BMJ Open

Renin-Angiotensin System Blockade and Risk of Acute Kidney Injury: A Population-Based Cohort Study

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2016-012690
Article Type:	Research
Date Submitted by the Author:	18-May-2016
Complete List of Authors:	Mansfield, Kathryn; London School of Hygiene and Tropical Medicine Faculty of Epidemiology and Population Health, Non-communicable Disease Epidemiology Nitsch, Dorothea; London School of Hygiene and Tropical Medicine Faculty of Epidemiology and Population Health, Non-communicable Disease Epidemiology Smeeth, Liam; London School of Hygiene and Tropical Medicine Faculty of Epidemiology and Population Health, Non-communicable Disease Epidemiology Bhaskaran, Krishnan; London School of Hygiene and Tropical Medicine Faculty of Epidemiology and Population Health, Non-communicable Disease Epidemiology Tomlinson, Laurie; London School of Hygiene and Tropical Medicine Faculty of Epidemiology and Population Health, Non-communicable Disease Epidemiology
Primary Subject Heading:	Renal medicine
Secondary Subject Heading:	Epidemiology, Pharmacology and therapeutics, General practice / Family practice
Keywords:	acute kidney injury, angiotensin-converting enzyme inhibitors, angiotensin receptor antagonists, cohort study, renin-angiotensin system

Renin-Angiotensin System Blockade and Risk of Acute Kidney Injury: A Population-Based Cohort Study

Authors: Kathryn E Mansfield,[1] Dorothea Nitsch,[1] Liam Smeeth,[1] Krishnan Bhaskaran,[1] Laurie A Tomlinson[1]

Affiliations
[1] Department of Non-Communicable Disease Epidemiology, London School of Hygiene and Tropical Medicine, London, WC1E 7HT, United Kingdom

Corresponding author
Kathryn Mansfield, kathryn.mansfield@lshtm.ac.uk
The London School of Hygiene and Tropical Medicine, Keppel Street, London, WC1E 7HT
Telephone: 0207 927 2922

Key words: acute kidney injury; angiotensin-converting enzyme inhibitors; angiotensin receptor antagonists; cohort study; renin-angiotensin system

Word count
Abstract: 297 (BMJ open: max 300)
Text: 3,709 (BMJ open: recommended max 4,000)
Tables/Figures: 1 tables, 2 figures
References: 33
Supplementary material: 4 tables, 2 figures, 1 text

ABSRTACT

Objective: To investigate whether there is an association between use of ACE inhibitors (ACEI) and angiotensin receptor blockers (ARB), and risk of acute kidney injury (AKI).

Study Design: We conducted a new-user cohort study of the rate of AKI among users of common antihypertensives.

Setting: UK primary care practices contributing to the Clinical Practice Research Datalink (CPRD) eligible for linkage to hospital records data from the Hospital Episode Statistics (HES) database between April 1997 and March 2014.

Participants: New users of antihypertensives: ACEI/ARB, beta-blockers, calcium channel blockers and thiazide diuretics.

Outcomes: The outcome was first episode of AKI. We estimated incidence rate ratio (RR) for AKI during time exposed to ACEI/ARB compared to time unexposed, adjusting for age, sex, comorbidities, use of other antihypertensive drugs, and calendar period using Poisson regression. Covariates were time-updated.

Results: Among 570,445 participants, 303,761 were prescribed ACEI/ARB with a median follow-up of 2.8 years. The adjusted rate ratio of AKI during time exposed to ACEI/ARB compared to time unexposed was 1.12 (95% CI 1.07–1.17). This relative risk varied depending on absolute risk of AKI, with lower or no increased relative risk from the drugs among those at greatest absolute risk. For example, among people with stage 4 chronic kidney disease (who had 6.69 [95% CI 5.57–8.03] times higher rate of AKI compared to those without chronic kidney disease) the adjusted rate ratio of AKI during time exposed to ACEI/ARB compared to time unexposed was 0.66 (95% CI 0.44–0.97) in contrast to 1.17 (95% CI 1.09–1.25) among people without chronic kidney disease.

Conclusions: Treatment with ACEI/ARB is associated with only a small increase in AKI risk while individual patient characteristics are much more strongly associated with the rate of AKI. The degree of increased risk varies between patient groups.

ARTICLE SUMMARY

Strengths and limitations of this study

- This is the largest study of this topic to date, it examines an inclusive population-based cohort and reflects routine clinical use of these medications.
- By comparing ACEI/ARB use to use of other antihypertensives, we were able to reduce confounding by indication compared to previous case-control studies.
- We were able to clearly define and adjust for covariates, including renal function, prior to starting the medication. The time-updated analysis reduced residual confounding, while restriction to only incident users reduced adherence bias.
- However, there are a number of important limitations. Our assessment of drug exposure was based on prescriptions so we cannot be certain that people prescribed the drug were taking the medication.
- We did not have inpatient biochemical data so could only use ICD-10 coding to define AKI. Therefore, we have captured only a proportion of the cases defined by current biochemical definitions of AKI, although this includes a greater proportion of more severe cases.

INTRODUCTION

Acute kidney injury (AKI) is a sudden decline in renal function, affecting up to 20% of people admitted to hospital, and is strongly associated with increased mortality and longer duration of hospital stay.[1] Prevention and better management of patients with AKI is the focus of national programmes[2] and global campaigns.[3]

It is strongly believed that angiotensin converting enzyme inhibitors (ACEI) and angiotensin receptor blockers (ARB) are associated with development of AKI, particularly during acute illness. However, surprisingly, the evidence to support this belief is limited. The incidence of AKI in randomised controlled trials of ACEI and ARBs compared to placebo is poorly described due to variable definitions or absent reporting of kidney related adverse events.[4] Previous observational studies have compared the risk of AKI in patients using ACEI/ARB alone to the risks among ACEI/ARB users also taking diuretics and/or non-steroidal anti-inflammatory drugs (NSAIDs),[5–7] or with ACEI/ARB alone under specific circumstances.[8,9] However, the risk of AKI in patients taking ACEI or ARBs alone compared to other comparator drugs has not been examined in a population cohort using individual patient data. By contrast, high quality evidence from randomised trials of increased risk of AKI associated with dual prescription of ACEI and ARB[10,11] compared to single agent therapy has led to a restriction on the use of these drugs in combination.[12]

Despite this limited evidence there is a growing consensus that ACEI/ARB should be withheld during acute illness.[13,14] Guidelines for patients to self-manage medications linked to AKI during these situations, known as 'sick day rules', are being widely introduced.[15] Therefore, we aimed to investigate the association between AKI and the use of ACEI/ARB in a large population-based cohort study of people starting treatment with commonly used antihypertensive drugs (ACEI/ARB, beta-blockers, calcium channel blockers, thiazide diuretics). We chose to compare new users of different classes of anti-hypertensive drugs to reduce confounding by indication.

METHODS

Study design and setting

We undertook a cohort study using the UK Clinical Practice Research Datalink (CPRD) and linked hospital record data from the Hospital Episode Statistics (HES) database. CPRD is a database of routinely collected primary care electronic health record data from 7% of the UK population.[16] Included patients are largely representative of the UK population.[16–18] HES records cover all admissions for NHS funded patients treated in either English NHS trusts or by independent providers.[19] Fifty-eight percent of general practices included in CPRD are linked to HES data.[16] The study period was from 1st April 1997 to 31st March 2014, the latest date for which there is HES data linkage to CPRD. This study was approved by the LSHTM Research Ethics Committee (reference 6536) and by the CPRD independent scientific advisory committee (ISAC protocol number: 14-208).

Participants, exposures and outcomes

To minimise confounding by indication, rather than comparing ACEI/ARB users to otherwise healthy individuals, we identified a cohort of new-users of drugs that prescribed for similar indications to ACEI/ARBs. We developed a cohort of all HES-linked CPRD patients aged 18 years or older who were new users of antihypertensive drugs (ACEI/ARB, beta-blockers, calcium channel blockers or thiazide diuretics) during the study period. The primary exposure was use of ACEI/ARB and other drugs were treated as potential confounders. To ensure that we had reliable measures of drug use and baseline covariates, we required that all participants had at least one year continuous registration in CPRD before the first recorded antihypertensive drug prescription. We calculated the length of each prescription using the quantity of medication prescribed and the daily dose recorded, excluding patients for whom dosing information was inadequate to obtain a robust duration of exposure. Exposure to medications was assumed to start on the date of the prescription. We identified continuous courses of therapy by allowing for a 60-day gap between the end date of one prescription and the start of the next consecutive prescription (to allow for stock piling of medications). Drug exposure status was time-updated based on continuous courses of therapy.

Follow-up started at first prescription for the first of any of the antihypertensive drugs and ended at either occurrence of the outcome or the earliest of: i) end of final prescription; ii) death; iii) left GP practice; iv) last data collection; or v) diagnosis of end-stage renal disease (ESRD) (Supplementary Text S1). We excluded patients with ESRD prior to cohort entry.

We defined the outcome as the first episode of AKI identified within 28 days of the start of a hospital admission identified using ICD-10 morbidity coding in HES (Supplementary Table S1), to capture

cases of AKI that were present at hospital admission but may have not been immediately diagnosed, without excluding cases that resulted in a prolonged admission.

Covariates

Due to the complex and overlapping potential risk factors for AKI, we used a directed acyclic graph (DAG) approach to visualise our *a priori* assumptions about the potential biological mechanisms between exposure and outcome and to guide adjustment for confounding in sequentially adjusted regression models (Supplementary Figure S1).[20]

We adjusted for baseline CKD stage, established by calculating eGFR using the CKD-EPI equation.[21] We used serum creatinine results recorded in the 12 months before first prescription to calculate eGFR, using either the highest eGFR from the most recent two serum creatinine results, separated by a minimum of three months or, if only one creatinine result was available, the single most recent serum creatinine recorded prior to first prescription. Serum creatinine measurements were not routinely IDMS-standardised until 2013. We therefore assumed that all creatinine results were unstandardised and multiplied results with a correction factor of 0.95 before calculating eGFR without regard to ethnicity.[22] To avoid selection bias, we included an absent CKD category for those with no recorded serum creatinine result in the 12 months prior to first antihypertensive prescription.

Other chronic comorbidities included as confounders were: diabetes mellitus, hypertension, cardiac failure, cardiac arrhythmia, and ischaemic heart disease, identified both from CPRD and HES data. In regression analyses these comorbidities were recorded as time-updating variables representing "ever diagnosed," whose status changed with the first recorded code for each specific condition. Age group was entered as a time-updating variable. We adjusted for time-updated exposure to loop and potassium sparing diuretics in addition to antihypertensive drugs.[6]

We used existing morbidity code lists and algorithms for ethnicity,[17] smoking status, alcohol intake, BMI,[18] and chronic comorbidities.[23–27] Socioeconomic status was defined using quintiles of index of multiple deprivation scores for 2004.

We included calendar period as a covariate to adjust for the many changes in clinical, diagnostic and administrative practices over the study period that may influence the measurement of baseline renal function and number of reported AKI cases.

Statistical analysis

For the main analysis we classified exposure status using a time-updated binary indicator variable for ACEI/ARB. We estimated rate ratios associated with time exposed to ACEI/ARB compared to time

unexposed, adjusting for potential confounders using Poisson regression. We used robust standard errors to account for clustering by general practice. We initially adjusted for age and sex only, and then fitted an adjusted model including DAG-informed time-updated confounders (age, sex, chronic comorbidities, other antihypertensive drugs, loop and potassium-sparing diuretics, and calendar period). Further adjustments were for smoking, alcohol, BMI and socioeconomic status. All data management and analyses were performed using Stata version 13 (StataCorp, Texas).

We have made code lists for all covariates available in online repository at: https://clinicalcodes.rss.mhs.man.ac.uk/.[28]

Sensitivity analyses

To determine the impact of including individuals with unknown baseline renal function, we repeated the main analysis in the subgroup of the cohort with known baseline renal function. Next, we repeated the main analysis in new entrants to the cohort, who had ethnicity recorded in CPRD or HES, after 2006 when recording of ethnicity was rewarded in primary care leading to improvements in CPRD data completeness.[17] We included ethnicity both in the equation used to calculate eGFR and as a covariate in the analysis. Finally, we tested the robustness of the definition of AKI in a range of sensitivity analyses including limiting the defining ICD-10 code to just N17, which has a high positive predictive value for AKI.[29]

Additional analyses

We conducted three additional analyses. Firstly, we investigated the impact of including interaction terms between treatment with loop diuretics and, separately, potassium-sparing diuretics and ACEI/ARB – as concurrent use of ACEI/ARB and diuretics has been linked to increased risk of AKI.[5,6] In our second additional analysis, renal function was time updated to examine how the relationship between AKI and ACEI/ARB exposure was related to renal function at the time that AKI occurred, rather than at entry to the cohort. To minimize misclassification of CKD stage by renal function measured during an AKI episode we excluded all measurements of kidney function that occurred within one week of an admission with AKI.[30] Finally, we investigated whether there was any difference in rate of AKI during time exposed to ACEI compared to ARB, and during combination therapy.[10,11]

RESULTS

Study population and baseline characteristics

Of 1,373,441 individuals aged 18 years or older with a new prescription for an ACEI/ARB, beta-blocker, calcium channel blocker or thiazide diuretic identified in the Clinical Practice Research

Datalink (CPRD) between April 1997 and March 2014, 570,445 were included in the final cohort (Figure 1). Of these, 303,763 (53%) were prescribed an ACEI/ARB during follow-up. Total follow-up time for the whole cohort was over 2.3 million person years and 56% (1,320,001/2,345,098) of that was time exposed to ACEI/ARB. Follow-up ended a mean of 4.1 years (SD 4.1) after first antihypertensive drug prescription. 14,907 people developed AKI. The characteristics of the overall cohort, and the cohort during time exposed and unexposed to ACEI/ARB are presented in Table 1. Those exposed to ACEI/ARB were more likely to be male with cardiac comorbidities, and to have had renal function measured prior to starting an antihypertensive. Fifty-three percent of time exposed to ACEI/ARB was between 2009 and 2014 compared to 38% of time unexposed.

Table 1. Person-time under follow-up broken down by patient-level characteristics and ACEI/ARB exposure status. Data are person years unless otherwise stated. Numbers in brackets are column percentages unless otherwise specified.

		Whole cohort	Cohort during time exposed to ACEI/ARBs	Cohort during time unexposed to ACEI/ARBs
	Total person years at risk	2,345,098	1,320,001	1,025,097
	Median person years at risk (IQR)	2.8 (0.4–7)	3.6 (1.1–6.9)	0.8 (0.2–3.4)
	Range of person years at risk	0.0–17.0	0.0–17.0	0.0–17.0
AKI	Number of events	14,907	10,157	4,750
Sex	Female	1,152,897 (49.2)	577,957 (43.8)	574,940 (56.1)
Age (years)	18–44	151,515 (6.5)	73,332 (5.6)	78,183 (7.6)
	45–54	350,170 (14.9)	211,576 (16.0)	138,593 (13.5)
	55–59	274,706 (11.7)	161,826 (12.3)	112,881 (11.0)
	60–64	324,416 (13.8)	188,097 (14.2)	136,319 (13.3)
	65–69	326,139 (13.9)	184,344 (14.0)	141,795 (13.8)
	70–74	308,156 (13.1)	171,103 (13.0)	137,053 (13.4)
	75–84	467,754 (19.9)	255,577 (19.4)	212,178 (20.7)
	85+	142,242 (6.1)	74,146 (5.6)	68,096 (6.6)
CKD stage (eGFR in ml/ min/1.73m^2)	No CKD (eGFR >=60)	934,070 (39.8)	580,871 (44.0)	353,199 (34.5)
	CKD stage 3a (eGFR 45–59)	113,238 (4.8)	68,074 (5.2)	45,163 (4.4)
	CKD stage 3b (eGFR 30–44)	18,435 (0.8)	10,873 (0.8)	7,562 (0.7)
	CKD stage 4 (eGFR 15–29)	1,926 (0.1)	1,036 (0.1)	890 (0.1)
	Baseline CKD status absent	1277429 (54.5)	659,145 (49.9)	618,283 (60.3)
Comorbidities	Diabetes mellitus	504,053 (21.5)	371,423 (28.1)	132,630 (12.9)
	Ischaemic heart disease	735,949 (31.4)	437,433 (33.1)	298,516 (29.1)
	Cardiac failure	152,904 (6.5)	116,449 (8.8)	36,456 (3.6)
	Arrhythmia	281,141 (12.0)	156,555 (11.9)	124,586 (12.2)
	Hypertension	2,036,050 (86.8)	1,194,641 (90.5)	841,409 (82.1)
Other antihypertensive drugs	Beta blockers	764,584 (32.6)	289,190 (21.9)	475,394 (46.4)
	Calcium channel blockers	732,628 (31.2)	331,429 (25.1)	401,199 (39.1)
	Thiazides	742,535 (31.7)	328,679 (24.9)	413,855 (40.4)
Non-thiazide diuretic drugs	Loop diuretics	155,911 (6.6)	118,565 (9.0)	37,346 (3.6)
	Potassium sparing diuretics	42,047 (1.8)	25,015 (1.9)	17,033 (1.7)
Ethnicity	White	982,377 (41.9)	569,946 (43.2)	412,431 (40.2)
	South Asian	26,933 (1.1)	17,647 (1.3)	9,286 (0.9)
	Black	14,8301 (0.6)	6,723 (0.5)	8,108 (0.8)
	Other	7,832 (0.3)	4,792 (0.4)	3,041 (0.3)
	Mixed heritage	2,553 (0.1)	1,490 (0.1)	1,063 (0.1)
	Not stated or missing	1,310,572 (55.9)	719,403 (54.5)	591,169 (57.7)
Calendar period	1997–2000	93,628 (4.0)	26,446 (2.0)	67,182 (6.6)
	2001–2004	418,412 (17.8)	170,465 (12.9)	247,947 (24.2)
	2005–2008	742,558 (31.7)	422,466 (32.0)	320,092 (31.2)
	2009–2011	646,221 (27.6)	416,685 (31.6)	229,535 (22.4)
	2012–2014	444,280 (18.9)	283,938 (21.5)	160,342 (15.6)

[#]note exposed and unexposed numbers do not total the whole cohort number as individuals may be included in both columns.
ACEI/ARB: Angiotensin converting enzyme inhibitor/angiotensin receptor blocker
IQR: Interquartile range
CKD: Chronic kidney disease
eGFR: Estimated glomerular filtration rate

Association of ACEI or ARB prescription with rate of AKI

Over the whole study period, the age and sex adjusted incidence rate ratio (RR) for first AKI comparing time exposed to ACEI/ARB to time unexposed was 1.69 (95% CI 1.63–1.76), which fell to 1.12 (95% CI 1.07–1.17) after full adjustment (Supplementary Table S3). Further adjustment for lifestyle covariates and socioeconomic status made marginal difference to all results and is not presented. Among subgroups with the highest absolute rates of AKI such as those with cardiac failure and chronic kidney disease (CKD) stage 4 there is no measurable association (or an apparent protective effect) of AKI with ACEI/ARB treatment (Figure 2).

Sensitivity analyses

Inclusion of only those with known baseline CKD stage, adjustment for ethnicity, and varying the way that AKI was defined from ICD-10 coding made minimal differences to the RR for AKI comparing time exposed to ACEI/ARB to time unexposed (Supplementary Table S3).

Interaction between diuretics and ACEI/ARB treatment

There was an interaction between loop diuretics and ACEI/ARB treatment; there was no apparent increase in risk of AKI associated with ACEI/ARB exposure during periods of treatment with loop diuretic. Among people exposed to loop diuretics the RR for AKI during time exposed to ACEI/ARB compared to time unexposed was 0.98 (95% CI 0.91–1.24) while among those not requiring loop diuretics the RR was 1.18 (95% CI 1.13–1.24) ($p<0.001$). Absolute rates of AKI stratified by ACEI/ARB treatment and comorbidity, modelled with inclusion of the interaction term, highlight the higher rates of AKI among people taking loop diuretics within each stratum (Supplementary Table S4 and Figure S2). There was no evidence for an interaction between potassium-sparing diuretics and ACEI/ARB treatment (RR for AKI among those prescribed potassium-sparing diuretics during time exposed to ACEI/ARB compared to time unexposed 1.09 (95% CI 0.96–1.24) while among those not requiring potassium-sparing diuretics the RR was 1.12 (95% CI 1.08–1.17: $p=0.667$).

Impact of change in renal function on rate of AKI

When renal function was time-updated, the RR for AKI during time exposed and unexposed to ACEI/ARB was attenuated to 1.02 (95% CI 0.98–1.07) (Supplementary Table S2). Among people who developed AKI, the median number of days between last measurement of estimated glomerular filtration rate (eGFR) and admission with the AKI episode was 116 days (IQR 44–258 days).

