS inhibitor interruptions or cessations and time to clinical outcomes

As described previously, of 433 952 patients with available data on interruptions or cessations, 73.7% experienced an interruption or cessation of RAAS inhibitor therapy: 8.6, 57.6 and 7.5% of patients experienced both interruptions and cessations, interruptions only and cessations only, respectively [21].

Among patients who experienced at least one interruption, the median (25–75th percentile) time to interruption was 0.86 (0.34–1.93) years over a median follow-up period of 5.11 (3.08–6.73) years. The median (25–75th percentile) time to re-initiation was 13 (6–28) days. Of patients who experienced a cessation only, the median (25–75th percentile) time to cessation was 0.40 (0.19–1.37) years over a median (25–75th percentile) follow-up period of 3.47 (1.89–5.32) years [21].

After adjusting for demographic characteristics and comorbidities, there was a statistically significant association between experiencing interruptions or cessations in RAAS inhibitor therapy and the time to first occurrence of each of the clinical outcomes analysed during the study.

All-cause mortality and all-cause hospitalization. The risk of all-cause mortality was reduced by 75% for patients on RAAS inhibitor treatment compared with those experiencing interruptions or cessations (HR = 0.25, 95% CI 0.25–0.26; Figure 1). The risk of first all-cause hospitalization was reduced by 8% for patients on RAAS inhibitor treatment compared with those experiencing interruptions or cessations (HR = 0.92, 95% CI 0.91–0.93; Figure 1).

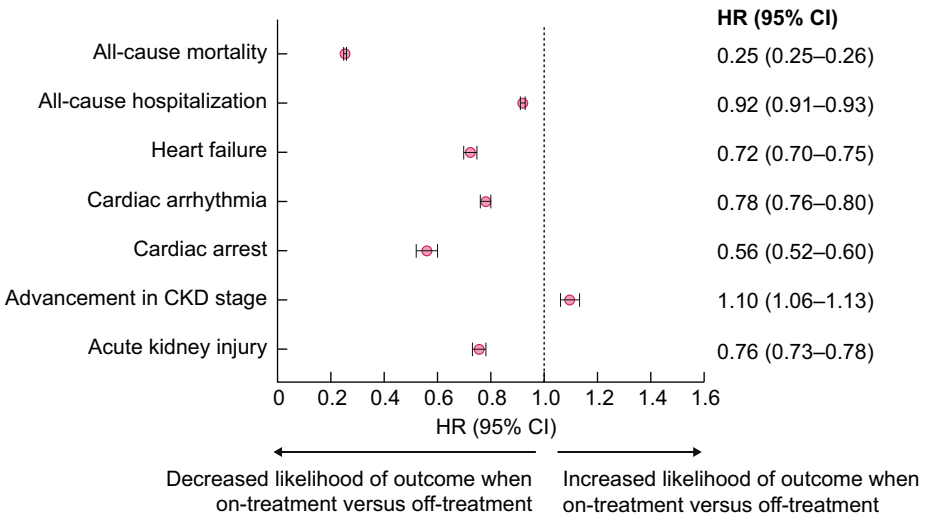

FIGURE 1: Time to first clinical outcomes during the study period, comparing patients on versus off RAAS inhibitors.

Cardiovascular outcomes. The risks of first heart failure hospitalization, first cardiac arrhythmia and first cardiac arrest were reduced by 28% (HR = 0.72, 95% CI 0.70–0.75), 22% (HR = 0.78, 95% CI 0.76–0.80) and 44% (HR = 0.56, 95% CI 0.52–0.60), respectively, for patients on RAAS inhibitor treatment compared with those experiencing interruptions or cessations (Figure 1).

Renal outcomes. The risk of first advancement in CKD stage increased by 10% (HR = 1.10, 95% CI 1.06–1.13) in patients on RAAS inhibitor treatment, compared with those experiencing interruptions or cessations. Conversely, the risk of first acute kidney injury was decreased by 24% (HR = 0.76, 95% CI 0.73–0.78) in patients on RAAS inhibitor treatment compared with those experiencing interruptions or cessations (Figure 1).