Rate of AKI in users of ACEI compared to ARB, or both combined

Compared to time not exposed to either drug, exposure to an ACEI was associated with an adjusted RR for AKI of 1.14 (95% CI 1.09–1.19), while exposure to an ARB was associated with a RR of 1.06

(95% CI 1.00–1.12). Dual therapy with both an ACEI and an ARB with associated with nearly twice the rate of AKI compared to time unexposed to either drug (RR 1.83 95% CI 1.53–2.17).

DISCUSSION

Among antihypertensive users we found a 12% (95% CI 1.07–1.17) increase in the rate of AKI during time exposed to ACEI/ARB compared to unexposed time (after adjustment for comorbidities, additional drug exposure, and calendar period). However, this relative risk varied markedly among different subgroups, and was highest among those with the lowest absolute risk of acute kidney injury. There was no evidence of increased AKI risk for ACEI/ARB users among those at greatest absolute risk of AKI (e.g. those with comorbidities or those also prescribed loop diuretics). Adjustment for most recent renal function attenuated the risk of AKI due to ACEI/ARB exposure. In addition we show a near doubling of risk of AKI during time exposed to both ACEI and ARB.

Our results suggest that there would be limited benefit – in terms of reducing population rates of AKI – by an intervention aimed at ACEI/ARB cessation during acute illness. Assuming that differences in AKI rates were directly attributable to ACEI/ARB exposure, in a low risk group – such as those with normal renal function – despite a 17% increase in relative risk of AKI during ACEI/ARB treatment, removal of the drug would prevent less than two cases of AKI for 1000 treated people during one year. In contrast, in a group at high absolute risk of AKI – such as those with cardiac failure – we would not anticipate prevention of any cases of AKI by removing ACEI/ARB exposure. However, this conclusion rests on the assumption that there is no residual confounding, and given the complex interplay between confounding factors in this study (illustrated by the inverse relationship observed between AKI risk and CKD stage or cardiac failure) this seems unlikely.

Our results do not support the commonly accepted view that treatment with ACEI or ARB is a strong risk factor for AKI.[14] However, previous high quality evidence in this area is scarce. Estimates of the increase in AKI risk associated with use of ACEI/ARB from randomised trials are limited.[4] Many commonly cited observational studies are cross-sectional or address the risk of AKI in relation to specific diseases or interventions.[7–9] Two recent nested case-control studies using UK primary care data reported only relative risks for AKI among users of NSAIDS in addition to ACEI/ARB and diuretics.[5,6] Only one population-based study has examined the relative risk of AKI among ACEI/ARB users compared to non-users. This study, despite limited data quality, found similar results to our own with a fully adjusted OR of 1.11 (95% CI 1.02–1.20) comparing those prescribed and not prescribed ACEI/ARB.[31]

High quality evidence does exist in relation to the risks of AKI associated with combined ACEI and ARB therapy. Here, recent clinical trials using this regime have reported hazard ratios for renal

adverse events ranging from 1.20 (95% CI 0.96–1.50) to 2.19 (95% CI 1.13–4.22), compared to single agent treatment alone.[10,11] Our results, showing a near doubling of rate for AKI with dual blockade, are similar to these findings and strongly support the validity of our study.

Among those at the highest absolute risk of AKI (e.g. those with additional comorbidities), we found rates of AKI for ACEI/ARB users were lower than for non-users. One explanation for these findings is that, in patients with multiple comorbidities that are indications for ACEI/ARB treatment, not being treated with ACEI or ARB is a marker of unmeasured poor health status or frailty. For example, an individual may have stopped ACEI/ARB treatment when they became unwell, perhaps due to worsening renal function, and the reason for stopping ACEI/ARB places them at higher risk of AKI during subsequent follow-up.

We have also shown that patients taking loop diuretics have higher rates of AKI than similar patients not prescribed the drugs. This may be causal, due to salt and water depletion during acute illness, or additional loop diuretic treatment may be a marker of severity of comorbidities. We anticipated that pharmacological interaction between loop diuretics and ACEI/ARB would be associated with an increased risk of AKI compared to treatment with loop diuretics alone but we have shown the converse. Again, this is likely to be explained by confounding by underlying health status. While this may mean that our results underestimate the true causal effect of taking ACEI/ARB on the risk of AKI, it reinforces the importance of assessing overall risk of AKI in planning potential interventions aimed at lowering risk. Patients with multiple risk factors but not taking ACEI/ARB may be those who would benefit most from close monitoring of fluid balance and intensive monitoring during acute illness, but they may be overlooked if the clinical focus is on drug cessation.

This is the largest study of this topic to date, it examines an inclusive population-based cohort and reflects routine clinical use of these medications. By comparing ACEI/ARB use to use of other antihypertensives, we were able to reduce confounding by indication compared to previous case-control studies. We were able to clearly define and adjust for covariates including renal function prior to starting the medication. The time-updated analysis reduced residual confounding, while restriction to only incident users reduced adherence bias.

However, there are a number of important limitations. Our assessment of drug exposure was based on prescriptions so we cannot be certain that people prescribed the drug were taking the medication; importantly we were unable to take into account any temporary discontinuation in medication use during acute illness or hospitalisation. We did not have inpatient biochemical data so could only use ICD-10 coding to define AKI. Therefore, we have captured only a proportion of the cases defined by current biochemical definitions of AKI, although this includes a greater proportion

of more severe cases,[32,33] and were not able to grade the severity of AKI. We examined first episode of AKI only. We cannot be certain that AKI was present at the time of hospital admission, or developed while in hospital although we have conducted several sensitivity analyses to address this. We did not examine the additional effects of NSAIDs because these have been examined in previous studies.[5–7] We did not adjust for surveillance bias but would anticipate that patients taking ACEI/ARB had closer monitoring of renal function, which would bias our results to a higher rate ratio than the true effect. Finally, there is limited data on proteinuria from primary care records so we were not able to adjust for this potentially important covariate.

In conclusion, our results show that treatment with ACEI/ARB appears to be associated with only a small increase in AKI risk while patient characteristics are much more strongly associated with the rate of AKI. This suggests that current strategies to promote patient-initiated drug cessation will have minimal impact in reducing the population rates of AKI when targeted at low-risk individuals. While people may benefit from optimised medicines management during acute illness, our results suggest that these interventions should be targeted at individuals at highest risk of AKI rather than targeting all ACEI/ARB users.

FUNDING

LT is funded by a Wellcome Trust intermediate clinical fellowship (101143/Z/13/Z). KB is funded by a Wellcome Trust/Royal Society Sir Henry Dale fellowship (107731/Z/15/Z). LS is supported by a Wellcome Trust Senior Research Fellowship in Clinical Science (098504/Z/12/Z).The funders had no role in study design; collection, analysis, and interpretation of data; writing the report; and the decision to submit the report for publication.

CONTRIBUTIONS

LT had the original idea for the study. All authors were involved in the study design. KM undertook the data management, primary analysis and wrote the first draft. All authors contributed to further drafts and approved the final manuscript. KM and LT had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

COMPETING INTERESTS

All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years, no other relationships or activities that could appear to have influenced the submitted work.

ETHICAL APPROVAL

This study was approved by the LSHTM Research Ethics Committee (reference 6536) and by the CPRD independent scientific advisory committee (ISAC protocol number: 14-208).

DATA SHARING

No additional data available.

REFERENCES

1 Chertow GM, Burdick E, Honour M, *et al.* Acute kidney injury, mortality, length of stay, and costs in hospitalized patients. *J Am Soc Nephrol* 2005;**16**:3365–70. doi:10.1681/ASN.2004090740

2 Think Kidneys. Acute Kidney injury: The NHS campaign to improve the care of people at risk of, or with, acute kideny injury. [internet]. 2016. Available from: https://www.thinkkidneys.nhs.uk/aki/ (accessed Jan 2016)

3 Mehta RL, Cerdá J, Burdmann EA, *et al.* International Society of Nephrology's 0by25 initiative for acute kidney injury (zero preventable deaths by 2025): a human rights case for nephrology. *Lancet* 2015;**6736**:1–28. doi:10.1016/S0140-6736(15)60126-X

4 Palmer SC, Mavridis D, Navarese E, *et al.* Comparative effi cacy and safety of blood pressure-lowering agents in adults with diabetes and kidney disease: a network meta-analysis. *Lancet* 2015;**385**:2047–56. doi:10.1016/S0140-6736(14)62459-4

5 Lapi F, Azoulay L, Yin H, *et al.* Concurrent use of diuretics, angiotensin converting enzyme inhibitors, and angiotensin receptor blockers with non-steroidal anti-inflammatory drugs and risk of acute kidney injury: nested case-control study. *Br Med J* 2013;**346**:8525. doi:10.1136/bmj.e8525

6 Dreischulte T, Morales DR, Bell S, *et al.* Combined use of nonsteroidal anti-inflammatory drugs with diuretics and/or renin–angiotensin system inhibitors in the community increases the risk of acute kidney injury. *Kidney Int* 2015;:1–8. doi:10.1038/ki.2015.101

7 Loboz KK, Shenfield GM. Drug combinations and impaired renal function – the ' triple whammy '. *B J Pharmacol* 2004;**59**:239–43. doi:10.1111/j.1365-2125.2004.02188.x

8 Plataki M, Kashani K, Cabello-Garza J, *et al.* Predictors of acute kidney injury in septic shock patients: an observational cohort study. *Clin J Am Soc Nephrol* 2011;**6**:1744–51. doi:10.2215/CJN.05480610

9 Arora P, Rajagopalam S, Ranjan R, *et al.* Preoperative use of angiotensin-converting enzyme inhibitors/angiotensin receptor blockers is associated with increased risk for acute kidney injury after cardiovascular surgery. *Clin J Am Soc Nephrol* 2008;**3**:1266–73. doi:10.2215/CJN.05271107

10 Fried LF, Emanuele N, Zhang JH, *et al.* Combined angiotensin inhibition for the treatment of diabetic nephropathy. *N Engl J Med* 2013;**369**:1892–903. doi:10.1056/NEJMoa1303154

11 Mann JFE, Schmieder RE, McQueen M, *et al.* Renal outcomes with telmisartan, ramipril, or both, in people at high vascular risk (the ONTARGET study): a multicentre, randomised, double-blind, controlled trial. *Lancet* 2008;**372**:547–53.http://www.ncbi.nlm.nih.gov/pubmed/18707986 (accessed 1 May2014).

12 European Medicines Agency. Combined use of medicines affecting the renin-angiotensin system (RAS) to be restricted – CHMP endorses PRAC recommendation. 2014.http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2014/05/news_detail_002107.jsp&mid=WC0b01ac058004d5c1 (accessed 18 Sep2015).

13 Feehally J, Gilmore I, Barasi S, *et al.* RCPE UK Consensus Conference Statement Management of acute kidney injury: the role of fluids, e-alerts and biomarkers. *JR Coll Physicians* 2013;**43**:37–8.http://www.lumison.co.uk/~rcpe/journal/issue/journal_43_1/acutekidneyinjury.pdf (accessed 4 Sep2014).

14 National Institute for Health and Care Excellence. NICE clincal guideline 169: Acute kidney injury - Prevention, detection and management of acute kidney injury up to the point of renal replacement therapy. [internet] 2013. Available from: http://www.nice.org.uk/nicemedia/live/14258/65056/65056.pdf (accessed 14 Aug 2015 Aug)

15 Scottish Patient Safety Programme. Medicine Sick Day Rules Card. Healthc. Improv. Scotl. 2015.Available from: http://www.scottishpatientsafetyprogramme.scot.nhs.uk/programmes/primary-care/medicine-sick-day-rules-card (accessed 16 Jun2015).

16 Herrett E, Gallagher AM, Bhaskaran K, *et al.* Data Resource Profile: Clinical Practice Research Datalink (CPRD). *Int J Epidemiol* 2015;:1–10. doi:10.1093/ije/dyv098

17 Mathur R, Bhaskaran K, Chaturvedi N, *et al.* Completeness and usability of ethnicity data in UK-based primary care and hospital databases. *J Public Health (Oxf)* 2013;**36**:684–92. doi:10.1093/pubmed/fdt116

18 Bhaskaran K, Forbes HJ, Douglas I, *et al.* Representativeness and optimal use of body mass index (BMI) in the UK Clinical Practice Research Datalink (CPRD). *BMJ Open* 2013;**3**:e003389. doi:10.1136/bmjopen-2013-003389

19 HSCIC. Hospital Episode Statistics. http://www.hscic.gov.uk/hes (accessed 25 Jun2015).

20 Hernán MA, Hernández-Díaz S, M.Werler M, *et al.* Causal Knowledge as a Prerequisite for Confounding Evaluation: An Application to Birth Defects Epidemiology. *Am J Epidemiol* 2002;**155**:176–84. doi:10.1093/aje/155.2.176

21 Levey AS, Stevens LA, Schmid CH, *et al.* A new equation to estimate glomerular filtration rate. *Ann Intern Med* 2009;**150**:604–12.http://annals.org/article.aspx?articleid=744469 (accessed 28 Mar2014).

22 Fox CS, Matsushita K, Woodward M, *et al.* Associations of kidney disease measures with mortality and end-stage renal disease in individuals with and without diabetes: a meta-analysis. *Lancet* 2012;**380**:1662–73. doi:10.1016/S0140-6736(12)61350-6

23 McDonald HI, Thomas SL, Millett ERC, *et al.* CKD and the Risk of Acute, Community-Acquired Infections Among Older People With Diabetes Mellitus: A Retrospective Cohort Study Using Electronic Health Records. *Am J Kidney Dis* 2015;**66**:60–8. doi:doi:10.1053/j.ajkd.2014.11.027

24 Quint JK, Herrett E, Bhaskaran K, *et al.* Effect of β blockers on mortality after myocardial infarction in adults with COPD: population based cohort study of UK electronic healthcare records. *BMJ* 2013;**347**:f6650. doi:10.1136/bmj.f6650

25 Brauer R, Smeeth L, Anaya-Izquierdo K, *et al.* Antipsychotic drugs and risks of myocardial infarction: a self-controlled case series study. *Eur Heart J* 2014;:ehu263. doi:10.1093/eurheartj/ehu263

26 Herrett E, Shah AD, Boggon R, *et al.* Completeness and diagnostic validity of recording hospital care disease registry and national mortality. *Br Med J* 2013;**346**. doi:10.1136/bmj.f2350

27 Douglas IJ, Evans SJW, Hingorani AD, *et al.* Clopidogrel and interaction with proton pump inhibitors: comparison between cohort and within person study designs. *BMJ* 2012;**345**:e4388. doi:10.1136/bmj.e4388

28 Springate DA, Kontopantelis E, Ashcroft DM, *et al.* ClinicalCodes: an online clinical codes repository to improve the validity and reproducibility of research using electronic medical records. *PLoS One* 2014;**9**:e99825. doi:10.1371/journal.pone.0099825

29 Tomlinson LA, Riding AM, Payne RA, *et al.* The accuracy of diagnostic coding for acute kidney injury in England - a single centre study. *BMC Nephrol* 2013;**14**:58. doi:10.1186/1471-2369-14-58

30 Siew ED, Ikizler TA, Matheny ME, *et al.* Estimating baseline kidney function in hospitalized patients with impaired kidney function. *Clin J Am Soc Nephrol* 2012;**7**:712–9. doi:10.2215/CJN.10821011

31 Bedford M, Farmer CK, Irving J, *et al.* Acute kidney injury: an acceptable risk of treatment with renin-angiotensin system blockade in primary care? *Can J Kidney Heal Dis* 2015;**2**:14. doi:10.1186/s40697-015-0044-y

32 Sawhney S, Fluck N, Marks A, *et al.* Acute kidney injury - How does automated detection perform? *Nephrol Dial Transplant* 2015;**30**:1853–61. doi:10.1093/ndt/gfv094

33 Grams ME, Waikar SS, Macmahon B, *et al.* Performance and Limitations of Administrative Data in the Identification of AKI. *Clin J Am Soc Nephrol* 2014;:1–8. doi:10.2215/CJN.07650713

FIGURE LEGENDS

Figure 1. Flow diagram showing the creation of the cohort and reasons for exclusion.

<<Insert Figure 1>>

ACEI/ARB: Angiotensin converting enzyme inhibitor/angiotensin receptor blocker
BB: Beta blocker
CCB: Calcium channel blocker
CPRD: Clinical Practice Research Datalink
HES: Hospital Episode Statistics
ESRD: End stage renal disease

Figure 2. Modelled rates* of AKI (during the calendar period 2012–2014) per 1,000 person years at risk for AKI during time exposed to ACEI/ARBs compared to time unexposed, stratified by characteristics and comorbidities.

<<Insert Figure 2>>

*Absolute rates (unless otherwise stated) are for men, aged 75–84, with CKD stage 3a, and no comorbidities – chosen as a large, clinically important, high risk group.
**Adjusted using Poisson regression for: age, sex, chronic comorbidities (CKD, hypertension, diabetes mellitus, cardiac failure, ischaemic heart disease, and arrhythmia), time exposed to other antihypertensive drugs (beta-blockers, calcium channel blockers, and thiazides), time exposed to loop and potassium-sparing diuretics, and calendar period.
AKI: Acute kidney injury
ACEI/ARB: Angiotensin converting enzyme inhibitor/angiotensin receptor blocker
pyar: Person years at risk
CKD: Chronic kidney disease

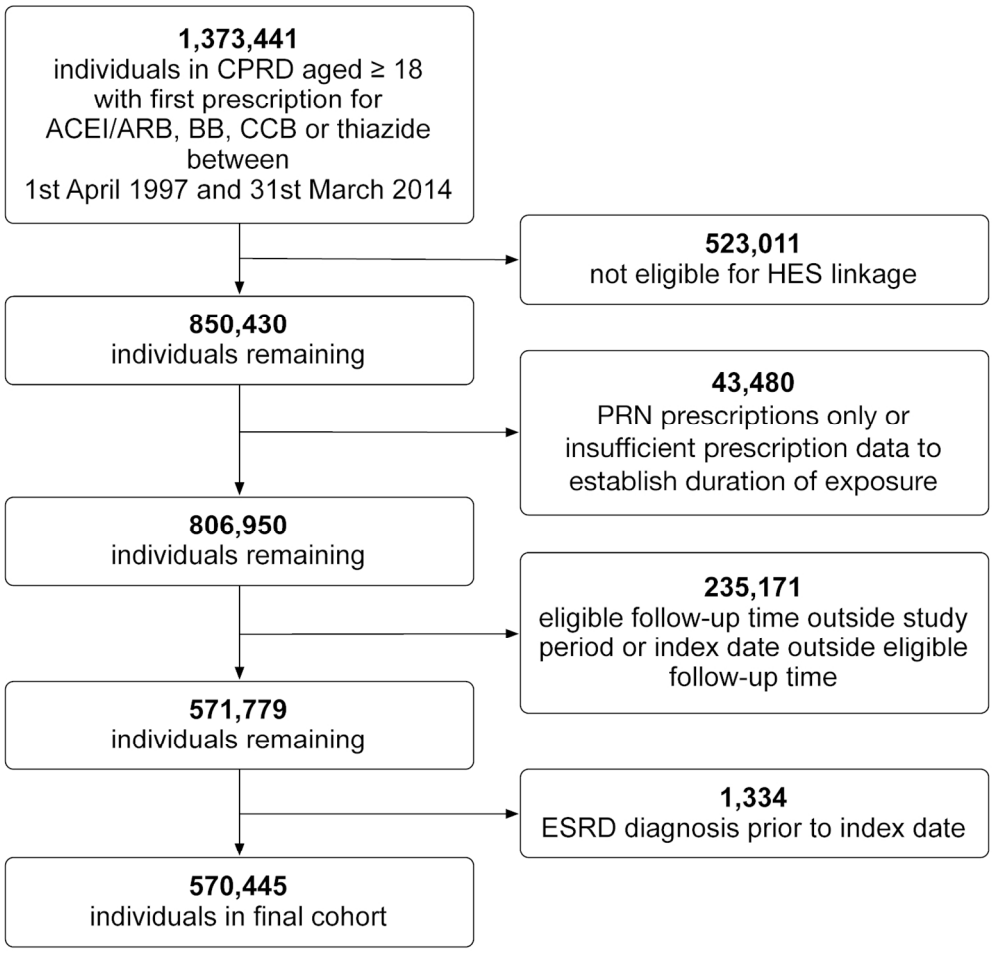


Figure 1. Flow diagram showing the creation of the cohort and reasons for exclusion.
Figure 1
129x124mm (300 x 300 DPI)

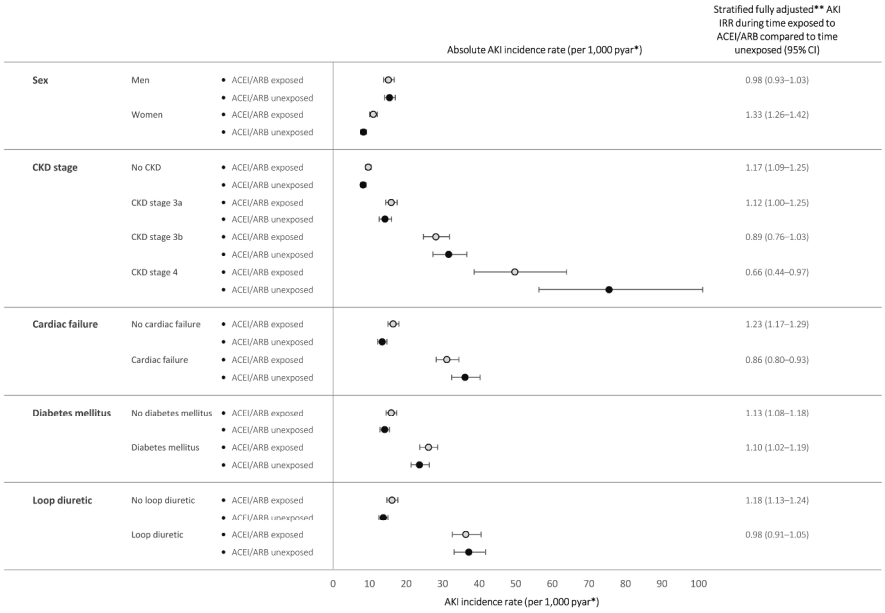


Figure 2. Modelled rates* of AKI (during the calendar period 2012–2014) per 1,000 person years at risk for AKI during time exposed to ACEI/ARBs compared to time unexposed, stratified by characteristics and comorbidities

Figure 2
271x169mm (300 x 300 DPI)

Definition of acute kidney injury

Table S1. ICD-10 codes used to define of acute kidney injury in HES data.

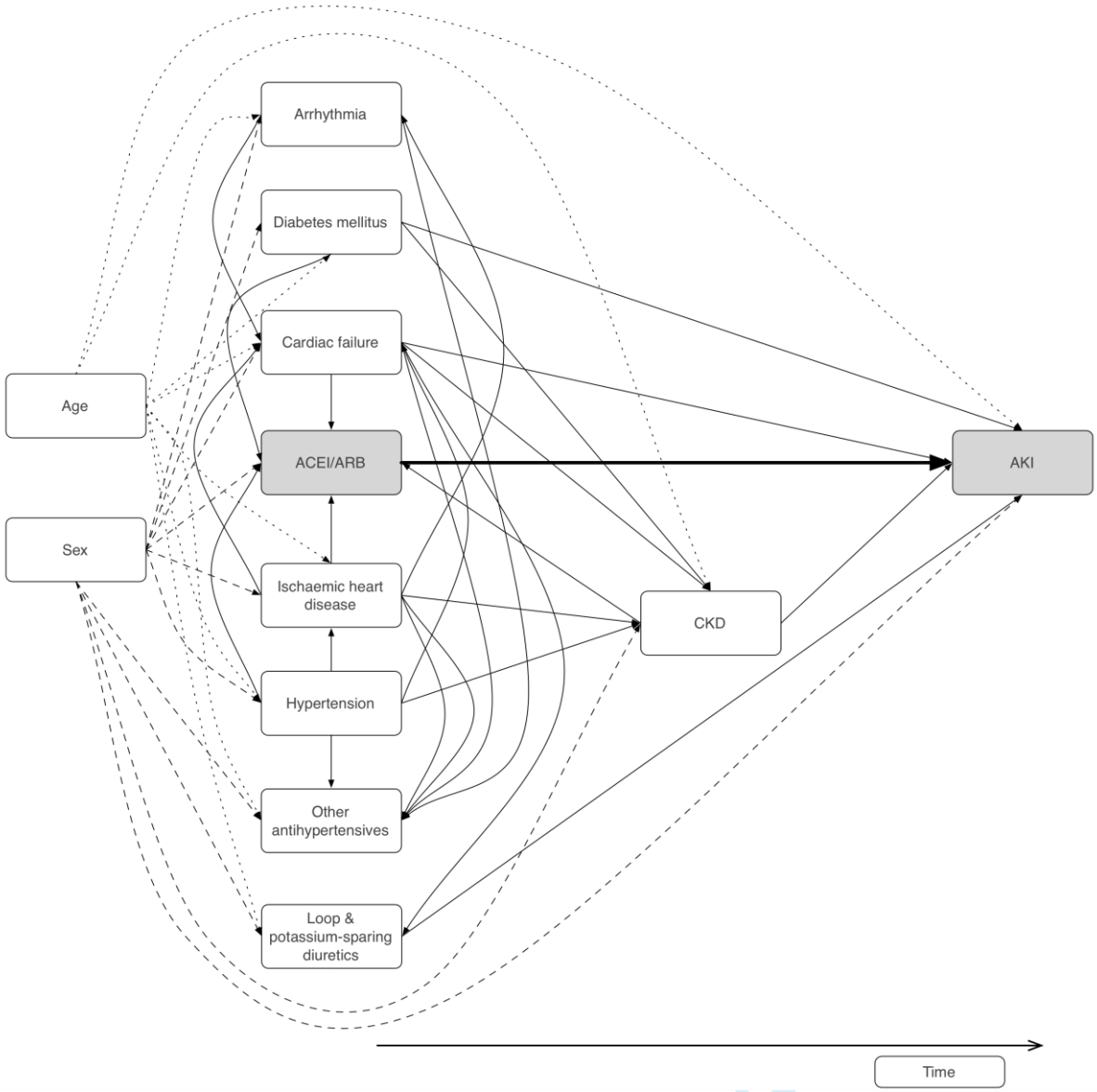
ICD-10 code	Clinical term	% of cases of AKI cases defined by code
N14.1	Nephropathy induced by other drugs, medicaments and biological substances	0.12
N14.2	Nephropathy induced by unspecified drug, medicament or biological substance	0.03
N17.0	Acute renal failure with tubular necrosis	0.78
N17.1	Acute renal failure with acute cortical necrosis	0.04
N17.2	Acute renal failure with medullary necrosis	0.03
N17.8	Other acute renal failure	0.28
N17.9	Acute renal failure, unspecified	70.14
N19	Unspecified kidney failure	25.31
N99.0	Postprocedural renal failure	1.29
R34	Anuria and oliguria	0.90
R94.4	Abnormal results of kidney function studies	0.99

Text S1. Definition of end-stage renal disease

ESRD was defined using hospital and primary care morbidity coding, and hospital procedure coding as the presence of:

i) An ESRD morbidity code.
ii) A code for renal transplant.
iii) A code for peritoneal or haemodialysis.
iv) Stage 5 chronic kidney disease (identified using morbidity coding and estimated glomerular filtration rate (eGFR).
v) Stage 4 CKD with a fistula, suggesting ESRD is anticipated.

Figure S1. Simplified directed acyclic graph (DAG) illustrating implicitly assumed causal structure underlying our adjusted models.



➔ Represents causal path of interest

Under this assumed framework, adjusting for all measured variables blocks confounding pathways.

AKI: Acute kidney injury
ACEI/ARB: Angiotensin converting enzyme inhibitor/angiotensin receptor blocker
CKD: Chronic kidney disease

Table S2. Age and sex, and fully adjusted* incidence rate ratios (95% CIs) for AKI in sequentially adjusted models.

	AKI incidence rate ratio (95% CI)		
	Age & sex adjusted	Fully adjusted*	Fully adjusted* with CKD stage as a time-updated variable
	n=570,445	n=570,445	n=570,445
Exposure of interest			
ACEI/ARB	1.69 (1.63–1.76)	1.12 (1.07–1.17)	1.02 (0.98–1.07)
Sex			
Female	0.61 (0.59–0.63)	0.66 (0.64–0.68)	0.63 (0.61–0.65)
Age			
18–44	reference	reference	reference
45–54	0.85 (0.74–0.97)	0.81 (0.71–0.93)	0.89 (0.77–1.02)
55–59	1.08 (0.94–1.23)	0.97 (0.85–1.12)	1.07 (0.93–1.22)
60–64	1.41 (1.24–1.61)	1.18 (1.03–1.35)	1.25 (1.09–1.42)
65–69	2.11 (1.86–2.38)	1.59 (1.41–1.80)	1.55 (1.36–1.76)
70–74	3.15 (2.80–3.55)	2.17 (1.92–2.45)	1.84 (1.62–2.09)
75–84	6.03 (5.37–6.78)	3.34 (2.96–3.76)	2.26 (2.00–2.56)
85+	15.06 (13.34–17.01)	5.54 (4.87–6.30)	2.98 (2.61–3.41)
Comorbidity			
CKD stage			
No CKD	N/A	reference	reference
CKD stage 3a	N/A	1.67 (1.57–1.77)	2.60 (2.46–2.75)
CKD stage 3b	N/A	3.19 (2.91–3.51)	5.77 (5.42–6.15)
CKD stage 4	N/A	6.69 (5.57–8.03)	13.44 (12.45–14.51)
Baseline CKD status absent	N/A	1.18 (1.13–1.23)	1.90 (1.74–2.08)
Diabetes mellitus	N/A	1.65 (1.59–1.72)	1.52 (1.46–1.58)
Ischaemic heart disease	N/A	1.14 (1.09–1.19)	1.12 (1.07–1.17)
Cardiac failure	N/A	2.09 (1.97–2.20)	1.92 (1.82–2.03)
Arrhythmia	N/A	1.42 (1.36–1.48)	1.45 (1.38–1.51)
Hypertension	N/A	1.09 (1.04–1.15)	1.01 (0.96–1.06)
Other antihypertensive drugs			
Beta-blocker	N/A	0.99 (0.95–1.03)	0.90 (0.87–0.94)
Calcium channel blocker	N/A	0.97 (0.93–1.01)	0.93 (0.90–0.97)
Thiazide	N/A	0.99 (0.95–1.04)	0.91 (0.87–0.96)
Non-thiazide diuretics			
Loop	N/A	2.36 (2.23–2.50)	1.77 (1.67–1.88)
Potassium sparing	N/A	1.86 (1.74–1.98)	1.67 (1.56–1.79)
Calendar period			
1997–2000	N/A	reference	reference
2001–2004	N/A	1.17 (1.03–1.34)	1.14 (0.99–1.32)
2005–2008	N/A	1.62 (1.42–1.85)	1.61 (1.39–1.86)
2009–2011	N/A	2.26 (1.99–2.57)	2.38 (2.06–2.75)
2012–2014	N/A	3.29 (2.89–3.74)	3.62 (3.12–4.19)

*Adjusted using Poisson regression for: age, sex, chronic comorbidities (CKD, hypertension, diabetes mellitus, cardiac failure, ischaemic heart disease, and arrhythmia), time exposed to other antihypertensive drugs (beta-blockers, calcium channel blockers and thiazides), time exposed to loop and potassium-sparing diuretics, and calendar period

AKI: Acute kidney injury

ACEI/ARB: Angiotensin converting enzyme inhibitor/angiotensin receptor blocker

CKD: Chronic kidney disease

eGFR: Estimated glomerular filtration rate

Table S3. Incidence rate ratios (95% CIs) for AKI during time exposed to ACEI/ARB compared to time unexposed in the main analysis and additional sensitivity analyses.

	Number of individuals	Number of AKI cases identified	AKI incidence rate ratio (95% CI) for ACEI/ARB therapy (compared to time unexposed)	
			Age and sex adjusted	Fully adjusted*
Main analysis: AKI defined using all ICD-10 codes in any position and any episode within 28 days of the start of a hospital admission.	570,445	14,907	1.69 (1.63–1.76)	1.12 (1.07–1.17)
AKI defined using only code N17 in any position and any episode within 28 days of the start of a hospital admission.	570,445	11,174	1.76 (1.68–1.84)	1.12 (1.06–1.17)
AKI defined using all ICD-10 codes in any diagnostic position in the 1st or 2nd episode for episodes that occur within 7 days of admission.	570,445	14,377	1.70 (1.64–1.77)	1.13 (1.09–1.18)
AKI defined using all ICD-10 codes in the 1st diagnostic position of the 1st or 2nd episode for episodes that start within 7 days of admission.	570,445	3,009	1.83 (1.69–1.97)	1.21 (1.11–1.33)
Restricted to those with known baseline CKD status.	268,456	7,312	1.56 (1.47–1.65)	1.09 (1.02–1.16)
Including time-updated CKD stage rather than baseline CKD stage.	570,445	14,907	1.69 (1.63–1.76)	1.02 (0.98–1.07)
Restricted to those entering the cohort from 2006 with known ethnicity**.	132,847	1,944	1.37 (1.24–1.52)	1.07 (0.95–1.21)

*Adjusted using Poisson regression for: age, sex, chronic comorbidities (CKD, hypertension, diabetes mellitus, cardiac failure, ischaemic heart disease, and arrhythmia), time exposed to other antihypertensive drugs (beta-blockers, calcium channel blockers and thiazides), time exposed to loop and potassium sparing diuretics, and calendar period.

**Additionally adjusted for ethnicity and with race used to calculate eGFR

AKI: Acute kidney injury

ACEI/ARB: Angiotensin converting enzyme inhibitor/angiotensin receptor blocker

CKD: Chronic kidney disease

eGFR: Estimated glomerular filtration rate

Renin-Angiotensin System Blockade and Risk of Acute Kidney Injury: A Population-Based Cohort Study
Kathryn E Mansfield, Dorothea Nitsch, Liam Smeeth, Krishnan Bhaskaran, Laurie A Tomlinson

Table S4. Descriptive table of modelled rates of AKI (during the calendar period 2012–2014) per 1000 person years at risk stratified by characteristics and comorbidities. This model includes an interaction term for loop diuretic use.

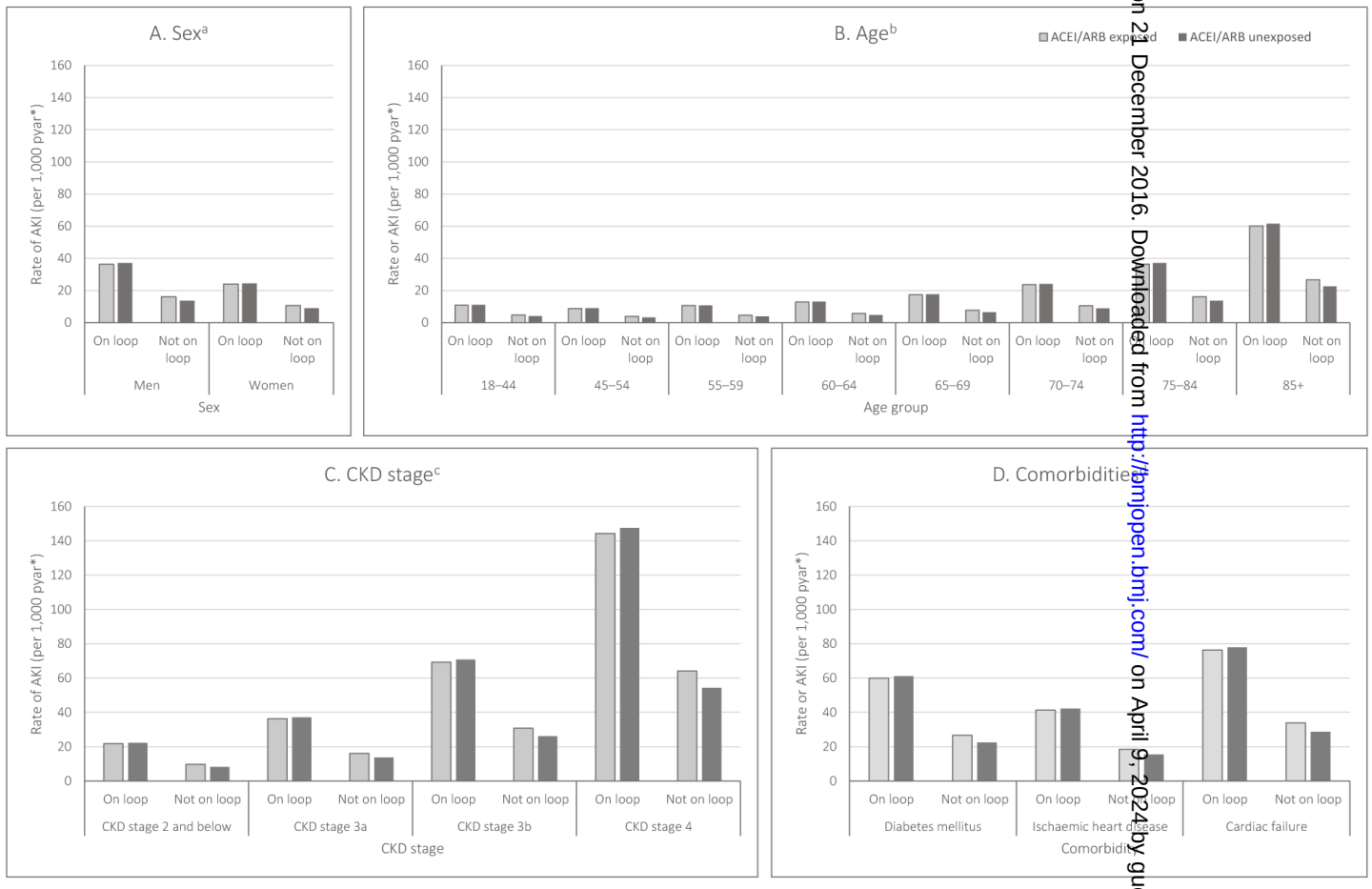
	Rate of AKI in ACEI/ARB exposed per 1000 pyar*		Rate of AKI in ACEI/ARB unexposed per 1000 pyar*		Absolute rate difference per 1000 pyar	
	On loop	Not on loop	On loop	Not on loop	On loop	Not on loop
Sex (rates for each sex aged 75-84 with CKD stage 3A and no comorbidities)						
Men	36.3	16.1	37.1	13.7	1.8	2.4
Women	24.0	10.6	24.5	9.0	0.5	1.6
Age (rates for each age group for men with CKD stage 3A and no comorbidities)						
18–44	10.9	4.8	11.1	4.1	0.2	0.7
45–54	8.8	3.9	9.0	3.3	0.2	0.6
55–59	10.6	4.7	10.8	4.0	0.2	0.7
60–64	12.8	5.7	13.1	4.8	0.3	0.9
65–69	17.3	7.7	17.7	6.5	0.4	1.2
70–74	23.6	10.5	24.1	8.9	0.5	1.6
75–84	36.3	16.1	37.1	13.7	0.8	2.4
85+	60.1	26.7	61.5	22.6	1.4	4.1
CKD stage (rates for each CKD stage for men with no comorbidities)						
No CKD (eGFR >=60)	21.8	9.7	22.3	8.2	0.5	1.5
CKD stage 3a (eGFR 45–59)	36.3	16.1	37.1	13.7	0.8	2.4
CKD stage 3b (eGFR 30–44)	69.3	30.8	70.8	26.1	1.5	4.7
CKD stage 4 (eGFR 15–29)	144.3	64.1	147.5	54.3	3.2	9.8
Comorbidity (rates for men aged 75-84 with CKD stage 3A and only the specified comorbidity)						
Diabetes mellitus	59.9	26.6	61.2	22.5	1.3	4.1
Ischaemic heart disease	41.3	18.4	42.2	15.5	0.9	2.9
Cardiac failure	76.3	33.9	78.0	28.7	1.7	5.2
Risk group						
Lowest risk group [1]	4.3	1.9	4.4	1.6	0.1	0.3
Highest risk group [2]	648.7	288.3	663.1	244.1	14.4	44.2

[1] Low risk: women aged 18-44 without CKD and no comorbidities

[2] High risk: men aged 85+ with CKD stage 4 and all of: ischaemic heart disease, cardiac failure and diabetes mellitus.

*Adjusted using Poisson regression for: age, sex, chronic comorbidities (CKD, hypertension, diabetes mellitus, cardiac failure, ischaemic heart disease, and arrhythmia), time exposed to other antihypertensive drugs (beta-blockers, calcium channel blockers and thiazides), time exposed to loop and potassium sparing diuretic, and calendar period. Also includes an interaction term for loop diuretic use.

Figure S2. Modelled rates of AKI (during the calendar period 2012–2014) per 1,000 person years at risk stratified by characteristics and comorbidities. This model includes an interaction term for loop diuretic use.