Factors associated with clinical outcomes

Factors associated with time to first occurrence of the seven clinical outcomes, regardless of RAAS inhibitor treatment status, are shown in Table 1 (all-cause mortality and all-cause hospitalization), Table 2 (cardiovascular outcomes) and Table 3 (renal outcomes). Several factors were found to be consistently associated with the HR for time to first event for most of the clinical outcomes assessed. These included increasing age, being a current or ex-smoker and having comorbidities, particularly heart failure, diabetes and CKD (Tables 1–3). There was a reduced association between female sex and clinical outcomes compared with male sex for all clinical outcomes except for time to first hospitalization and first advancement in CKD stage. Some associations were seen between ethnicity and the time to first occurrence of clinical outcomes, but these may have been confounded by lower numbers of non-White patients in this analysis.

Demographic factors. The HR for the first occurrence of all outcomes increased with age. This was particularly pronounced for all-cause mortality, where there was a risk difference of >23-fold in patients aged ≥80 years, relative to age 18–29 years (HR = 23.17, 95% CI 16.20–33.15; Tables 1–3). Being a current or ex-smoker was associated with an increased risk of all clinical outcomes compared with being a non-smoker [HR range across clinical outcomes: 1.06–1.92 (current smokers); 1.04–1.18 (ex-smokers); Tables 1–3]. Being overweight or obese was associated with a reduced risk of all-cause mortality, first hospitalization and first cardiac arrest, but with an increased risk of first advancement in CKD stage, compared with being at normal weight.

Comorbidities. Having concomitant heart failure or diabetes was associated with an increased risk of the first occurrence of all clinical outcomes (HR range across clinical outcomes: heart failure, 1.24–5.14 versus not having heart failure for all outcomes; diabetes, 1.09–1.85 versus not having diabetes; (Tables 1–3). The presence of hypertension at baseline was associated with an increased risk of the first occurrence of advancement in CKD stage (HR = 1.05, 95% CI 1.03–1.08) and acute kidney injury (HR = 1.05, 95% CI 1.02–1.08) (Table 3). However, hypertension was not associated with increased risk of mortality or hospitalization (Table 1) and was conversely associated with a reduced HR for time to first heart failure hospitalization (Table 2).

Having CKD of any stage at baseline was associated with an increased HR for all-cause mortality, all-cause hospitalization, all cardiac outcomes and first acute kidney injury (HR range across clinical outcomes: 1.07–1.92 versus not having CKD; Tables 1–3). In contrast, having CKD at baseline was associated with a small reduction in the HR for first advancement in CKD stage (HR = 0.89 versus no CKD at baseline; Table 3).

DISCUSSION

In this study, we investigated the association between interruptions or cessations in RAAS inhibitor therapy and the time to first occurrence of adverse clinical outcomes in users of RAAS inhibitors. Among this cohort of 434 027 patients, we found that interruptions or cessations in RAAS inhibitor use were associated with an increased risk of adverse clinical outcomes. Other factors independently associated with an increased risk of adverse clinical outcomes were increased age and presence of comorbidities, particularly heart failure, diabetes and CKD.

Several factors have been associated with RAAS inhibitor down-titration or discontinuation, including acute deterioration of renal function, hyperkalaemia and hypotension [12].

Table 1. Factors associated with time to all-cause mortality and time to first all-cause hospitalization in users of RAAS inhibitors

Characteristics	Time to all-cause mortality, HR (95% CI)	Time to first all-cause hospitalization, HR (95% CI)
Age, years		
18–29	1.00 (ref)	1.00 (ref)
30–39	1.23 (0.83–1.82)	0.93 (0.86–1.00)
40–49	**1.55 (1.08–2.23)**	0.95 (0.88–1.02)
50–59	**2.50 (1.75–3.58)**	1.01 (0.94–1.08)
60–69	**4.81 (3.36–6.88)**	**1.14 (1.06–1.22)**
70–79	**9.82 (6.86–14.05)**	**1.39 (1.30–1.49)**
80+	**23.17 (16.20–33.15)**	**1.72 (1.60–1.84)**
Sex		
Male	1.00 (ref)	1.00 (ref)
Female	**0.85 (0.84–0.87)**	1.00 (0.99–1.01)
Race		
White	1.00 (ref)	1.00 (ref)
Black	**0.90 (0.81–1.00)**	1.02 (0.98–1.06)
Asian	**0.73 (0.66–0.80)**	**1.05 (1.01–1.08)**
Smoking status		
No	1.00 (ref)	1.00 (ref)
Yes	**1.92 (1.86–1.97)**	**1.12 (1.11–1.14)**
Ex	**1.18 (1.16–1.20)**	**1.04 (1.03–1.05)**
Unknown	**1.22 (1.07–1.39)**	0.99 (0.92–1.06)
BMI		
Normal (<25 kg/m^2)	1.00 (ref)	1.00 (ref)
Overweight (25 to ≤30 kg/m^2)	**0.72 (0.71–0.74)**	**0.93 (0.92–0.94)**
Obese (>30 kg/m^2)	**0.77 (0.75–0.79)**	**0.95 (0.94–0.97)**
Unknown	**1.04 (1.01–1.06)**	**0.98 (0.97–0.99)**
Comorbidities[a]		
Ischaemic heart disease (including MI)	**1.17 (1.15–1.20)**	**1.17 (1.16–1.18)**
Arrhythmia (including AFib)	**1.43 (1.40–1.46)**	**1.21 (1.20–1.22)**
Hypertension	**0.97 (0.95–0.99)**	**0.99 (0.98–1.00)**
Cerebrovascular disease	**1.39 (1.36–1.42)**	**1.15 (1.14–1.17)**
Hyperlipidaemia	**0.89 (0.87–0.90)**	**1.03 (1.03–1.04)**
Chronic liver disease	**1.87 (1.80–1.94)**	**1.37 (1.34–1.39)**
Obstructive lung disease	**1.36 (1.33–1.38)**	**1.23 (1.22–1.24)**
Heart failure	**1.92 (1.88–1.96)**	**1.24 (1.22–1.25)**
Diabetes (Type 1 or 2)	**1.49 (1.46–1.52)**	**1.17 (1.16–1.18)**
CKD	**1.20 (1.18–1.23)**	**1.09 (1.08–1.10)**

Analysis of factors associated with time to all-cause mortality and first all-cause hospitalization. HRs were adjusted for demographic characteristics (age, sex, race, smoking status and BMI), the calendar year of the index date and comorbidities [ischaemic heart disease, arrhythmia, hypertension, cerebrovascular disease, hyperlipidaemia, chronic liver disease, obstructive lung disease, heart failure, diabetes (Type 1 or 2) and CKD]; statistically significant ($P < 0.05$) differences versus the reference group are written in bold type.

[a]Versus not having the comorbidity (reference value of 1.00).

AFib, atrial fibrillation; MI, myocardial infarction.

Hyperkalaemia has been shown to be associated with both discontinuation and down-titration of RAAS inhibitors in both CKD and heart failure populations [10–12, 22–25], as well as being a reason for not initiating RAAS inhibitors in patients with CKD [12]. Risk of hyperkalaemia is, therefore, an important consideration that requires monitoring in patients receiving RAAS inhibitors. In a previous analysis of the same cohort used in this study, 73.7% of RAAS inhibitor users experienced an interruption or cessation of their treatment during follow-up, with one-third experiencing at least one RAAS inhibitor interruption or cessation by 1 year. Among these patients, severe hyperkalaemia was independently associated with an increased risk of treatment interruptions and cessations [21].

The results from the present analysis extend the findings of the previous analysis by Wetmore *et al.* [21] and suggest that interruptions or cessations in RAAS inhibitor treatment put patients at increased risk of adverse clinical outcomes. This is likely due to downstream effects of RAAS re-activation and withdrawal of the protective effects of RAAS inhibitors on cardiovascular and renal function, as well as on blood pressure. Subsequently, patients become at elevated risk of experiencing adverse clinical outcomes related to their underlying conditions for which RAAS inhibitors are indicated. It could also be hypothesized that, when hyperkalaemia is the reason for interruptions or cessations in RAAS inhibitor therapy, patients may remain hyperkalaemic after treatment disruption. Therefore, hyperkalaemia itself could still contribute to adverse clinical outcomes in some cases. A recent study found increased mortality risk and increased risk of RAAS inhibitor discontinuation with hyperkalaemia, although it could not be concluded whether hyperkalaemia was a cause or only a marker of the increased mortality risk [24].