*Adjusted using Poisson regression for: age, sex, chronic comorbidities (CKD, hypertension, diabetes mellitus, cardiac failure, ischaemic heart disease, and arrhythmia), time exposed to other antihypertensive drugs (beta-blockers, calcium channel blockers and thiazides), time exposed to loop and potassium sparing diuretics, and calendar period. Also includes an interaction term for loop diuretic use.
Absolute rates (unless otherwise stated) are for men, aged 75–84, with CKD stage 3a, and no comorbidities – chosen as a large, clinically important, high risk group.
[a]rates for each sex aged 75-84 with CKD stage 3A and no comorbidities.
[b]rates for each age group for men with CKD stage 3A and no comorbidities.
[c]rates for each CKD stage for men with no comorbidities.
[d]rates for men aged 75-84 with CKD stage 3A and only the specified comorbidity.
ACEI/ARB: Angiotensin converting enzyme inhibitor/angiotensin receptor blocker.
AKI: Acute kidney injury
pyar: Person years at risk
CKD: Chronic kidney disease

The RECORD statement – checklist of items, extended from the STROBE statement, which should be reported in observational studies using routinely collected health data.

	Item No.	STROBE items	Location in manuscript where items are reported	RECORD items	Location in manuscript where items are reported
Title and abstract					
	1	(a) Indicate the study's design with a commonly used term in the title or the abstract (b) Provide in the abstract an informative and balanced summary of what was done and what was found	(a) Reference made to cohort study design in title and abstract (p2) (b) Methods summarised in abstract (p2).	RECORD 1.1: The type of data used should be specified in the title or abstract. When possible, the name of the databases used should be included. RECORD 1.2: If applicable, the geographic region and timeframe within which the study took place should be reported in the title or abstract. RECORD 1.3: If linkage between databases was conducted for the study, this should be clearly stated in the title or abstract.	(1.1) Reference made to Clinical Practice Research Datalink (CPRD) and Hospital Episode Statistics (HES) made in abstract (p2). (1.2) Abstract outlines that study in UK between April 1997 and March 2014 (p2). (1.3) Use of linkage between HES and CPRD databases stated in the abstract (p2).
Introduction					
Background rationale	2	Explain the scientific background and rationale for the investigation being reported	Scientific background and rationale for study is presented in the Introduction section (p4).		
Objectives	3	State specific objectives, including any prespecified hypotheses	Specific aims of the study presented are in Introduction section (p4).		
Methods					
Study Design	4	Present key elements of study design early in the paper	Key elements of the study design are introduced in the Introduction section of the paper (p4) and expanded in the Methods section (p5).		
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Setting, locations, study dates are presented under the 'Study design and setting' subheading in the Methods section (p5).		

	Item No.	STROBE items	Location in manuscript where items are reported	RECORD items	Location in manuscript where items are reported
Participants	6	*(a) Cohort study* - Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study* - Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study* - Give the eligibility criteria, and the sources and methods of selection of participants *(b) Cohort study* - For matched studies, give matching criteria and number of exposed and unexposed *Case-control study* - For matched studies, give matching criteria and the number of controls per case	(a) Eligibility criteria, and cohort entry and exit criteria are presented under the 'Participants, exposures and outcomes' subheading in the Methods section (p5). (b) This study is not matched.	RECORD 6.1: The methods of study population selection (such as codes or algorithms used to identify subjects) should be listed in detail. If this is not possible, an explanation should be provided. RECORD 6.2: Any validation studies of the codes or algorithms used to select the population should be referenced. If validation was conducted for this study and not published elsewhere, detailed methods and results should be provided. RECORD 6.3: If the study involved linkage of databases, consider use of a flow diagram or other graphical display to demonstrate the data linkage process, including the number of individuals with linked data at each stage.	(6.1) A detailed explanation of how the study population were identified is presented in the Methods section under the 'Participants, exposures and outcomes' subheading (p5). (6.2) Codes used to identify the outcome definition (acute kidney injury) have been validated in another study referenced in the manuscript (p7 ref29). Other code lists/algorithms have either been developed using those applied in other published studies (also referenced, p6). (6.3) The flow diagram presented in Figure 1 illustrates the number of individuals excluded from the study due to being ineligible for HES linkage.
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable.	Outcomes and exposures are defined under the 'Participants, exposures and outcomes' subheading of the Methods section (p5). Definitions for potential confounders are presented under the 'Covariates' subheading of the Methods section (p6).	RECORD 7.1: A complete list of codes and algorithms used to classify exposures, outcomes, confounders, and effect modifiers should be provided. If these cannot be reported, an explanation should be provided.	A complete list of codes and algorithms used to classify all variables is available for download from: https://clinicalcodes.rss.mhs.man.ac.uk/ An online clinical codes repository (p7).

	Item No.	STROBE items	Location in manuscript where items are reported	RECORD items	Location in manuscript where items are reported
Data sources/ measurement	8	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Each variable used is identified in CPRD or HES data. A clear definition of all variables used is presented in the appropriate sections of the Methods section (pp5-7). Variable definitions are the same for different groups of patients.		
Bias	9	Describe any efforts to address potential sources of bias	Covariates used are presented (p6). We present details of how study design was used to address possible selection bias and confounding by indication (under 'Participants, exposures and outcomes' subheading of Methods section, p5). In addition, we undertook a number of sensitivity analyses to test any variable definitions in order to address information and/or selection bias ('Sensitivity analysis' subheading of Methods section, p7).		
Study size	10	Explain how the study size was arrived at	The flow diagram presented in Figure 1 illustrates the creation of the cohort and reasons for exclusions. When developing the protocol we found that, based on a cautious estimate of a sample size (n= 102,524), we would have greater than 90% power (alpha 0.05) to detect a relative risk of 1.2 or more for incident AKI. The final sample size was nearly 5 x our cautious estimate (n=570,433).		

	Item No.	STROBE items	Location in manuscript where items are reported	RECORD items	Location in manuscript where items are reported
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why	Groupings for quantitative variables (age, eGFR) are presented in Tables 1 (p9) and S2 (Appendix)		
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding (b) Describe any methods used to examine subgroups and interactions (c) Explain how missing data were addressed (d) *Cohort study* - If applicable, explain how loss to follow-up was addressed *Case-control study* - If applicable, explain how matching of cases and controls was addressed *Cross-sectional study* - If applicable, describe analytical methods taking account of sampling strategy (e) Describe any sensitivity analyses	(a) Statistical methods used are presented under the 'Statistical analysis' subheading of the Methods section {pp6-7). (b) Methods used to examine subgroups are presented under the 'Additional analyses' subheading of the Methods section (p7). (c) Missing data were addressed using sensitivity analyses (documented under the 'Sensitivity analysis' subheading of the Methods section, p7). (d) Loss to follow-up is not applicable to this design as patients are followed-up until no longer eligible. (e) Sensitivity analyses are described under the appropriate subheading in the Methods section (p7).		
Data access and cleaning methods		..		RECORD 12.1: Authors should describe the extent to which the investigators had access to the database population used to create the study population. RECORD 12.2: Authors should provide information on the data cleaning methods used in the study.	(12.1) Investigators had full access to the CPRD dataset – documented in declarations section at the end of the manuscript (p14). (12.2) Data cleaning methods are described in the Methods section (p5).

	Item No.	STROBE items	Location in manuscript where items are reported	RECORD items	Location in manuscript where items are reported
Linkage		..		RECORD 12.3: State whether the study included person-level, institutional-level, or other data linkage across two or more databases. The methods of linkage and methods of linkage quality evaluation should be provided.	(12.3) The study included person-level data linkage. Data linkage of CPRD and HES data is undertaken by a trusted third party: the Health and Social Care Information Centre.
Results					
Participants	13	(a) Report the numbers of individuals at each stage of the study (*e.g.*, numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed) (b) Give reasons for non-participation at each stage. (c) Consider use of a flow diagram	(a) The number of individuals at each stage of the study is presented in Figure 1. (b) Reasons for exclusions at each stage are also presented in Figure 1 (c) See Figure 1.	RECORD 13.1: Describe in detail the selection of the persons included in the study (*i.e.,* study population selection) including filtering based on data quality, data availability and linkage. The selection of included persons can be described in the text and/or by means of the study flow diagram.	See Figure 1.
Descriptive data	14	(a) Give characteristics of study participants (*e.g.*, demographic, clinical, social) and information on exposures and potential confounders (b) Indicate the number of participants with missing data for each variable of interest (c) *Cohort study* - summarise follow-up time (*e.g.*, average and total amount)	(a) See Table 1 (p9) (b) See Table 1 (p9) (c) See Table 1 (p9)		
Outcome data	15	*Cohort study* - Report numbers of outcome events or summary measures over time *Case-control study* - Report numbers in each exposure category, or summary measures of exposure *Cross-sectional study* - Report numbers of outcome events or summary measures	See Table 1 (p9)		
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (e.g., 95% confidence interval). Make clear which confounders were adjusted for and why they were included (b) Report category boundaries when continuous variables were categorized (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	(a) See Table S2 in the supplementary appendix and also presented in the text of the Results section (p10). (b) Age, CKD, and calendar period boundaries clearly presented in Tables 1 (p9) and S2 (appendix). (c) Absolute risk presented in Figures 2 and S2 (appendix), and Table S4 (appendix).		

	Item No.	STROBE items	Location in manuscript where items are reported	RECORD items	Location in manuscript where items are reported
Other analyses	17	Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses	Results of sensitivity and secondary analyses presented in the Results section (p10) and Appendix Table S3.		
Discussion					
Key results	18	Summarise key results with reference to study objectives	Presented at beginning of Discussion section (p11).		
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Limitations discussed in the Discussion section (p12-13).	RECORD 19.1: Discuss the implications of using data that were not created or collected to answer the specific research question(s). Include discussion of misclassification bias, unmeasured confounding, missing data, and changing eligibility over time, as they pertain to the study being reported.	Limitations related specifically to using routinely collected health data for research are discussed in the Discussion section (pp12-13).
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Overall interpretation of the results are presented in the Discussion section (pp11-12).		
Generalisability	21	Discuss the generalisability (external validity) of the study results	Generalisability of study results discussed in Discussion section (p11).		
Other Information					
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Source of funding acknowledged at the end of the manuscript under the 'Funding' subheading (p14).		
Accessibility of protocol, raw data, and programming code		..		RECORD 22.1: Authors should provide information on how to access any supplemental information such as the study protocol, raw data, or programming code.	Study protocol number provided. Due to CPRD guidelines on data sharing of patient level data we are unable to share raw data (p14).

*Reference: Benchimol EI, Smeeth L, Guttmann A, Harron K, Moher D, Petersen I, Sørensen HT, von Elm E, Langan SM, the RECORD Working Committee. The REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) Statement. *PLoS Medicine* 2015; in press.

BMJ Open

Prescription of Renin-Angiotensin System Blockers and Risk of Acute Kidney Injury: A Population-Based Cohort Study

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2016-012690.R1
Article Type:	Research
Date Submitted by the Author:	06-Sep-2016
Complete List of Authors:	Mansfield, Kathryn; London School of Hygiene and Tropical Medicine Faculty of Epidemiology and Population Health, Non-communicable Disease Epidemiology Nitsch, Dorothea; London School of Hygiene and Tropical Medicine Faculty of Epidemiology and Population Health, Non-communicable Disease Epidemiology Smeeth, Liam; London School of Hygiene and Tropical Medicine Faculty of Epidemiology and Population Health, Non-communicable Disease Epidemiology Bhaskaran, Krishnan; London School of Hygiene and Tropical Medicine Faculty of Epidemiology and Population Health, Non-communicable Disease Epidemiology Tomlinson, Laurie; London School of Hygiene and Tropical Medicine Faculty of Epidemiology and Population Health, Non-communicable Disease Epidemiology
Primary Subject Heading:	Renal medicine
Secondary Subject Heading:	Epidemiology, Pharmacology and therapeutics, General practice / Family practice
Keywords:	acute kidney injury, angiotensin-converting enzyme inhibitors, angiotensin receptor antagonists, cohort study, renin-angiotensin system

Prescription of Renin-Angiotensin System Blockers and Risk of Acute Kidney Injury: A Population-Based Cohort Study

Authors: Kathryn E Mansfield,[1] Dorothea Nitsch,[1] Liam Smeeth,[1] Krishnan Bhaskaran,[1] Laurie A Tomlinson[1]

Affiliations
[1] Department of Non-Communicable Disease Epidemiology, London School of Hygiene and Tropical Medicine, London, WC1E 7HT, United Kingdom

Corresponding author
Kathryn Mansfield, kathryn.mansfield@lshtm.ac.uk
The London School of Hygiene and Tropical Medicine, Keppel Street, London, WC1E 7HT
Telephone: 0207 927 2922

Key words: acute kidney injury; angiotensin-converting enzyme inhibitors; angiotensin receptor antagonists; cohort study; renin-angiotensin system

Word count
Abstract: 298 (BMJ open: max 300)
Text: 4,198 (BMJ open: recommended max 4,000)
Tables/Figures: 1 table, 2 figures
References: 37
Supplementary material: 4 tables, 3 figures, 2 texts

ABSTRACT

Objective: To investigate whether there is an association between use of ACE inhibitors (ACEI) and angiotensin receptor blockers (ARB), and risk of acute kidney injury (AKI).

Study Design: We conducted a new-user cohort study of the rate of AKI among users of common antihypertensives.

Setting: UK primary care practices contributing to the Clinical Practice Research Datalink (CPRD) eligible for linkage to hospital records data from the Hospital Episode Statistics (HES) database between April 1997 and March 2014.

Participants: New users of antihypertensives: ACEI/ARB, beta-blockers, calcium channel blockers and thiazide diuretics.

Outcomes: The outcome was first episode of AKI. We estimated incidence rate ratio (RR) for AKI during time exposed to ACEI/ARB compared to time unexposed, adjusting for age, sex, comorbidities, use of other antihypertensive drugs, and calendar period using Poisson regression. Covariates were time updated.

Results: Among 570,445 participants, 303,761 were prescribed ACEI/ARB with a mean follow-up of 4.1 years. The adjusted rate ratio of AKI during time exposed to ACEI/ARB compared to time unexposed was 1.12 (95% CI 1.07–1.17). This relative risk varied depending on absolute risk of AKI, with lower or no increased relative risk from the drugs among those at greatest absolute risk. For example, among people with stage 4 chronic kidney disease (who had 6.69 [95% CI 5.57–8.03] times higher rate of AKI compared to those without chronic kidney disease) the adjusted rate ratio of AKI during time exposed to ACEI/ARB compared to time unexposed was 0.66 (95% CI 0.44–0.97) in contrast to 1.17 (95% CI 1.09–1.25) among people without chronic kidney disease.

Conclusions: Treatment with ACEI/ARB is associated with only a small increase in AKI risk while individual patient characteristics are much more strongly associated with the rate of AKI. The degree of increased risk varies between patient groups.

ARTICLE SUMMARY

Strengths and limitations of this study

- This is the largest study of this topic to date, it examines an inclusive population-based cohort and reflects routine clinical use of these medications.
- By comparing ACEI/ARB use to use of other antihypertensives, we were able to reduce confounding by indication compared to previous case-control studies.
- We were able to clearly define and adjust for covariates, including renal function, prior to starting the medication. The time-updated analysis reduced residual confounding, while restriction to only incident users reduced adherence bias.
- However, there are a number of important limitations. Our assessment of drug exposure was based on prescriptions so we cannot be certain that people prescribed the drug were taking the medication.
- We did not have inpatient biochemical data so could only use ICD-10 coding to define AKI. Therefore, we have captured only a proportion of the cases defined by current biochemical definitions of AKI, although this includes a greater proportion of more severe cases.

INTRODUCTION

Acute kidney injury (AKI) is a sudden decline in renal function, affecting up to 20% of people admitted to hospital, and is strongly associated with increased mortality and longer duration of hospital stay.[1] Prevention and better management of patients with AKI is the focus of national programmes[2] and global campaigns.[3]

It is strongly believed that angiotensin converting enzyme inhibitors (ACEI) and angiotensin receptor blockers (ARB) are associated with development of AKI, particularly during acute illness. Like other antihypertensives, ACEI/ARB reduce renal perfusion by systemic blood pressure reduction, an effect that is amplified by volume depletion in acute illness. However, in addition ACEI/ARB also cause a greater reduction in renal perfusion than other antihypertensives due to vasodilation of the efferent arterioles, the small blood vessels that leave the glomeruli, and by inhibition of renal autoregulation of glomerular filtration.[4] While biologically plausible, evidence to support the belief that ACEI/ARB use causes AKI is limited. The incidence of AKI in randomised controlled trials of ACEI and ARB compared to placebo is poorly described due to variable definitions or absent reporting of kidney related adverse events.[5] Previous observational studies have compared the risk of AKI in patients using ACEI/ARB alone to the risks among ACEI/ARB users also taking diuretics and/or non-steroidal anti-inflammatory drugs (NSAIDs),[6–8] or with ACEI/ARB alone under specific circumstances.[9–11] However, the risk of AKI in patients taking ACEI or ARB alone compared to other comparator drugs has not been examined in a population cohort using individual patient data. By contrast, high quality evidence from randomised trials of increased risk of AKI associated with dual prescription of ACEI and ARB[12,13] compared to single agent therapy has led to a restriction on the use of these drugs in combination.[14]

Despite this limited evidence there is a growing consensus that ACEI/ARB should be withheld during acute illness.[15,16] Guidelines for patients to self-manage medications linked to AKI during these situations, known as ‘sick day rules’, are being widely introduced.[17] Therefore, we aimed to investigate the association between AKI and the use of ACEI/ARB in a large population-based cohort study of people starting treatment with commonly used antihypertensive drugs (ACEI/ARB, beta-blockers, calcium channel blockers, thiazide diuretics). We chose to compare new users of different classes of anti-hypertensive drugs to reduce confounding by indication.

METHODS

Study design and setting

We undertook a cohort study using the UK Clinical Practice Research Datalink (CPRD) and linked hospital record data from the Hospital Episode Statistics (HES) database. CPRD is a database of routinely collected primary care electronic health record data from 7% of the UK population.[18] Included patients are largely representative of the UK population.[18–20] HES records cover all admissions for NHS funded patients treated in either English NHS trusts or by independent providers.[21] Fifty-eight percent of general practices included in CPRD are linked to HES data (representing 75% of English practices).[18] We used only fully linked data from CPRD and HES to ensure that all participants had complete data regarding the exposure (antihypertensive prescribing in primary care) and the outcome (hospital admission with AKI). The study period was from 1st April 1997 to 31st March 2014, the latest date for which there is HES data linkage to CPRD. This study was approved by the LSHTM Research Ethics Committee (reference 6536) and by the CPRD independent scientific advisory committee (ISAC protocol number: 14-208).

Participants, exposures and outcomes

To minimise confounding by indication, rather than comparing ACEI/ARB users to otherwise healthy individuals, we identified a cohort of new-users of drugs that were prescribed for similar indications to ACEI/ARB. We developed a cohort of all HES-linked CPRD patients aged 18 years or older who were new users of antihypertensive drugs (ACEI/ARB, beta-blockers, calcium channel blockers or thiazide diuretics) during the study period. The primary exposure was use of ACEI/ARB and other drugs were treated as potential confounders. To ensure that we had reliable measures of drug use and baseline covariates, we required that all participants had at least one year of continuous registration in CPRD before the first recorded antihypertensive drug prescription. We calculated the length of each prescription using the quantity of medication prescribed and the daily dose recorded, excluding patients for whom dosing information was inadequate to obtain a robust duration of exposure. Exposure to medications was assumed to start on the date of the prescription. We identified continuous courses of therapy by allowing for a 60-day gap between the end date of one prescription and the start of the next consecutive prescription (to allow for stock piling of medications).

Drug exposure status was time updated based on continuous courses of therapy. We defined exposure status using four time-varying, binary indicator variables to indicate exposure to each antihypertensive, with exposure status ‘switching on’ when an individual was prescribed a drug and ‘off’ when their prescription ended (example scenarios illustrating the assignment of indicator

variables are included in **Supplementary Text S1** and **Figure S1**). This allowed us to maximise the available follow-up time, control for exposure to other antihypertensives, allowed drug combinations to be investigated through interaction terms, and more closely modelled real life prescribing patterns.

Follow-up started at first prescription for the first of any of the antihypertensive drugs and ended at either occurrence of the outcome or the earliest of: i) end of final prescription; ii) death; iii) left GP practice; iv) last data collection; or v) diagnosis of end-stage renal disease (ESRD) (**Supplementary Text S2**). We excluded patients with ESRD prior to cohort entry.

We defined the outcome as the first episode of AKI identified within 28 days of the start of a hospital admission identified using ICD-10 morbidity coding in HES (**Supplementary Table S1**), to capture cases of AKI that were present at hospital admission but may have not been immediately diagnosed, without excluding cases that resulted in a prolonged admission. The actual number of AKI cases is likely to be higher than that captured by ICD-10 coding as less severe cases may not result in hospitalisation or may not be coded in hospital records.