Of the seven adverse clinical outcomes assessed in this analysis, the risk of first occurrence of six (all-cause mortality,

Table 2. Factors associated with time to first cardiovascular outcomes in users of RAAS inhibitors

Characteristics	Time to first heart failure hospitalization, HR (95% CI)	Time to first cardiac arrhythmia, HR (95% CI)	Time to first cardiac arrest, HR (95% CI)
Age, years			
18–29	1.00 (ref)	1.00 (ref)	1.00 (ref)
30–39	**0.57 (0.42–0.78)**	1.19 (0.79–1.77)	0.68 (0.29–1.58)
40–49	**0.57 (0.44–0.75)**	**1.47 (1.01–2.13)**	0.79 (0.37–1.70)
50–59	**0.67 (0.51–0.88)**	**2.27 (1.56–3.29)**	1.12 (0.53–2.38)
60–69	0.92 (0.71–1.20)	**4.06 (2.80–5.89)**	1.44 (0.68–3.03)
70–79	**1.36 (1.04–1.77)**	**7.01 (4.84–10.16)**	**2.17 (1.03–4.58)**
80+	**2.08 (1.60–2.71)**	**11.07 (7.64–16.04)**	**3.22 (1.53–6.79)**
Sex			
Male	1.00 (ref)	1.00 (ref)	1.00 (ref)
Female	**0.83 (0.80–0.85)**	**0.85 (0.83–0.86)**	**0.65 (0.61–0.70)**
Race			
White	1.00 (ref)	1.00 (ref)	1.00 (ref)
Black	**1.18 (1.03–1.35)**	**0.68 (0.61–0.77)**	1.25 (0.92–1.71)
Asian	1.02 (0.90–1.15)	**0.61 (0.55–0.68)**	1.19 (0.92–1.55)
Smoking status			
No	1.00 (ref)	1.00 (ref)	1.00 (ref)
Yes	**1.36 (1.30–1.42)**	**1.10 (1.07–1.14)**	**1.80 (1.63–1.99)**
Ex	**1.11 (1.08–1.15)**	**1.05 (1.03–1.07)**	**1.12 (1.04–1.20)**
Unknown	0.84 (0.66–1.08)	1.08 (0.93–1.24)	0.63 (0.30–1.32)
BMI			
Normal (<25 kg/m^2)	1.00 (ref)	1.00 (ref)	1.00 (ref)
Overweight (25 to ≤30 kg/m^2)	**0.88 (0.84–0.91)**	**0.91 (0.89–0.94)**	**0.72 (0.66–0.79)**
Obese (>30 kg/m^2)	1.00 (0.96–1.04)	**1.07 (1.04–1.10)**	**0.70 (0.63–0.77)**
Unknown	1.03 (0.99–1.07)	**1.05 (1.02–1.08)**	0.97 (0.88–1.06)
Comorbidities[a]			
Ischaemic heart disease (including MI)	**1.48 (1.44–1.53)**	**1.11 (1.09–1.13)**	**1.23 (1.14–1.33)**
Arrhythmia (including AFib)	**1.75 (1.70–1.80)**	**6.49 (6.37–6.61)**	**1.50 (1.38–1.62)**
Hypertension	**0.85 (0.82–0.88)**	0.99 (0.97–1.02)	0.99 (0.91–1.08)
Cerebrovascular disease	**1.16 (1.12–1.20)**	**1.23 (1.21–1.26)**	**1.26 (1.16–1.38)**
Hyperlipidaemia	1.03 (1.00–1.06)	**0.94 (0.92–0.96)**	**1.09 (1.01–1.16)**
Chronic liver disease	**1.29 (1.21–1.37)**	**1.26 (1.21–1.31)**	**1.48 (1.28–1.70)**
Obstructive lung disease	**1.38 (1.34–1.42)**	**1.19 (1.17–1.21)**	**1.23 (1.14–1.33)**
Heart failure	**5.14 (4.98–5.30)**	**1.66 (1.62–1.70)**	**2.08 (1.90–2.27)**
Diabetes (Type 1 or 2)	**1.33 (1.29–1.38)**	**1.09 (1.07–1.12)**	**1.71 (1.59–1.85)**
CKD	**1.23 (1.19–1.27)**	**1.07 (1.05–1.09)**	**1.42 (1.32–1.53)**