Covariates

Due to the complex and overlapping potential risk factors for AKI, we used a directed acyclic graph (DAG) approach to visualise our *a priori* assumptions about the potential biological mechanisms between exposure and outcome and to guide adjustment for confounding in sequentially adjusted regression models (**Supplementary Figure S2**).[22] By asking researchers to produce an illustration of the *a priori* paths between exposure, outcome and potential confounders, causal diagrams offer a "starting point for identifying variables that must be measured and controlled [for] to obtain unconfounded effect estimates".[23] We identified potential confounders based on clinical knowledge and previous research investigating predictors of AKI.[6,7,9,10]

We adjusted for baseline CKD stage, established by calculating eGFR using the CKD-EPI equation.[24] We used serum creatinine results recorded in the 12 months before first prescription to calculate eGFR, using either the highest eGFR from the most recent two serum creatinine results, separated by a minimum of three months or, if only one creatinine result was available, the single most recent serum creatinine recorded prior to first prescription. Serum creatinine measurements were not routinely IDMS-standardised until 2013. We therefore assumed that all creatinine results were unstandardised and multiplied results with a correction factor of 0.95 before calculating eGFR without regard to ethnicity.[25] To avoid selection bias, we included an absent CKD category for those with no recorded serum creatinine result in the 12 months prior to first antihypertensive prescription.

Other chronic comorbidities included as confounders were: diabetes mellitus, hypertension, cardiac failure, cardiac arrhythmia, and ischaemic heart disease, identified both from CPRD and HES data. In regression analyses these comorbidities were recorded as time-varying variables representing "ever diagnosed," whose status changed with the first recorded code for each specific condition. Age group was entered as a time-updating variable. We adjusted for time-varying exposure to loop and potassium sparing diuretics in addition to antihypertensive drugs.[7]

We used existing morbidity code lists and algorithms for ethnicity,[19] smoking status, alcohol intake, BMI,[20] and chronic comorbidities.[26–30] Socioeconomic status was defined using quintiles of index of multiple deprivation scores for 2004.

We included calendar period as a covariate to adjust for the many changes in clinical, diagnostic and administrative practices over the study period that may influence the measurement of baseline renal function and number of reported AKI cases.

Statistical analysis

When variables (such as drug exposure, age, and comorbidities) did not remain constant over time we defined them as a time-varying variables. We did this by splitting the data for each study subject into several observations, each observation started on the date of a change in that subject's status (for example, the prescription of a new drug, the diagnosis of a new comorbidity, or a change in age). In the main analysis we classified exposure status using a time-varying binary indicator variable for person-time prescribed an ACEI/ARB. Rather than comparing a group of individual patients prescribed a particular class of drugs to another group prescribed a different class, we compared person-time taking one drug to person-time taking another. To avoid immortal time bias we excluded all time when patients were not taking any antihypertensive drugs. We estimated rate ratios associated with time exposed to antihypertensive treatment *including* an ACEI/ARB, compared to time exposed to antihypertensive treatment that *did not include* an ACEI/ARB, adjusting for potential confounders using Poisson regression. We used robust standard errors to account for clustering by general practice. We initially adjusted for age and sex only, and then fitted an adjusted model including DAG-informed time-varying confounders (age, sex, chronic comorbidities, other antihypertensive drugs, loop and potassium-sparing diuretics, and calendar period). Further adjustments were for smoking, alcohol, BMI and socioeconomic status. All data management and analyses were performed using Stata version 13 (StataCorp, Texas).

We have made code lists for all covariates available in online repository at: https://clinicalcodes.rss.mhs.man.ac.uk/.[31]

Sensitivity analyses

To determine the impact of including individuals with unknown baseline renal function, we repeated the main analysis in the subgroup of the cohort with known baseline renal function. Next, we repeated the main analysis in new entrants to the cohort, who had ethnicity recorded in CPRD or HES, after 2006 when recording of ethnicity was rewarded in primary care leading to improvements in CPRD data completeness.[19] We included ethnicity both in the equation used to calculate eGFR and as a covariate in the analysis. Finally, we tested the robustness of the definition of AKI in a range of sensitivity analyses including limiting the defining ICD-10 code to just N17, which has a high positive predictive value for AKI.[32]

Additional analyses

We conducted three additional analyses. Firstly, we investigated the impact of including interaction terms between treatment with loop diuretics and, separately, potassium-sparing diuretics and ACEI/ARB – as concurrent use of ACEI/ARB and diuretics has been linked to increased risk of AKI.[6,7] In our second additional analysis, renal function was time updated to examine how the relationship between AKI and ACEI/ARB exposure was related to renal function at the time that AKI occurred, rather than at entry to the cohort. To minimize misclassification of CKD stage by renal function measured during an AKI episode we excluded all measurements of kidney function that occurred within one week of an admission with AKI.[33] Finally, we investigated whether there was any difference in rate of AKI during time exposed to ACEI compared to ARB, and during combination therapy.[12,13]

RESULTS

Study population and baseline characteristics

Of 1,373,441 individuals aged 18 years or older with a new prescription for an ACEI/ARB, beta-blocker, calcium channel blocker or thiazide diuretic identified in the Clinical Practice Research Datalink (CPRD) between April 1997 and March 2014, 570,445 were included in the final cohort (**Figure 1**). Of these, 303,763 (53%) were prescribed an ACEI/ARB during follow-up. Total follow-up time for the whole cohort was over 2.3 million person years and 56% (1,320,001/2,345,098) of that was time exposed to ACEI/ARB. Follow-up ended a mean of 4.1 years (SD 4.1) after first antihypertensive drug prescription. 14,907 people developed AKI. The characteristics of the overall cohort, and the cohort during time exposed to antihypertensive treatment regimens that either included or excluded an ACEI/ARB are presented in **Table 1**. Those exposed to ACEI/ARB were more likely to be male with cardiac comorbidities, and to have had renal function measured prior to starting an antihypertensive. Fifty-three percent of time exposed to antihypertensive treatment

including an ACEI/ARB was between 2009 and 2014 compared to 38% of time exposed to antihypertensive treatment *excluding* an ACEI/ARB.

Table 1. Person-time under follow-up broken down by patient-level characteristics and ACEI/ARB exposure status. Data are person years unless otherwise stated. Numbers in brackets are column percentages unless otherwise specified.

		Whole cohort	Cohort during time exposed to antihypertensive treatment *including* an ACEI/ARB	Cohort during time exposed to antihypertensive treatment *excluding* an ACEI/ARB
	Total person years at risk	2,345,098	1,320,001	1,025,097
	Median person years at risk (IQR)	2.8 (0.4–7)	3.6 (1.1–6.9)	0.8 (0.2–3.4)
	Range of person years at risk	0.0–17.0	0.0–17.0	0.0–17.0
AKI	Number of events	14,907	10,157	4,750
Sex	Female	1,152,897 (49.2)	577,957 (43.8)	574,940 (56.1)
Age (years)	18–44	151,515 (6.5)	73,332 (5.6)	78,183 (7.6)
	45–54	350,170 (14.9)	211,576 (16.0)	138,593 (13.5)
	55–59	274,706 (11.7)	161,826 (12.3)	112,881 (11.0)
	60–64	324,416 (13.8)	188,097 (14.2)	136,319 (13.3)
	65–69	326,139 (13.9)	184,344 (14.0)	141,795 (13.8)
	70–74	308,156 (13.1)	171,103 (13.0)	137,053 (13.4)
	75–84	467,754 (19.9)	255,577 (19.4)	212,178 (20.7)
	85+	142,242 (6.1)	74,146 (5.6)	68,096 (6.6)
CKD stage (eGFR in ml/ min/1.73m^2)	No CKD (eGFR >=60)	934,070 (39.8)	580,871 (44.0)	353,199 (34.5)
	CKD stage 3a (eGFR 45–59)	113,238 (4.8)	68,074 (5.2)	45,163 (4.4)
	CKD stage 3b (eGFR 30–44)	18,435 (0.8)	10,873 (0.8)	7,562 (0.7)
	CKD stage 4 (eGFR 15–29)	1,926 (0.1)	1,036 (0.1)	890 (0.1)
	Baseline CKD status absent	1277429 (54.5)	659,145 (49.9)	618,283 (60.3)
Comorbidities	Diabetes mellitus	504,053 (21.5)	371,423 (28.1)	132,630 (12.9)
	Ischaemic heart disease	735,949 (31.4)	437,433 (33.1)	298,516 (29.1)
	Cardiac failure	152,904 (6.5)	116,449 (8.8)	36,456 (3.6)
	Arrhythmia	281,141 (12.0)	156,555 (11.9)	124,586 (12.2)
	Hypertension	2,036,050 (86.8)	1,194,641 (90.5)	841,409 (82.1)
Other antihypertensive drugs	Beta blockers	764,584 (32.6)	289,190 (21.9)	475,394 (46.4)
	Calcium channel blockers	732,628 (31.2)	331,429 (25.1)	401,199 (39.1)
	Thiazides	742,535 (31.7)	328,679 (24.9)	413,855 (40.4)
Non-thiazide diuretic drugs	Loop diuretics	155,911 (6.6)	118,565 (9.0)	37,346 (3.6)
	Potassium sparing diuretics	42,047 (1.8)	25,015 (1.9)	17,033 (1.7)
Ethnicity	White	982,377 (41.9)	569,946 (43.2)	412,431 (40.2)
	South Asian	26,933 (1.1)	17,647 (1.3)	9,286 (0.9)
	Black	14,8301 (0.6)	6,723 (0.5)	8,108 (0.8)
	Other	7,832 (0.3)	4,792 (0.4)	3,041 (0.3)
	Mixed heritage	2,553 (0.1)	1,490 (0.1)	1,063 (0.1)
	Not stated or missing	1,310,572 (55.9)	719,403 (54.5)	591,169 (57.7)
Calendar period	1997–2000	93,628 (4.0)	26,446 (2.0)	67,182 (6.6)
	2001–2004	418,412 (17.8)	170,465 (12.9)	247,947 (24.2)
	2005–2008	742,558 (31.7)	422,466 (32.0)	320,092 (31.2)
	2009–2011	646,221 (27.6)	416,685 (31.6)	229,535 (22.4)
	2012–2014	444,280 (18.9)	283,938 (21.5)	160,342 (15.6)

[#]note numbers exposed to antihypertensive treatment regimens *including* an ACEI/ARB and *excluding* an ACEI/ARB do not total the whole cohort number as individuals may be included in both columns.
ACEI/ARB: Angiotensin converting enzyme inhibitor/angiotensin receptor blocker
IQR: Interquartile range
CKD: Chronic kidney disease
eGFR: Estimated glomerular filtration rate

Association of ACEI or ARB prescription with rate of AKI

The association between covariates including age and comorbidities is shown in **Supplementary Table S2.** In the fully-adjusted model, age above 70 years, baseline CKD stage 3B and above, loop diuretic treatment and cardiac failure were all associated with a greater than doubling of AKI risk. Over the whole study period, the age and sex adjusted incidence rate ratio (RR) for first AKI comparing time exposed to antihypertensive treatment *including* an ACEI/ARB to that *excluding* an ACEI/ARB was 1.69 (95% CI 1.63–1.76), which fell to 1.12 (95% CI 1.07–1.17) after full adjustment (**Supplementary Table S2**). Further adjustment for lifestyle covariates and socioeconomic status made marginal difference to all results (**Supplementary Table S3**). Among subgroups with the highest absolute rates of AKI such as those with cardiac failure and chronic kidney disease (CKD) stage 4 there was no measurable association (or an apparent protective effect) of AKI with ACEI/ARB treatment (**Figure 2**).

Sensitivity analyses

Inclusion of only those with known baseline CKD stage, adjustment for ethnicity, and varying the way that AKI was defined from ICD-10 coding made minimal differences to the RR for AKI comparing time exposed to antihypertensive treatment including an ACEI/ARB to that excluding an ACEI/ARB (**Supplementary Table S3**).

Interaction between diuretics and ACEI/ARB treatment

There was an interaction between loop diuretics and ACEI/ARB treatment; there was no apparent increase in risk of AKI associated with ACEI/ARB exposure during periods of treatment with loop diuretic. Among people exposed to loop diuretics the RR for AKI during time exposed to treatment including an ACEI/ARB compared to that excluding an ACEI/ARB was 0.98 (95% CI 0.91–1.24) while among those not requiring loop diuretics the RR was 1.18 (95% CI 1.13–1.24) ($p<0.001$). Absolute rates of AKI stratified by ACEI/ARB treatment and comorbidity, modelled with inclusion of the interaction term, highlight the higher rates of AKI among people taking loop diuretics within each stratum (**Supplementary Table S4 and Figure S4**). There was no evidence for an interaction between potassium-sparing diuretics and ACEI/ARB treatment (RR for AKI among those prescribed potassium-sparing diuretics during time exposed to ACEI/ARB compared to time unexposed 1.09 (95% CI 0.96–1.24) while among those not requiring potassium-sparing diuretics the RR was 1.12 (95% CI 1.08–1.17: p=0.667)).

Impact of change in renal function on rate of AKI

When renal function was time updated, the RR for AKI during time exposed to antihypertensive treatment including and excluding an ACEI/ARB was attenuated to 1.02 (95% CI 0.98–1.07) (**Supplementary Table S2**). Among people who developed AKI, the median number of days between last measurement of estimated glomerular filtration rate (eGFR) and admission with the AKI episode was 116 days (IQR 44–258 days).

Rate of AKI in users of ACEI compared to ARB, or both combined

Compared to time not exposed to either drug, exposure to an ACEI was associated with an adjusted RR for AKI of 1.14 (95% CI 1.09–1.19), while exposure to an ARB was associated with a RR of 1.06 (95% CI 1.00–1.12). Dual therapy with both an ACEI and an ARB with associated with nearly twice the rate of AKI compared to time unexposed to either drug (RR 1.83 95% CI 1.53–2.17).

DISCUSSION

Among antihypertensive users we found a 12% (95% CI 1.07–1.17) increase in the rate of AKI during time exposed to ACEI/ARB compared to time unexposed (after adjustment for comorbidities, additional drug exposure, and calendar period). However, this relative risk varied markedly among different subgroups, and was highest among those with the lowest absolute risk of acute kidney injury. There was no evidence of increased AKI risk for ACEI/ARB users among those at greatest absolute risk of AKI (e.g. those with comorbidities or those also prescribed loop diuretics). Adjustment for most recent renal function further attenuated the risk of AKI due to ACEI/ARB exposure. We have shown that treatment with ACEI is associated with a similar magnitude of risk of AKI as ARB, but there is a near doubling of risk of AKI during time exposed to both ACEI and ARB. In addition to examining the effect of antihypertensives on AKI risk, we have calculated absolute rates of AKI in a general population cohort and the impact of important comorbidities and age upon these rates.

To illustrate our results, it is useful to consider the number of cases of AKI associated with ACEI/ARB use within different subgroups. Assuming that differences in AKI rates were directly attributable to ACEI/ARB exposure, in a low risk group – such as those with normal renal function – despite a 17% increase in relative risk of AKI during ACEI/ARB treatment, for 1,000 people, removal of the drug would reduce the number of AKI cases from 10 to 8 per year. In contrast, in a group at high absolute risk of AKI – such as those with cardiac failure treated with loop diuretics – exposure to ACEI/ARB has minimal impact. Among 1000 such people there are 76 cases of AKI in those treated with ACEI/ARB and 78 cases among those not treated.

Strengths and limitations

This is the largest study of this topic to date, it examines an inclusive population-based cohort from primary care and reflects routine clinical use of these medications. By comparing ACEI/ARB use to other antihypertensives, we were able to reduce confounding by indication compared to previous case-control studies. We were able to clearly define and adjust for covariates including renal function prior to starting the medication. The time-updated analysis reduced residual confounding, while restriction to only incident users reduced adherence bias.

However, there are a number of important limitations. Our assessment of drug exposure was based on prescriptions so we cannot be certain that people prescribed the drug were taking the medication; importantly we were unable to take into account any temporary discontinuation in medication use during acute illness or hospitalisation. We did not have inpatient biochemical data so could only use ICD-10 coding to define AKI. Therefore, we have captured only a proportion of the cases defined by current biochemical definitions of AKI (although this includes a greater proportion of more severe cases [34,35]) and we were not able to grade the severity of AKI. We examined first episode of AKI only. We cannot be certain that AKI was present at the time of hospital admission, or developed while in hospital although we have conducted several sensitivity analyses to address this. It is possible that there is bias in classification of the outcome. For example, due to awareness of an association, hospital staff may be more likely to recognise and code AKI in patients taking ACEI/ARB. Alternately, patients taking these drug may have more frequent monitoring of renal function and therefore be more likely to have AKI detected. However, these sources of bias would lead to an overestimate of the association between ACEI/ARB and AKI. We did not examine the additional effects of NSAIDs because these have been examined in previous studies.[6–8] There is limited and selective data on proteinuria from primary care records so we were not able to adjust for this potentially important covariate. Finally, this study is limited to NHS patients in England, which may restrict its generalisability.

Comparison to other studies

Previous high quality evidence regarding the association between ACEI/ARB and AKI is scarce. Estimates of the increase in AKI risk associated with use of ACEI/ARB from randomised trials are limited.[5] Many commonly cited observational studies are cross-sectional or address the risk of AKI in relation to specific diseases or interventions.[8–10] Two recent nested case-control studies using UK primary care data reported only relative risks for AKI among users of NSAIDS in addition to ACEI/ARB and diuretics.[6,7] Only one population-based study has examined the relative risk of AKI among ACEI/ARB users compared to non-users. This study, despite limited data quality, found similar

results to our own with a fully adjusted OR of 1.11 (95% CI 1.02–1.20) comparing those prescribed and not prescribed ACEI/ARB.[36]

However, strong evidence does exist in relation to the risks of AKI associated with combined ACEI and ARB therapy. Here, recent clinical trials using this regime have reported hazard ratios for renal adverse events ranging from 1.20 (95% CI 0.96–1.50) to 2.19 (95% CI 1.13–4.22), compared to single agent treatment alone.[12,13] Our results, showing a near doubling of rate for AKI with dual blockade, are similar to these findings and strongly support the validity of our study.

Finally, similar to other recent studies, we show that the rate of AKI detected by ICD-10 coding has increased markedly over the time period of this study. This is well documented and likely to be multifactorial, attributable to better hospital coding, increased recognition of AKI and possibly a true increase in incidence.[37]

Possible explanations and implications for clinicians and policymakers

Although surprising, we believe that this study has provided the most accurate estimates of the strength of the association between ACEI/ARB use and AKI to date. One alternate explanation for the small effect size is that we have compared time exposed to ACEI/ARB to other antihypertensives, with no untreated comparison group. While this design reduces confounding by indication, it is possible that all antihypertensives increase AKI risk during acute illness. In addition, among those at the highest absolute risk of AKI (e.g. those with additional comorbidities), we found rates of AKI for ACEI/ARB users were lower than for non-users. The probable explanation for these findings is that, in patients with multiple comorbidities that are indications for ACEI/ARB treatment, not being treated with ACEI or ARB is a marker of unmeasured poor health status or frailty. For example, an individual may have stopped ACEI/ARB treatment when they became unwell, perhaps due to worsening renal function, and the reason for stopping ACEI/ARB places them at higher risk of AKI during subsequent follow-up. This is likely to have attenuated the estimate of the strength of association between ACEI/ARB and AKI over the whole study population, although the proportion of patients with multiple comorbidities is small. Finally, our results do not exclude that AKI among users of ACEI/ARB is more severe compared to users of other antihypertensives. However, even when the AKI definition was restricted to code positions representing the primary diagnosis, ACEI/ARB treatment was only associated with a 21% (95% CI 11–33%) increase in AKI rate.

We have also shown that patients taking loop diuretics have higher rates of AKI than similar patients not prescribed the drugs. This may be causal, due to salt and water depletion during acute illness, or additional loop diuretic treatment may be a marker of severity of comorbidities. We anticipated that

pharmacological interaction between loop diuretics and ACEI/ARB would be associated with an increased risk of AKI compared to treatment with loop diuretics alone but we have shown the converse. Again, this is likely to be explained by confounding by underlying health status where the most severely unwell patients at highest risk of AKI are not treated with both diuretics and ACEI/ARB. Finally, we have shown that when adjusted for most recent renal function, there was no measurable association between ACEI/ARB use and AKI. The findings of this analysis have to be considered in light of possible misclassification of CKD stage by renal function measured during an AKI episode, although we excluded all measurements of kidney function that occurred before of an admission with AKI.