Analysis of factors associated with time to all-cause mortality and first heart failure hospitalization, first cardiac arrhythmia and first cardiac arrest. HRs were adjusted for demographic characteristics (age, sex, race, smoking status and BMI), the calendar year of the index date and comorbidities [ischaemic heart disease, arrhythmia, hypertension, cerebrovascular disease, hyperlipidaemia, chronic liver disease, obstructive lung disease, heart failure, diabetes (Type 1 or 2) and CKD]; statistically significant ($P < 0.05$) differences versus the reference group are written in bold type.

[a]Versus not having the comorbidity (reference value of 1.00).

AFib, atrial fibrillation; MI, myocardial infarction.

all-cause hospitalization, heart failure hospitalization, cardiac arrhythmia, cardiac arrest and acute kidney injury) was reduced in patients who did not experience interruptions or cessations to their RAAS inhibitor therapy compared with those who did experience interruptions or cessations. The magnitude of risk reduction was substantially greater for all-cause mortality (75%) than for all other outcomes, including all-cause hospitalization, where the risk reduction was modest (8%).

The propensity of RAAS inhibitors to cause an initial reduction in renal function is well documented [26]. Interruption or cessation of RAAS inhibitor therapy in this study was associated with a small but significant decrease of 10% in the risk of first advancement in CKD stage compared with patients who experienced no periods of interruption or cessation in their RAAS inhibitor therapy. This was likely due to a small increase in eGFR in some patients who discontinued their RAAS inhibitor therapy, as the case definition used for advancement of CKD stage included eGFR assessments.

There is some evidence to suggest that discontinuing RAAS inhibitors in advanced CKD (Stages 4 and 5) increases eGFR levels significantly in the long term, thereby delaying the onset of renal replacement therapy [27]. The small decrease in risk of advancement in CKD stage seen in the present analysis may have been influenced by some patients experiencing a similar effect of RAAS inhibitor discontinuation. Notably, the ongoing Multicentre Randomized Controlled Trial of ACEI/ARB Withdrawal in Advanced Renal Disease (STOP-ACEI) trial, a multicentre, randomized controlled trial, is investigating whether discontinuation of ACEI/ARB therapy can improve or stabilize renal function in advanced progressive CKD [28] and will provide

Table 3. Factors associated with time to first renal outcomes in users of RAAS inhibitors