Treatment with ACEI and ARB are widely believed to be risk factors for AKI, particularly during acute illness. This underlies the 'sick-day rules' recommendation for patients to stop taking these drugs when they become acutely unwell with symptoms of gastroenteritis or fevers.[17] This study was not designed to examine the effect of temporary cessation of these drugs on the development of AKI. However, we have demonstrated that patient comorbidities are much stronger risk factors for the development of AKI than these drugs, and that there is no measurable effect of the drugs among those at highest risk of AKI. This reinforces the importance of assessing overall risk of AKI in planning potential interventions aimed at lowering hospital admissions with AKI. Patients with multiple risk factors but not taking ACEI/ARB may be those who would benefit most from close review of fluid balance and intensive monitoring during acute illness, but they may be overlooked if the clinical focus is on drug cessation.

Conclusions

In conclusion, our results show that treatment with ACEI/ARB appears to be associated with only a small increase in AKI risk while patient characteristics (such as age and comorbidities) are much more strongly associated with the rate of AKI. While people may benefit from optimised medicines management during acute illness, our results suggest that these interventions should be targeted at individuals at highest risk of AKI rather than focussing on users of ACEI/ARB.

FUNDING

LT is funded by a Wellcome Trust intermediate clinical fellowship (101143/Z/13/Z). KB is funded by a Wellcome Trust/Royal Society Sir Henry Dale fellowship (107731/Z/15/Z). LS is supported by a Wellcome Trust Senior Research Fellowship in Clinical Science (098504/Z/12/Z). The funders had no role in study design; collection, analysis, and interpretation of data; writing the report; and the decision to submit the report for publication.

CONTRIBUTIONS

LT had the original idea for the study. All authors were involved in the study design. KM undertook the data management, primary analysis and wrote the first draft. All authors contributed to further drafts and approved the final manuscript. KM and LT had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

COMPETING INTERESTS

All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years, no other relationships or activities that could appear to have influenced the submitted work.

ETHICAL APPROVAL

This study was approved by the LSHTM Research Ethics Committee (reference 6536) and by the CPRD independent scientific advisory committee (ISAC protocol number: 14-208).

DATA SHARING

No additional data available.

REFERENCES

1 Chertow GM, Burdick E, Honour M, *et al.* Acute kidney injury, mortality, length of stay, and costs in hospitalized patients. *J Am Soc Nephrol* 2005;**16**:3365–70. doi:10.1681/ASN.2004090740

2 Think Kidneys. Acute Kidney injury: The NHS campaign to improve the care of people at risk of, or with, acute kidney injury. [internet]. 2016. Available from: https://www.thinkkidneys.nhs.uk/aki/ (accessed Jan 2016)

3 Mehta RL, Cerdá J, Burdmann EA, *et al.* International Society of Nephrology's 0by25 initiative for acute kidney injury (zero preventable deaths by 2025): a human rights case for nephrology. *Lancet* 2015;**6736**:1–28. doi:10.1016/S0140-6736(15)60126-X

4 Schoolwerth AC, Sica DA, Ballermann BJ, *et al.* Renal considerations in angiotensin converting enzyme inhibitor therapy: a statement for healthcare professionals from the Council on the Kidney in Cardiovascular Disease and the Council for High Blood Pressure Research of the American Heart Association. *Circulation* 2001;**104**:1985–91. doi:10.1161/hc4101.096153

5 Palmer SC, Mavridis D, Navarese E, *et al.* Comparative efficacy and safety of blood pressure-lowering agents in adults with diabetes and kidney disease: a network meta-analysis. *Lancet* 2015;**385**:2047–56. doi:10.1016/S0140-6736(14)62459-4

6 Lapi F, Azoulay L, Yin H, *et al.* Concurrent use of diuretics, angiotensin converting enzyme inhibitors, and angiotensin receptor blockers with non-steroidal anti-inflammatory drugs and risk of acute kidney injury: nested case-control study. *Br Med J* 2013;**346**:8525. doi:10.1136/bmj.e8525

7 Dreischulte T, Morales DR, Bell S, *et al.* Combined use of nonsteroidal anti-inflammatory drugs with diuretics and/or renin–angiotensin system inhibitors in the community increases the risk of acute kidney injury. *Kidney Int* 2015;:1–8. doi:10.1038/ki.2015.101

8 Loboz KK, Shenfield GM. Drug combinations and impaired renal function – the ' triple whammy '. *B J Pharmacol* 2004;**59**:239–43. doi:10.1111/j.1365-2125.2004.02188.x

9 Plataki M, Kashani K, Cabello-Garza J, *et al.* Predictors of acute kidney injury in septic shock patients: an observational cohort study. *Clin J Am Soc Nephrol* 2011;**6**:1744–51. doi:10.2215/CJN.05480610

10 Arora P, Rajagopalam S, Ranjan R, *et al.* Preoperative use of angiotensin-converting enzyme inhibitors/angiotensin receptor blockers is associated with increased risk for acute kidney injury after cardiovascular surgery. *Clin J Am Soc Nephrol* 2008;**3**:1266–73. doi:10.2215/CJN.05271107

11 Chaumont M, Pourcelet A, van Nuffelen M, *et al.* Acute Kidney Injury in Elderly Patients With Chronic Kidney Disease: Do Angiotensin-Converting Enzyme Inhibitors Carry a Risk? *J Clin Hypertens* 2016;**18**:1–8. doi:10.1111/jch.12795

12 Fried LF, Emanuele N, Zhang JH, *et al.* Combined angiotensin inhibition for the treatment of diabetic nephropathy. *N Engl J Med* 2013;**369**:1892–903. doi:10.1056/NEJMoa1303154

13 Mann JFE, Schmieder RE, McQueen M, *et al.* Renal outcomes with telmisartan, ramipril, or both, in people at high vascular risk (the ONTARGET study): a multicentre, randomised, double-blind, controlled trial. *Lancet* 2008;**372**:547–53.http://www.ncbi.nlm.nih.gov/pubmed/18707986 (accessed 1 May2014).

14 European Medicines Agency. Combined use of medicines affecting the renin-angiotensin system (RAS) to be restricted – CHMP endorses PRAC recommendation. 2014.http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2014/05/news_detail_002107.jsp&mid=WC0b01ac058004d5c1 (accessed 18 Sep2015).

15 Feehally J, Gilmore I, Barasi S, *et al.* RCPE UK Consensus Conference Statement Management of acute kidney injury: the role of fluids, e-alerts and biomarkers. *JR Coll Physicians* 2013;**43**:37–8.http://www.lumison.co.uk/~rcpe/journal/issue/journal_43_1/acutekidneyinjury.pdf (accessed 4 Sep 2014).

16 National Institute for Health and Care Excellence. NICE clincal guideline 169: Acute kidney injury - Prevention, detection and management of acute kidney injury up to the point of renal replacement therapy. [internet] 2013. Available from: http://www.nice.org.uk/nicemedia/live/14258/65056/65056.pdf (accessed 14 Aug 2015)

17 Scottish Patient Safety Programme. Medicine Sick Day Rules Card. Healthc. Improv. Scotl. 2015.Available from: http://www.scottishpatientsafetyprogramme.scot.nhs.uk/programmes/primary-care/medicine-sick-day-rules-card (accessed 16 Jun2015).

18 Herrett E, Gallagher AM, Bhaskaran K, *et al.* Data Resource Profile: Clinical Practice Research Datalink (CPRD). *Int J Epidemiol* 2015;**44**:1–10. doi:10.1093/ije/dyv098

19 Mathur R, Bhaskaran K, Chaturvedi N, *et al.* Completeness and usability of ethnicity data in UK-based primary care and hospital databases. *J Public Health (Oxf)* 2013;**36**:684–92. doi:10.1093/pubmed/fdt116

20 Bhaskaran K, Forbes HJ, Douglas I, *et al.* Representativeness and optimal use of body mass index (BMI) in the UK Clinical Practice Research Datalink (CPRD). *BMJ Open* 2013;**3**:e003389. doi:10.1136/bmjopen-2013-003389

21 HSCIC. Hospital Episode Statistics. http://www.hscic.gov.uk/hes (accessed 25 Jun2015).

22 Hernán MA, Hernández-Díaz S, M.Werler M, *et al.* Causal Knowledge as a Prerequisite for Confounding Evaluation: An Application to Birth Defects Epidemiology. *Am J Epidemiol* 2002;**155**:176–84. doi:10.1093/aje/155.2.176

23 Greenland S, Pearl J, Robins3 JM. Causal Diagrams for Epidemiologic Research. *Epidemiology* 1999;**10**:37–48. doi:10.1097/00001648-199901000-00008

24 Levey AS, Stevens LA, Schmid CH, *et al.* A new equation to estimate glomerular filtration rate. *Ann Intern Med* 2009;**150**:604–12.http://annals.org/article.aspx?articleid=744469 (accessed 28 Mar2014).

25 Fox CS, Matsushita K, Woodward M, *et al.* Associations of kidney disease measures with mortality and end-stage renal disease in individuals with and without diabetes: a meta-analysis. *Lancet* 2012;**380**:1662–73. doi:10.1016/S0140-6736(12)61350-6

26 McDonald HI, Thomas SL, Millett ERC, *et al.* CKD and the Risk of Acute, Community-Acquired Infections Among Older People With Diabetes Mellitus: A Retrospective Cohort Study Using Electronic Health Records. *Am J Kidney Dis* 2015;**66**:60–8. doi:doi:10.1053/j.ajkd.2014.11.027

27 Quint JK, Herrett E, Bhaskaran K, *et al.* Effect of β blockers on mortality after myocardial infarction in adults with COPD: population based cohort study of UK electronic healthcare records. *BMJ* 2013;**347**:f6650. doi:10.1136/bmj.f6650

28 Brauer R, Smeeth L, Anaya-Izquierdo K, *et al.* Antipsychotic drugs and risks of myocardial infarction: a self-controlled case series study. *Eur Heart J* 2014;:ehu263. doi:10.1093/eurheartj/ehu263

29 Herrett E, Shah AD, Boggon R, *et al.* Completeness and diagnostic validity of recording hospital care disease registry and national mortality. *Br Med J* 2013;**346**. doi:10.1136/bmj.f2350

30 Douglas IJ, Evans SJW, Hingorani AD, *et al.* Clopidogrel and interaction with proton pump inhibitors: comparison between cohort and within person study designs. *BMJ* 2012;**345**:e4388. doi:10.1136/bmj.e4388

31 Springate DA, Kontopantelis E, Ashcroft DM, *et al.* ClinicalCodes: an online clinical codes repository to improve the validity and reproducibility of research using electronic medical records. *PLoS One* 2014;**9**:e99825. doi:10.1371/journal.pone.0099825

32 Tomlinson LA, Riding AM, Payne RA, *et al.* The accuracy of diagnostic coding for acute kidney injury in England - a single centre study. *BMC Nephrol* 2013;**14**:58. doi:10.1186/1471-2369-14-58

33 Siew ED, Ikizler TA, Matheny ME, *et al.* Estimating baseline kidney function in hospitalized patients with impaired kidney function. *Clin J Am Soc Nephrol* 2012;**7**:712–9. doi:10.2215/CJN.10821011

34 Sawhney S, Fluck N, Marks A, *et al.* Acute kidney injury - How does automated detection perform? *Nephrol Dial Transplant* 2015;**30**:1853–61. doi:10.1093/ndt/gfv094

35 Grams ME, Waikar SS, Macmahon B, *et al.* Performance and Limitations of Administrative Data in the Identification of AKI. *Clin J Am Soc Nephrol* 2014;:1–8. doi:10.2215/CJN.07650713

36 Bedford M, Farmer CK, Irving J, *et al.* Acute kidney injury: an acceptable risk of treatment with renin-angiotensin system blockade in primary care? *Can J Kidney Heal Dis* 2015;**2**:14. doi:10.1186/s40697-015-0044-y

37 Tomlinson LA, Abel GA, Chaudhry AN, *et al.* ACE inhibitor and angiotensin receptor-II antagonist prescribing and hospital admissions with acute kidney injury: a longitudinal ecological study. *PLoS One* 2013;**8**:e78465. doi:10.1371/journal.pone.0078465

FIGURE LEGENDS

Figure 1. Flow diagram showing the creation of the cohort and reasons for exclusion.

<<Insert Figure 1>>

ACEI/ARB: Angiotensin converting enzyme inhibitor/angiotensin receptor blocker
BB: Beta blocker
CCB: Calcium channel blocker
CPRD: Clinical Practice Research Datalink
HES: Hospital Episode Statistics
ESRD: End stage renal disease

Figure 2. Modelled rates* of AKI (during the calendar period 2012–2014) per 1,000 person years at risk for AKI during time exposed to antihypertensive treatment including ACEI/ARB compared to time exposed to antihypertensive treatment excluding ACEI/ARB, stratified by characteristics and comorbidities.

<<Insert Figure 2>>

*Absolute rates (unless otherwise stated) are for men, aged 75–84, with CKD stage 3a, and no comorbidities – chosen as a large, clinically important, high risk group.
**Adjusted using Poisson regression for: age, sex, chronic comorbidities (CKD, hypertension, diabetes mellitus, cardiac failure, ischaemic heart disease, and arrhythmia), time exposed to other antihypertensive drugs (beta-blockers, calcium channel blockers, and thiazides), time exposed to loop and potassium-sparing diuretics, and calendar period.
AKI: Acute kidney injury
ACEI/ARB: Angiotensin converting enzyme inhibitor/angiotensin receptor blocker
pyar: Person years at risk
CKD: Chronic kidney disease
ACEI/ARB exposed: Antihypertensive treatment including ACEI/ARB
ACEI/ARB unexposed: Antihypertensive treatment excluding ACEI/ARB
IRR: Incidence rate ratio
CI: Confidence interval

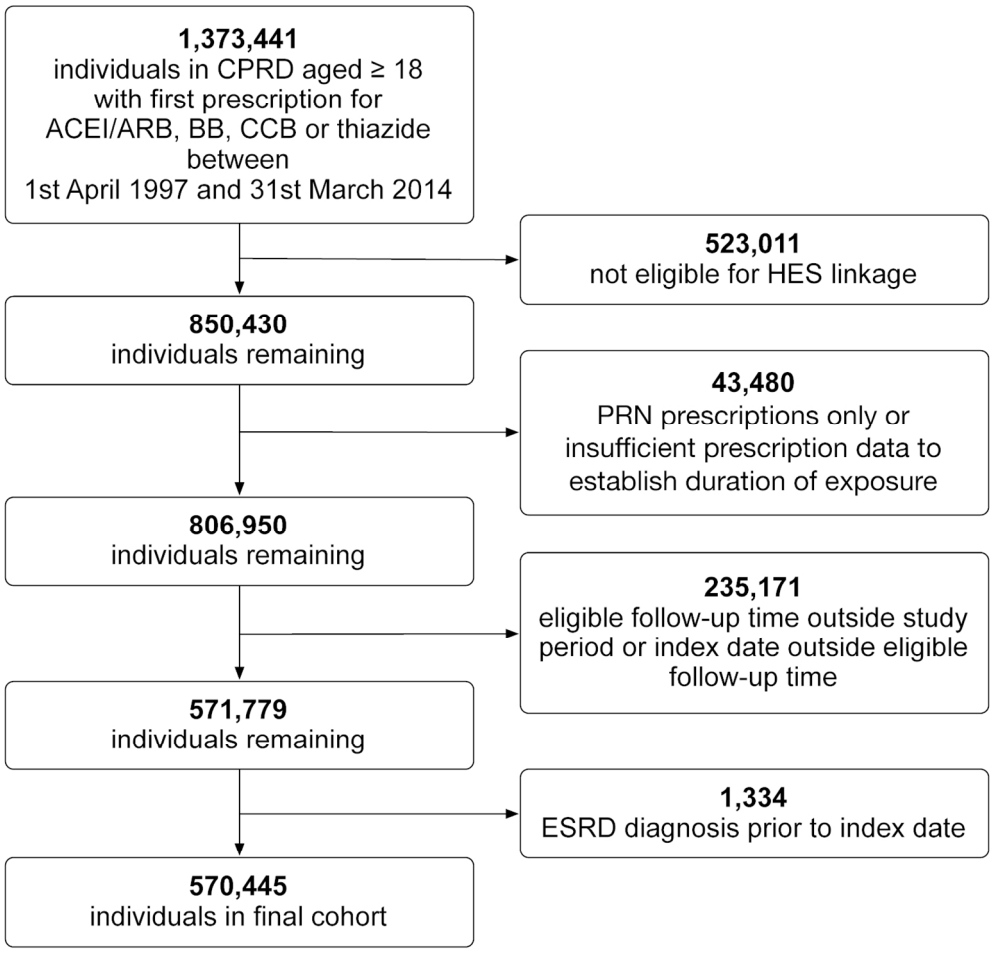


Figure 1. Flow diagram showing the creation of the cohort and reasons for exclusion.
Figure 1
129x124mm (300 x 300 DPI)

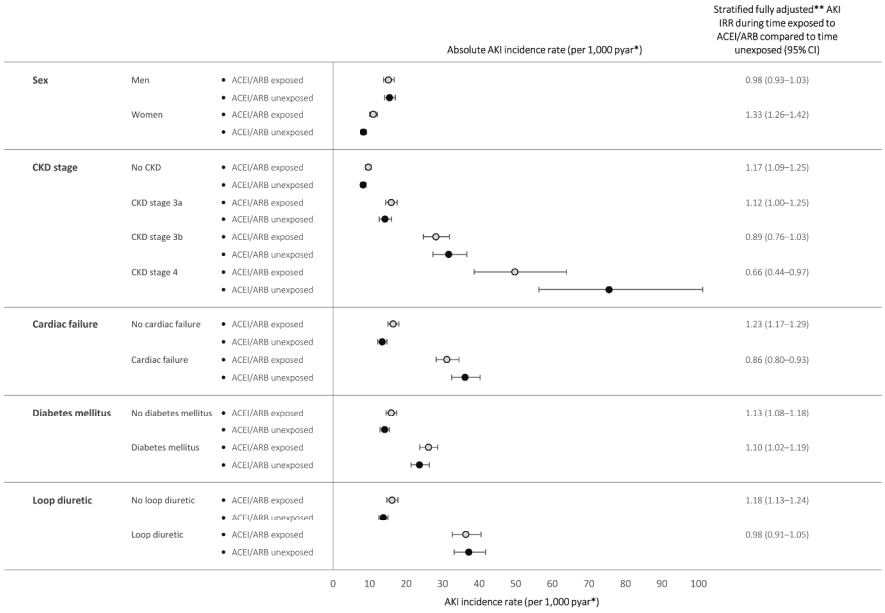


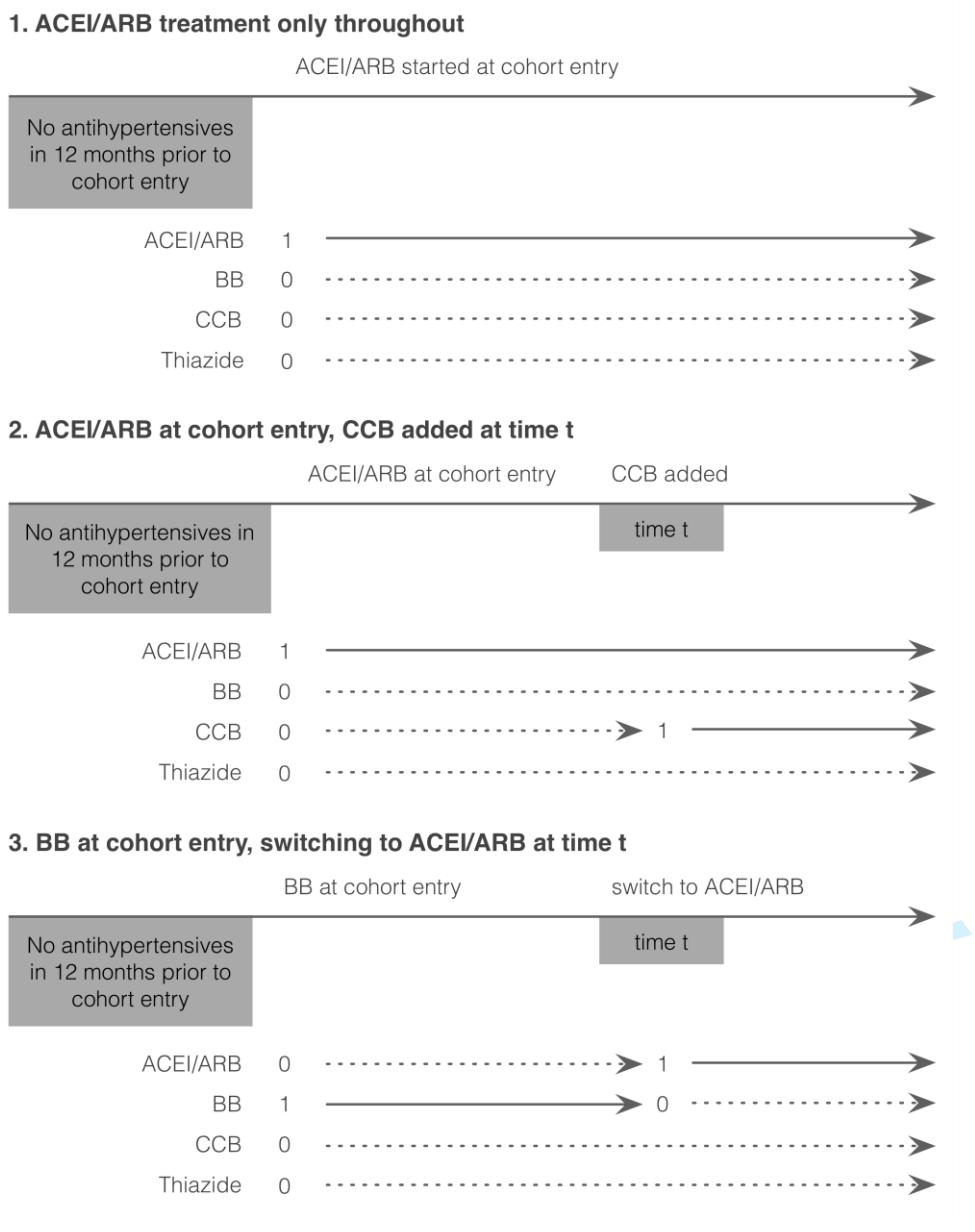
Figure 2. Modelled rates* of AKI (during the calendar period 2012–2014) per 1,000 person years at risk for AKI during time exposed to ACEI/ARBs compared to time unexposed, stratified by characteristics and comorbidities

Figure 2
271x169mm (300 x 300 DPI)

Text S1: Antihypertensive drug exposure defined by multiple binary indicators

Rather than a single variable representing time exposed to a single class of antihypertensive, we used four time-updating, binary indicator variables to indicate antihypertensive exposure status. Defining exposure status in this way allowed patients to be exposed to more than one class of antihypertensive at a time. Each indicator variable identified whether the associated period of time at risk was exposed (1) or unexposed (0) to a specific class of antihypertensive. Figure S1 illustrates how the indicator variables would be assigned in three example scenarios. In scenario one, the patient remains exposed to only one agent for the duration of the study. In scenario two, a second antihypertensive is added. In scenario three, the patient switches from one class of drug to a different class of drug.