Characteristics	Time to first advancement in CKD stage, HR (95% CI)	Time to first acute kidney injury, HR (95% CI)
Age, years		
18–29	1.00 (ref)	1.00 (ref)
30–39	**0.72 (0.56–0.93)**	0.80 (0.59–1.07)
40–49	**0.67 (0.53–0.85)**	**0.75 (0.57–0.99)**
50–59	0.99 (0.78–1.24)	0.90 (0.69–1.18)
60–69	**1.85 (1.47–2.33)**	1.29 (0.99–1.69)
70–79	**3.24 (2.57–4.08)**	**2.25 (1.73–2.94)**
80+	**4.23 (3.36–5.33)**	**4.42 (3.39–5.77)**
Sex		
Male	1.00 (ref)	1.00 (ref)
Female	**1.11 (1.09–1.13)**	**0.82 (0.80–0.83)**
Race		
White	1.00 (ref)	1.00 (ref)
Black	**1.28 (1.17–1.40)**	1.02 (0.91–1.15)
Asian	0.98 (0.90–1.06)	1.02 (0.93–1.13)
Smoking status		
No	1.00 (ref)	1.00 (ref)
Yes	**1.06 (1.03–1.10)**	**1.50 (1.45–1.55)**
Ex	**1.06 (1.04–1.08)**	**1.10 (1.08–1.13)**
Unknown	0.96 (0.81–1.14)	0.92 (0.76–1.11)
BMI		
Normal (<25 kg/m^2)	1.00 (ref)	1.00 (ref)
Overweight (25 to <30 kg/m^2)	**1.08 (1.05–1.11)**	**0.86 (0.83–0.89)**
Obese (30+ kg/m^2)	**1.18 (1.15–1.22)**	**1.06 (1.03–1.10)**
Unknown	**1.03 (1.00–1.06)**	**1.15 (1.11–1.19)**
Comorbidities[a]		
Ischaemic heart disease (including MI)	**1.06 (1.04–1.09)**	**1.09 (1.06–1.12)**
Arrhythmia (including AFib)	**1.11 (1.09–1.14)**	**1.32 (1.28–1.36)**
Hypertension	**1.05 (1.03–1.08)**	**1.05 (1.02–1.08)**
Cerebrovascular disease	**1.04 (1.01–1.07)**	**1.27 (1.23–1.30)**
Hyperlipidaemia	**1.03 (1.01–1.05)**	**0.96 (0.94–0.98)**
Chronic liver disease	**1.07 (1.02–1.12)**	**1.68 (1.60–1.76)**
Obstructive lung disease	**1.05 (1.03–1.07)**	**1.31 (1.28–1.35)**
Heart failure	**1.51 (1.47–1.55)**	**1.88 (1.83–1.94)**
Diabetes (Type 1 or 2)	**1.45 (1.42–1.49)**	**1.85 (1.81–1.90)**
CKD	**0.89 (0.87–0.91)**	**1.92 (1.87–1.96)**

Analysis of factors associated with time to first advancement in CKD stage and first acute kidney injury. HRs were adjusted for demographic characteristics (age, sex, race, smoking status and BMI), the calendar year of the index date and comorbidities [ischaemic heart disease, arrhythmia, hypertension, cerebrovascular disease, hyperlipidaemia, chronic liver disease, obstructive lung disease, heart failure, diabetes (Type 1 or 2) and CKD]; statistically significant ($P < 0.05$) differences versus the reference group are written in bold type.

[a]Versus not having the comorbidity (reference value of 1.00).

AFib, atrial fibrillation; MI, myocardial infarction.

additional data to address this important research question. It is important to monitor renal function as well as potassium levels in patients receiving RAAS inhibitors; however, these drugs also improve long-term outcomes and therefore the benefits and risks of discontinuation should be carefully considered for each individual patient [29].

Not unexpectedly, factors associated with clinical outcomes independently of RAAS inhibitor interruptions or cessations in this analysis included increasing age and the presence of baseline comorbidities such as heart failure, diabetes and CKD. These factors were also associated with both hyperkalaemia and RAAS inhibitor treatment interruptions in the previously published analysis [21]. The reduced associations between female sex and most clinical outcomes compared with male sex is also consistent with evidence that males develop cardiovascular disease at an earlier age than women, and have a lower life expectancy [30, 31].

In comparison with many of the comorbidities investigated, the relationship between BMI and clinical outcomes was less clear. Although obesity is a well-known risk factor for cardiovascular disease and mortality in the general population, the risk of all-cause mortality and first all-cause hospitalization was significantly lower in both overweight and obese patients compared with those who had a normal BMI. Although slightly counterintuitive, it is notable that no clear association has been demonstrated between BMI and risk of mortality in patients with CKD; indeed, there is some evidence that obesity is protective in patients with advanced CKD [32]. The high prevalence of CKD among patients in this study cohort could therefore have impacted this finding.