Figure S1: Assignment of time-varying exposure status during follow-up using multiple binary indicator exposure variables under three example scenarios.



0=indicator variable 'switched off' (drug not prescribed); 1=indicator variable 'switched on' (drug prescribed).
ACEI/ARB: Angiotensin converting enzyme inhibitor/angiotensin receptor blocker
BB: Beta-blocker
CCB: Calcium channel blocker

Table S1. Definition of acute kidney injury: ICD-10 codes used to define of acute kidney injury in HES data.

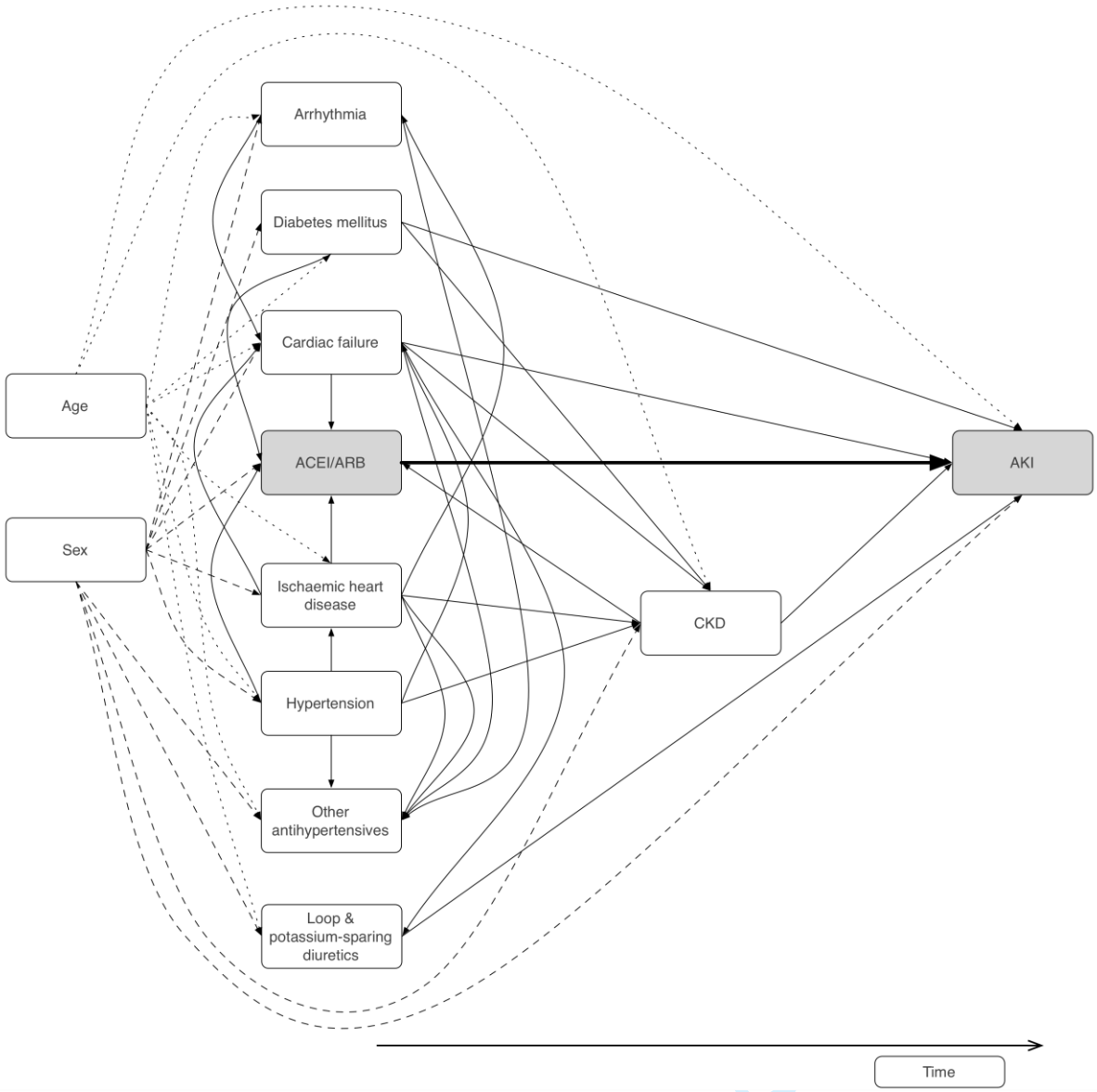
ICD-10 code	Clinical term	% of cases of AKI cases defined by code
N14.1	Nephropathy induced by other drugs, medicaments and biological substances	0.12
N14.2	Nephropathy induced by unspecified drug, medicament or biological substance	0.03
N17.0	Acute renal failure with tubular necrosis	0.78
N17.1	Acute renal failure with acute cortical necrosis	0.04
N17.2	Acute renal failure with medullary necrosis	0.03
N17.8	Other acute renal failure	0.28
N17.9	Acute renal failure, unspecified	70.14
N19	Unspecified kidney failure	25.31
N99.0	Post procedural renal failure	1.29
R34	Anuria and oliguria	0.90
R94.4	Abnormal results of kidney function studies	0.99

Text S2. Definition of end-stage renal disease

ESRD was defined using hospital and primary care morbidity coding, and hospital procedure coding as the presence of:

i) An ESRD morbidity code.
ii) A code for renal transplant.
iii) A code for peritoneal or haemodialysis.
iv) Stage 5 chronic kidney disease (identified using morbidity coding and estimated glomerular filtration rate (eGFR).
v) Stage 4 CKD with a fistula, suggesting ESRD is anticipated.

Figure S2. Simplified directed acyclic graph (DAG) illustrating implicitly assumed causal structure underlying our adjusted models.



➔ Represents causal path of interest

Under this assumed framework, adjusting for all measured variables blocks confounding pathways.

AKI: Acute kidney injury
ACEI/ARB: Angiotensin converting enzyme inhibitor/angiotensin receptor blocker
CKD: Chronic kidney disease

Table S2. Age and sex, and fully adjusted* incidence rate ratios (95% CIs) for AKI in sequentially adjusted models.

	AKI incidence rate ratio (95% CI)		
	Age & sex adjusted	Fully adjusted*	Fully adjusted* with CKD stage as a time-updated variable
	n=570,445	n=570,445	n=570,445
Exposure of interest			
ACEI/ARB	1.69 (1.63–1.76)	1.12 (1.07–1.17)	1.02 (0.98–1.07)
Sex			
Female	0.61 (0.59–0.63)	0.66 (0.64–0.68)	0.63 (0.61–0.65)
Age			
18–44	reference	reference	reference
45–54	0.85 (0.74–0.97)	0.81 (0.71–0.93)	0.89 (0.77–1.02)
55–59	1.08 (0.94–1.23)	0.97 (0.85–1.12)	1.07 (0.93–1.22)
60–64	1.41 (1.24–1.61)	1.18 (1.03–1.35)	1.25 (1.09–1.42)
65–69	2.11 (1.86–2.38)	1.59 (1.41–1.80)	1.55 (1.36–1.76)
70–74	3.15 (2.80–3.55)	2.17 (1.92–2.45)	1.84 (1.62–2.09)
75–84	6.03 (5.37–6.78)	3.34 (2.96–3.76)	2.26 (2.00–2.56)
85+	15.06 (13.34–17.01)	5.54 (4.87–6.30)	2.98 (2.61–3.41)
Comorbidity			
CKD stage			
No CKD	N/A	reference	reference
CKD stage 3a	N/A	1.67 (1.57–1.77)	2.60 (2.46–2.75)
CKD stage 3b	N/A	3.19 (2.91–3.51)	5.77 (5.42–6.15)
CKD stage 4	N/A	6.69 (5.57–8.03)	13.44 (12.45–14.51)
Baseline CKD status absent	N/A	1.18 (1.13–1.23)	1.90 (1.74–2.08)
Diabetes mellitus	N/A	1.65 (1.59–1.72)	1.52 (1.46–1.58)
Ischaemic heart disease	N/A	1.14 (1.09–1.19)	1.12 (1.07–1.17)
Cardiac failure	N/A	2.09 (1.97–2.20)	1.92 (1.82–2.03)
Arrhythmia	N/A	1.42 (1.36–1.48)	1.45 (1.38–1.51)
Hypertension	N/A	1.09 (1.04–1.15)	1.01 (0.96–1.06)
Other antihypertensive drugs			
Beta-blocker	N/A	0.99 (0.95–1.03)	0.90 (0.87–0.94)
Calcium channel blocker	N/A	0.97 (0.93–1.01)	0.93 (0.90–0.97)
Thiazide	N/A	0.99 (0.95–1.04)	0.91 (0.87–0.96)
Non-thiazide diuretics			
Loop	N/A	2.36 (2.23–2.50)	1.77 (1.67–1.88)
Potassium sparing	N/A	1.86 (1.74–1.98)	1.67 (1.56–1.79)
Calendar period			
1997–2000	N/A	reference	reference
2001–2004	N/A	1.17 (1.03–1.34)	1.14 (0.99–1.32)
2005–2008	N/A	1.62 (1.42–1.85)	1.61 (1.39–1.86)
2009–2011	N/A	2.26 (1.99–2.57)	2.38 (2.06–2.75)
2012–2014	N/A	3.29 (2.89–3.74)	3.62 (3.12–4.19)

*Adjusted using Poisson regression for: age, sex, chronic comorbidities (CKD, hypertension, diabetes mellitus, cardiac failure, ischaemic heart disease, and arrhythmia), time exposed to other antihypertensive drugs (beta-blockers, calcium channel blockers and thiazides), time exposed to loop and potassium-sparing diuretics, and calendar period

AKI: Acute kidney injury

ACEI/ARB: Angiotensin converting enzyme inhibitor/angiotensin receptor blocker

CKD: Chronic kidney disease

eGFR: Estimated glomerular filtration rate

Table S3. Incidence rate ratios (95% CIs) for AKI during time exposed to ACEI/ARB compared to time exposed to other antihypertensives in the main analysis and additional sensitivity analyses.

	Number of individuals	Number of AKI cases identified	AKI incidence rate ratio (95% CI) for ACEI/ARB therapy (compared to time exposed to other antihypertensives)	
			Age and sex adjusted	Fully adjusted*
Main analysis: AKI defined using all ICD-10 codes in any position and any episode within 28 days of the start of a hospital admission.	570,445	14,907	1.69 (1.63–1.76)	1.12 (1.07–1.17)
AKI defined using only code N17 in any position and any episode within 28 days of the start of a hospital admission.	570,445	11,174	1.76 (1.68–1.84)	1.12 (1.06–1.17)
AKI defined using all ICD-10 codes in any diagnostic position in the 1st or 2nd episode for episodes that occur within 7 days of admission.	570,445	14,377	1.70 (1.64–1.77)	1.13 (1.09–1.18)
AKI defined using all ICD-10 codes in the 1st diagnostic position of the 1st or 2nd episode for episodes that start within 7 days of admission.	570,445	3,009	1.83 (1.69–1.97)	1.21 (1.11–1.33)
Restricted to those with known baseline CKD status.	268,456	7,312	1.56 (1.47–1.65)	1.09 (1.02–1.16)
Including time-updated CKD stage rather than baseline CKD stage.	570,445	14,907	1.69 (1.63–1.76)	1.02 (0.98–1.07)
Additionally adjusting for smoking status, alcohol intake, and BMI.	485,139	12,583	N/A	1.17 (1.12–1.22)
Additionally adjusting for smoking status, alcohol intake, BMI, and socioeconomic status.	484,525	12,559	N/A	1.18 (1.12–1.23)
Restricted to those entering the cohort from 2006 with known ethnicity.**	132,847	1,944	1.37 (1.24–1.52)	1.07 (0.95–1.21)

*Adjusted using Poisson regression for: age, sex, chronic comorbidities (CKD, hypertension, diabetes mellitus, cardiac failure, ischaemic heart disease, and arrhythmia), time exposed to other antihypertensive drugs (beta-blockers, calcium channel blockers and thiazides), time exposed to loop and potassium sparing diuretics, and calendar period.
**Additionally adjusted for ethnicity and with race used to calculate eGFR
AKI: Acute kidney injury
ACEI/ARB: Angiotensin converting enzyme inhibitor/angiotensin receptor blocker
CKD: Chronic kidney disease
eGFR: Estimated glomerular filtration rate

Prescription for Renin-Angiotensin System Blockers and Risk of Acute Kidney Injury: A Population-Based Cohort Study
Kathryn E Mansfield, Dorothea Nitsch, Liam Smeeth, Krishnan Bhaskaran, Laurie A Tomlinson

Table S4. Descriptive table of modelled rates of AKI (during the calendar period 2012–2014) per 1000 person years at risk stratified by characteristics and comorbidities. This model includes an interaction term for loop diuretic use.

	Rate of AKI in ACEI/ARB exposed per 1000 pyar*		Rate of AKI in ACEI/ARB unexposed per 1000 pyar*		Absolute rate difference per 1000 pyar	
	On loop	Not on loop	On loop	Not on loop	On loop	Not on loop
Sex (rates for each sex aged 75-84 with CKD stage 3A and no comorbidities)						
Men	36.3	16.1	37.1	13.7	1.8	2.4
Women	24.0	10.6	24.5	9.0	0.5	1.6
Age (rates for each age group for men with CKD stage 3A and no comorbidities)						
18–44	10.9	4.8	11.1	4.1	0.2	0.7
45–54	8.8	3.9	9.0	3.3	0.2	0.6
55–59	10.6	4.7	10.8	4.0	0.2	0.7
60–64	12.8	5.7	13.1	4.8	0.3	0.9
65–69	17.3	7.7	17.7	6.5	0.4	1.2
70–74	23.6	10.5	24.1	8.9	0.5	1.6
75–84	36.3	16.1	37.1	13.7	0.8	2.4
85+	60.1	26.7	61.5	22.6	1.4	4.1
CKD stage (rates for each CKD stage for men with no comorbidities)						
No CKD (eGFR >=60)	21.8	9.7	22.3	8.2	0.5	1.5
CKD stage 3a (eGFR 45–59)	36.3	16.1	37.1	13.7	0.8	2.4
CKD stage 3b (eGFR 30–44)	69.3	30.8	70.8	26.1	1.5	4.7
CKD stage 4 (eGFR 15–29)	144.3	64.1	147.5	54.3	3.2	9.8
Comorbidity (rates for men aged 75-84 with CKD stage 3A and only the specified comorbidity)						
Diabetes mellitus	59.9	26.6	61.2	22.5	1.3	4.1
Ischaemic heart disease	41.3	18.4	42.2	15.5	0.9	2.9
Cardiac failure	76.3	33.9	78.0	28.7	1.7	5.2
Risk group						
Lowest risk group [1]	4.3	1.9	4.4	1.6	0.1	0.3
Highest risk group [2]	648.7	288.3	663.1	244.1	14.4	44.2

[1] Low risk: women aged 18-44 without CKD and no comorbidities

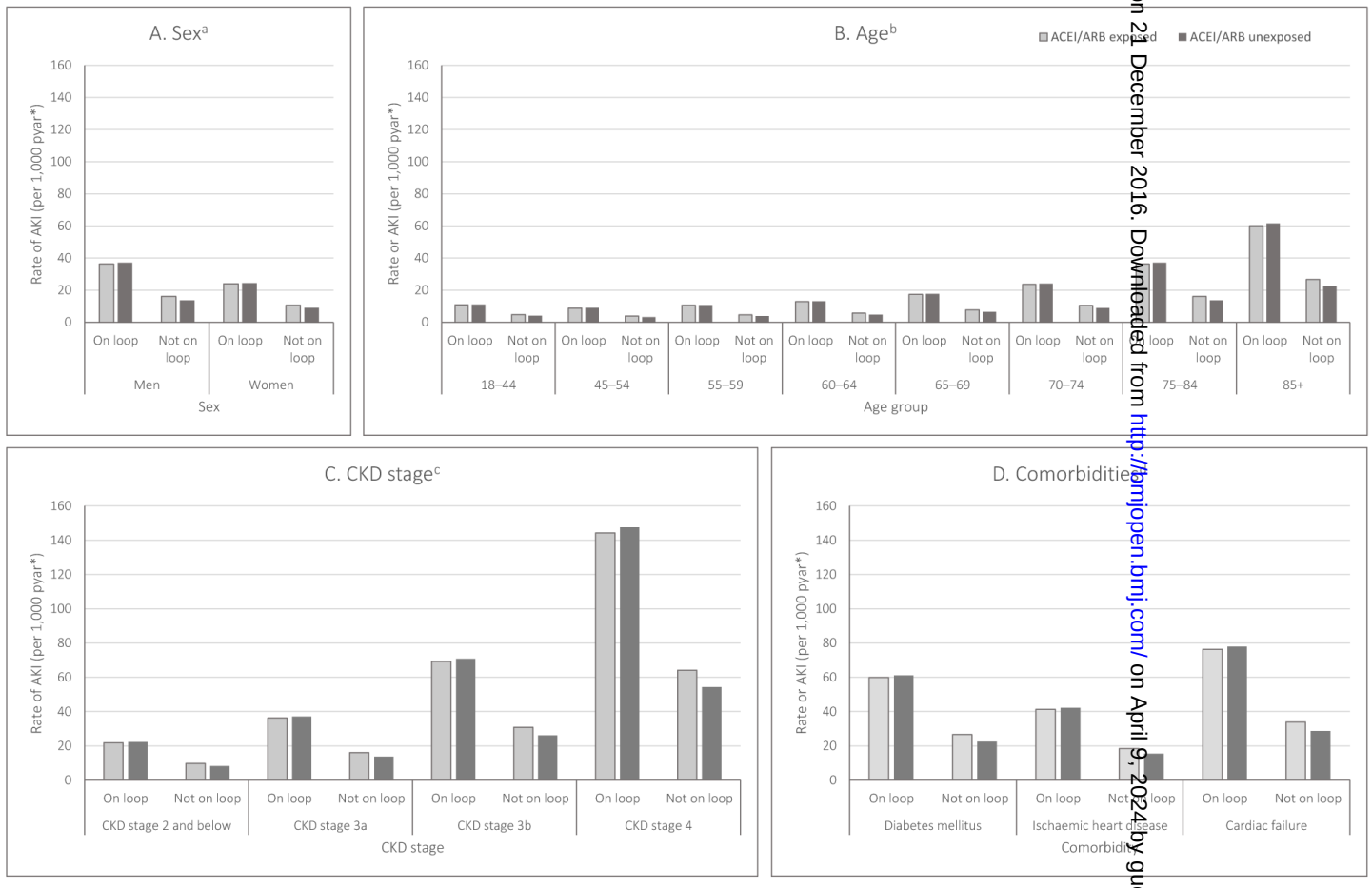
[2] High risk: men aged 85+ with CKD stage 4 and all of: ischaemic heart disease, cardiac failure and diabetes mellitus.