The association between interruptions or cessations in RAAS inhibitor therapy and adverse clinical outcomes has been reported in several recent studies. In a US cohort study of patients with cardiorenal comorbidities, cardiorenal adverse

events or mortality occurred in 34.3% of patients who discontinued RAAS inhibitor therapy, compared with 24.9 and 24.9% of patients on sub-maximum and maximum doses, respectively [11]. Moreover, in a retrospective analysis of patients with declining kidney function, discontinuation of RAAS inhibitors was associated with an increased risk of mortality (HR = 1.39, 95% CI 1.20–1.60) and MACE (HR = 1.37, 95% CI 1.20–1.56), but with no alteration of the risk of end-stage kidney disease [18]. RAAS inhibitor discontinuations (defined as use of RAAS inhibitors at baseline but not during follow-up) were also strongly associated with all-cause and cardiovascular mortality in an analysis of patients with congestive heart failure enrolled in the European Society of Cardiology Heart Failure Association EURObservational Research Programme Heart Failure Long-Term Registry [20]. Our results concur with the findings from these studies, particularly in terms of the association between the presence of cardiorenal comorbidities and adverse clinical outcomes.

Of note, 17% of patients included in this analysis were receiving ACEI and ARB treatment at baseline, although it was not possible to assess whether these patients were receiving both types of RAAS inhibitor concurrently or on different occasions. Data on dual ACEI and ARB use were not sufficiently reported in other studies examined to enable a comparison with the percentage use observed in this study [10, 11, 18–20]. However, dual blockade of RAAS with combination ACEI and ARB therapy is not recommended as it is associated with adverse clinical outcomes [33].

Collectively, the findings from this study add to the body of evidence supporting the adverse clinical outcomes associated with interruptions or cessations in RAAS inhibitor therapy. Although many reasons for treatment disruption, such as hyperkalaemia, are treatable, many patients who experience down-titration or discontinuation of therapy remain on a suboptimal RAAS inhibitor dose or are not re-challenged with RAAS inhibitors once the reason for discontinuation has been resolved, despite some guidelines explicitly recommending this [11, 34]. The increased risk of adverse clinical outcomes following RAAS inhibitor interruption or cessation emphasizes the need for consideration and, where possible, management of modifiable factors in order to allow patients to remain on the highest tolerated dose of RAAS inhibitor therapy.

Strengths of this study include the large number of patients, the robustness of the data and the linkage between the CRPD and HES databases [21]. Data may be generalizable to patients using RAAS inhibitors in other countries. The 30-day prescription length in the UK permitted a more accurate determination of interruptions in treatment than would be possible in countries with a longer prescription period.

This study has several limitations. Due to the retrospective design, it was only possible to establish association, rather than causality, between RAAS inhibitor interruptions or cessations and adverse clinical outcomes, and the reasons for interruptions or cessations were not available. Thus, all findings are exploratory in nature and require further investigation. As occurrence of clinical outcomes was determined by entries in the CPRD and HES databases without independent validation, there is a possibility of underreporting or misclassification of outcomes of interest, that events occurring in emergency care only will be missed and that diagnostic codes or laboratory data may lack the specificity required to ascertain whether a particular event of interest occurred.

In analyses, assessments of RAAS inhibitor exposure assumed that patients were using the drugs as prescribed, which might not always be the case. Moreover, the risks of clinical outcomes were not analysed for RAAS interruptions and cessations separately, and it cannot be assumed that both contributed equally to the findings reported here.

In conclusion, this real-world analysis of RAAS inhibitor users demonstrated that interruptions or cessations in RAAS inhibitor therapy were associated with an increased risk of all-cause mortality, first occurrence of all-cause hospitalization and adverse cardiovascular and renal outcomes. Other factors associated with adverse clinical outcomes in patients receiving RAAS inhibitor therapy included age and the presence of underlying comorbidities.

Although reasons for RAAS inhibitor disruption were not assessed, these findings suggest that potential risks for and against RAAS inhibitor treatment disruption need to be carefully considered in patients for whom guideline-recommended RAAS inhibitor therapy is indicated.

SUPPLEMENTARY DATA

Supplementary data are available at ckj online.

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AUTHORS' CONTRIBUTIONS

This was a secondary analysis of existing data. All authors contributed equally to analysis and interpretation of the data, drafting the manuscript, critically revising the content and approving the final version for publication.

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DATA AVAILABILITY STATEMENT

Full data sets underlying the findings described in this manuscript are not available, in accordance with the CPRD requirement that anonymized datasets are destroyed after use.

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