*Adjusted using Poisson regression for: age, sex, chronic comorbidities (CKD, hypertension, diabetes mellitus, cardiac failure, ischaemic heart disease, and arrhythmia), time exposed to other antihypertensive drugs (beta-blockers, calcium channel blockers and thiazides), time exposed to loop and potassium sparing diuretic, and calendar period. Also includes an interaction term for loop diuretic use.

Prescription for Renin-Angiotensin System Blockers and Risk of Acute Kidney Injury: A Population-Based Cohort Study

Kathryn E Mansfield, Dorothea Nitsch, Liam Smeeth, Krishnan Bhaskaran, Laurie A Tomlinson

Figure S4. Modelled rates of AKI (during the calendar period 2012–2014) per 1,000 person years at risk stratified by characteristics and comorbidities. This model includes an interaction term for loop diuretic use.



*Adjusted using Poisson regression for: age, sex, chronic comorbidities (CKD, hypertension, diabetes mellitus, cardiac failure, ischaemic heart disease, and arrhythmia), time exposed to other antihypertensive drugs (beta-blockers, calcium channel blockers and thiazides), time exposed to loop and potassium sparing diuretics, and calendar period. Also includes an interaction term for loop diuretic use.
Absolute rates (unless otherwise stated) are for men, aged 75–84, with CKD stage 3a, and no comorbidities – chosen as a large, clinically important, high risk group.
[a]rates for each sex aged 75-84 with CKD stage 3A and no comorbidities.
[b]rates for each age group for men with CKD stage 3A and no comorbidities.
[c]rates for each CKD stage for men with no comorbidities.
[d]rates for men aged 75-84 with CKD stage 3A and only the specified comorbidity.
ACEI/ARB: Angiotensin converting enzyme inhibitor/angiotensin receptor blocker.
AKI: Acute kidney injury
pyar: Person years at risk
CKD: Chronic kidney disease

The RECORD statement – checklist of items, extended from the STROBE statement, which should be reported in observational studies using routinely collected health data.

	Item No.	STROBE items	Location in manuscript where items are reported	RECORD items	Location in manuscript where items are reported
Title and abstract					
	1	(a) Indicate the study's design with a commonly used term in the title or the abstract (b) Provide in the abstract an informative and balanced summary of what was done and what was found	(a) Reference made to cohort study design in title and abstract (p2) (b) Methods summarised in abstract (p2).	RECORD 1.1: The type of data used should be specified in the title or abstract. When possible, the name of the databases used should be included. RECORD 1.2: If applicable, the geographic region and timeframe within which the study took place should be reported in the title or abstract. RECORD 1.3: If linkage between databases was conducted for the study, this should be clearly stated in the title or abstract.	(1.1) Reference made to Clinical Practice Research Datalink (CPRD) and Hospital Episode Statistics (HES) made in abstract (p2). (1.2) Abstract outlines that study in UK between April 1997 and March 2014 (p2). (1.3) Use of linkage between HES and CPRD databases stated in the abstract (p2).
Introduction					
Background rationale	2	Explain the scientific background and rationale for the investigation being reported	Scientific background and rationale for study is presented in the Introduction section (p4).		
Objectives	3	State specific objectives, including any prespecified hypotheses	Specific aims of the study presented are in Introduction section (p4).		
Methods					
Study Design	4	Present key elements of study design early in the paper	Key elements of the study design are introduced in the Introduction section of the paper (p4) and expanded in the Methods section (p5).		
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Setting, locations, study dates are presented under the 'Study design and setting' subheading in the Methods section (p5).		

	Item No.	STROBE items	Location in manuscript where items are reported	RECORD items	Location in manuscript where items are reported
Participants	6	*(a) Cohort study* - Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study* - Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study* - Give the eligibility criteria, and the sources and methods of selection of participants *(b) Cohort study* - For matched studies, give matching criteria and number of exposed and unexposed *Case-control study* - For matched studies, give matching criteria and the number of controls per case	(a) Eligibility criteria, and cohort entry and exit criteria are presented under the 'Participants, exposures and outcomes' subheading in the Methods section (p5). (b) This study is not matched.	RECORD 6.1: The methods of study population selection (such as codes or algorithms used to identify subjects) should be listed in detail. If this is not possible, an explanation should be provided. RECORD 6.2: Any validation studies of the codes or algorithms used to select the population should be referenced. If validation was conducted for this study and not published elsewhere, detailed methods and results should be provided. RECORD 6.3: If the study involved linkage of databases, consider use of a flow diagram or other graphical display to demonstrate the data linkage process, including the number of individuals with linked data at each stage.	(6.1) A detailed explanation of how the study population were identified is presented in the Methods section under the 'Participants, exposures and outcomes' subheading (p5). (6.2) Codes used to identify the outcome definition (acute kidney injury) have been validated in another study referenced in the manuscript (p8 ref 32). Other code lists/algorithms have either been developed using those applied in other published studies (also referenced, p7). (6.3) The flow diagram presented in Figure 1 illustrates the number of individuals excluded from the study due to being ineligible for HES linkage.
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable.	Outcomes and exposures are defined under the 'Participants, exposures and outcomes' subheading of the Methods section (p5). Definitions for potential confounders are presented under the 'Covariates' subheading of the Methods section (p6).	RECORD 7.1: A complete list of codes and algorithms used to classify exposures, outcomes, confounders, and effect modifiers should be provided. If these cannot be reported, an explanation should be provided.	A complete list of codes and algorithms used to classify all variables is available for download from: https://clinicalcodes.rss.mhs.man.ac.uk/ An online clinical codes repository (p7).

	Item No.	STROBE items	Location in manuscript where items are reported	RECORD items	Location in manuscript where items are reported
Data sources/ measurement	8	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Each variable used is identified in CPRD or HES data. A clear definition of all variables used is presented in the appropriate sections of the Methods section (pp5-7). Variable definitions are the same for different groups of patients.		
Bias	9	Describe any efforts to address potential sources of bias	Covariates used are presented (p6). We present details of how study design was used to address possible selection bias and confounding by indication (under 'Participants, exposures and outcomes' subheading of Methods section, p5). In addition, we undertook a number of sensitivity analyses to test any variable definitions in order to address information and/or selection bias ('Sensitivity analysis' subheading of Methods section, p7).		
Study size	10	Explain how the study size was arrived at	The flow diagram presented in Figure 1 illustrates the creation of the cohort and reasons for exclusions. When developing the protocol we found that, based on a cautious estimate of a sample size (n= 102,524), we would have greater than 90% power (alpha 0.05) to detect a relative risk of 1.2 or more for incident AKI. The final sample size was nearly 5 x our cautious estimate (n=570,433).		

	Item No.	STROBE items	Location in manuscript where items are reported	RECORD items	Location in manuscript where items are reported
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why	Groupings for quantitative variables (age, eGFR) are presented in Tables 1 (p9) and S2 (Appendix)		
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding (b) Describe any methods used to examine subgroups and interactions (c) Explain how missing data were addressed (d) *Cohort study* - If applicable, explain how loss to follow-up was addressed *Case-control study* - If applicable, explain how matching of cases and controls was addressed *Cross-sectional study* - If applicable, describe analytical methods taking account of sampling strategy (e) Describe any sensitivity analyses	(a) Statistical methods used are presented under the 'Statistical analysis' subheading of the Methods section {p7). (b) Methods used to examine subgroups are presented under the 'Additional analyses' subheading of the Methods section (p8). (c) Missing data were addressed using sensitivity analyses (documented under the 'Sensitivity analysis' subheading of the Methods section, p8). (d) Loss to follow-up is not applicable to this design as patients are followed-up until no longer eligible. (e) Sensitivity analyses are described under the appropriate subheading in the Methods section (p8).		
Data access and cleaning methods		..		RECORD 12.1: Authors should describe the extent to which the investigators had access to the database population used to create the study population. RECORD 12.2: Authors should provide information on the data cleaning methods used in the study.	(12.1) Investigators had full access to the CPRD dataset – documented in declarations section at the end of the manuscript (p15). (12.2) Data cleaning methods are described in the Methods section (p5).

	Item No.	STROBE items	Location in manuscript where items are reported	RECORD items	Location in manuscript where items are reported
Linkage		..		RECORD 12.3: State whether the study included person-level, institutional-level, or other data linkage across two or more databases. The methods of linkage and methods of linkage quality evaluation should be provided.	(12.3) The study included person-level data linkage. Data linkage of CPRD and HES data is undertaken by a trusted third party: the Health and Social Care Information Centre (pp5-8).
Results					
Participants	13	(a) Report the numbers of individuals at each stage of the study (*e.g.*, numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed) (b) Give reasons for non-participation at each stage. (c) Consider use of a flow diagram	(a) The number of individuals at each stage of the study is presented in Figure 1. (b) Reasons for exclusions at each stage are also presented in Figure 1 (c) See Figure 1.	RECORD 13.1: Describe in detail the selection of the persons included in the study (*i.e.,* study population selection) including filtering based on data quality, data availability and linkage. The selection of included persons can be described in the text and/or by means of the study flow diagram.	See Figure 1.
Descriptive data	14	(a) Give characteristics of study participants (*e.g.*, demographic, clinical, social) and information on exposures and potential confounders (b) Indicate the number of participants with missing data for each variable of interest (c) *Cohort study* - summarise follow-up time (*e.g.*, average and total amount)	(a) See Table 1 (p9) (b) See Table 1 (p9) (c) See Table 1 (p9)		
Outcome data	15	*Cohort study* - Report numbers of outcome events or summary measures over time *Case-control study* - Report numbers in each exposure category, or summary measures of exposure *Cross-sectional study* - Report numbers of outcome events or summary measures	See Table 1 (p9)		

	Item No.	STROBE items	Location in manuscript where items are reported	RECORD items	Location in manuscript where items are reported
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (e.g., 95% confidence interval). Make clear which confounders were adjusted for and why they were included (b) Report category boundaries when continuous variables were categorized (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	(a) See Table S2 in the supplementary appendix and also presented in the text of the Results section (p10). (b) Age, CKD, and calendar period boundaries clearly presented in Tables 1 (p9) and S2 (Appendix). (c) Absolute risk presented in Figures 2 and S2 (Appendix), and Table S4 (Appendix).		
Other analyses	17	Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses	Results of sensitivity and secondary analyses presented in the Results section (p10) and Appendix Table S3.		
Discussion					
Key results	18	Summarise key results with reference to study objectives	Presented at beginning of Discussion section (p11).		
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Limitations discussed in the Discussion section (pp11-12).	RECORD 19.1: Discuss the implications of using data that were not created or collected to answer the specific research question(s). Include discussion of misclassification bias, unmeasured confounding, missing data, and changing eligibility over time, as they pertain to the study being reported.	Limitations related specifically to using routinely collected health data for research are discussed in the Discussion section (pp11-12).
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Overall interpretation of the results are presented in the Discussion section (pp11-14).		
Generalisability	21	Discuss the generalisability (external validity) of the study results	Generalisability of study results discussed in Discussion section (p12).		
Other Information					
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Source of funding acknowledged at the end of the manuscript under the 'Funding' subheading (p15).		

	Item No.	STROBE items	Location in manuscript where items are reported	RECORD items	Location in manuscript where items are reported
Accessibility of protocol, raw data, and programming code		..		RECORD 22.1: Authors should provide information on how to access any supplemental information such as the study protocol, raw data, or programming code.	Study protocol number provided. Due to CPRD guidelines on data sharing of patient level data we are unable to share raw data (p15).

*Reference: Benchimol EI, Smeeth L, Guttmann A, Harron K, Moher D, Petersen I, Sørensen HT, von Elm E, Langan SM, the RECORD Working Committee. The REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) Statement. *PLoS Medicine* 2015; in press.

BMJ Open

Prescription of Renin-Angiotensin System Blockers and Risk of Acute Kidney Injury: A Population-Based Cohort Study

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2016-012690.R2
Article Type:	Research
Date Submitted by the Author:	31-Oct-2016
Complete List of Authors:	Mansfield, Kathryn; London School of Hygiene and Tropical Medicine Faculty of Epidemiology and Population Health, Non-communicable Disease Epidemiology Nitsch, Dorothea; London School of Hygiene and Tropical Medicine Faculty of Epidemiology and Population Health, Non-communicable Disease Epidemiology Smeeth, Liam; London School of Hygiene and Tropical Medicine Faculty of Epidemiology and Population Health, Non-communicable Disease Epidemiology Bhaskaran, Krishnan; London School of Hygiene and Tropical Medicine Faculty of Epidemiology and Population Health, Non-communicable Disease Epidemiology Tomlinson, Laurie; London School of Hygiene and Tropical Medicine Faculty of Epidemiology and Population Health, Non-communicable Disease Epidemiology
Primary Subject Heading:	Renal medicine
Secondary Subject Heading:	Epidemiology, Pharmacology and therapeutics, General practice / Family practice
Keywords:	acute kidney injury, angiotensin-converting enzyme inhibitors, angiotensin receptor antagonists, cohort study, renin-angiotensin system

Prescription of Renin-Angiotensin System Blockers and Risk of Acute Kidney Injury: A Population-Based Cohort Study

Authors: Kathryn E Mansfield,[1] Dorothea Nitsch,[1] Liam Smeeth,[1] Krishnan Bhaskaran,[1] Laurie A Tomlinson[1]

Affiliations
[1] Department of Non-Communicable Disease Epidemiology, London School of Hygiene and Tropical Medicine, London, WC1E 7HT, United Kingdom

Corresponding author
Kathryn Mansfield, kathryn.mansfield@lshtm.ac.uk
The London School of Hygiene and Tropical Medicine, Keppel Street, London, WC1E 7HT
Telephone: 0207 927 2922

Key words: acute kidney injury; angiotensin-converting enzyme inhibitors; angiotensin receptor antagonists; cohort study; renin-angiotensin system

Word count
Abstract: 298 (BMJ open: max 300)
Text: 4,193 (BMJ open: recommended max 4,000)
Tables/Figures: 1 table, 2 figures
References: 37
Supplementary material: 4 tables, 3 figures, 2 texts

ABSTRACT

Objective: To investigate whether there is an association between use of ACE inhibitors (ACEI) and angiotensin receptor blockers (ARB), and risk of acute kidney injury (AKI).

Study Design: We conducted a new-user cohort study of the rate of AKI among users of common antihypertensives.

Setting: UK primary care practices contributing to the Clinical Practice Research Datalink (CPRD) eligible for linkage to hospital records data from the Hospital Episode Statistics (HES) database between April 1997 and March 2014.

Participants: New users of antihypertensives: ACEI/ARB, beta-blockers, calcium channel blockers and thiazide diuretics.

Outcomes: The outcome was first episode of AKI. We estimated incidence rate ratio (RR) for AKI during time exposed to ACEI/ARB compared to time unexposed, adjusting for age, sex, comorbidities, use of other antihypertensive drugs, and calendar period using Poisson regression. Covariates were time updated.

Results: Among 570,445 participants, 303,761 were prescribed ACEI/ARB with a mean follow-up of 4.1 years. The adjusted rate ratio of AKI during time exposed to ACEI/ARB compared to time unexposed was 1.12 (95% CI 1.07–1.17). This relative risk varied depending on absolute risk of AKI, with lower or no increased relative risk from the drugs among those at greatest absolute risk. For example, among people with stage 4 chronic kidney disease (who had 6.69 [95% CI 5.57–8.03] times higher rate of AKI compared to those without chronic kidney disease) the adjusted rate ratio of AKI during time exposed to ACEI/ARB compared to time unexposed was 0.66 (95% CI 0.44–0.97) in contrast to 1.17 (95% CI 1.09–1.25) among people without chronic kidney disease.

Conclusions: Treatment with ACEI/ARB is associated with only a small increase in AKI risk while individual patient characteristics are much more strongly associated with the rate of AKI. The degree of increased risk varies between patient groups.

ARTICLE SUMMARY

Strengths and limitations of this study

- This is the largest study of this topic to date, it examines an inclusive population-based cohort and reflects routine clinical use of these medications.
- By comparing ACEI/ARB use to use of other antihypertensives, we were able to reduce confounding by indication compared to previous case-control studies.
- We were able to clearly define and adjust for covariates, including renal function, prior to starting the medication. The time-updated analysis reduced residual confounding, while restriction to only incident users reduced adherence bias.
- However, there are a number of important limitations. Our assessment of drug exposure was based on prescriptions so we cannot be certain that people prescribed the drug were taking the medication.
- We did not have inpatient biochemical data so could only use ICD-10 coding to define AKI. Therefore, we have captured only a proportion of the cases defined by current biochemical definitions of AKI, although this includes a greater proportion of more severe cases.

INTRODUCTION

Acute kidney injury (AKI) is a sudden decline in renal function, affecting up to 20% of people admitted to hospital, and is strongly associated with increased mortality and longer duration of hospital stay.[1] Prevention and better management of patients with AKI is the focus of national programmes[2] and global campaigns.[3]

It is strongly believed that angiotensin converting enzyme inhibitors (ACEI) and angiotensin receptor blockers (ARB) are associated with development of AKI, particularly during acute illness. ACEI/ARBs cause preferential vasodilation of the kidney's efferent arterioles (the small blood vessels that leave the kidney glomeruli) thereby reducing kidney filtration pressure for a given systemic blood pressure. During severe hypovolaemia or hypotension (for example, due to volume depletion in acute illness) this reduction of efferent vascular tone leads to reduced glomerular filtration and potentially AKI.[4] While biologically plausible, evidence to support the belief that ACEI/ARB use causes AKI is limited. The incidence of AKI in randomised controlled trials of ACEI and ARB compared to placebo is poorly described due to variable definitions or absent reporting of kidney related adverse events.[5] Previous observational studies have compared the risk of AKI in patients using ACEI/ARB alone to the risks among ACEI/ARB users also taking diuretics and/or non-steroidal anti-inflammatory drugs (NSAIDs),[6–8] or with ACEI/ARB alone under specific circumstances.[9–11] However, the risk of AKI in patients taking ACEI or ARB alone compared to other comparator drugs has not been examined in a population cohort using individual patient data. By contrast, high quality evidence from randomised trials of increased risk of AKI associated with dual prescription of ACEI and ARB[12,13] compared to single agent therapy has led to a restriction on the use of these drugs in combination.[14]

Despite this limited evidence there is a growing consensus that ACEI/ARB should be withheld during acute illness.[15,16] Guidelines for patients to self-manage medications linked to AKI during these situations, known as 'sick day rules', are being widely introduced.[17] Therefore, we aimed to investigate the association between AKI and the use of ACEI/ARB in a large population-based cohort study of people starting treatment with commonly used antihypertensive drugs (ACEI/ARB, beta-blockers, calcium channel blockers, thiazide diuretics). We chose to compare new users of different classes of anti-hypertensive drugs to reduce confounding by indication.

METHODS

Study design and setting

We undertook a cohort study using the UK Clinical Practice Research Datalink (CPRD) and linked hospital record data from the Hospital Episode Statistics (HES) database. CPRD is a database of routinely collected primary care electronic health record data from 7% of the UK population.[18] Included patients are largely representative of the UK population.[18–20] HES records cover all admissions for NHS funded patients treated in either English NHS trusts or by independent providers.[21] Fifty-eight percent of general practices included in CPRD are linked to HES data (representing 75% of English practices).[18] We used only fully linked data from CPRD and HES to ensure that all participants had complete data regarding the exposure (antihypertensive prescribing in primary care) and the outcome (hospital admission with AKI). The study period was from 1st April 1997 to 31st March 2014, the latest date for which there is HES data linkage to CPRD. This study was approved by the LSHTM Research Ethics Committee (reference 6536) and by the CPRD independent scientific advisory committee (ISAC protocol number: 14-208).

Participants, exposures and outcomes

To minimise confounding by indication, rather than comparing ACEI/ARB users to otherwise healthy individuals, we identified a cohort of new-users of drugs that were prescribed for similar indications to ACEI/ARB. We developed a cohort of all HES-linked CPRD patients aged 18 years or older who were new users of antihypertensive drugs (ACEI/ARB, beta-blockers, calcium channel blockers or thiazide diuretics) during the study period. The primary exposure was use of ACEI/ARB and other drugs were treated as potential confounders. To ensure that we had reliable measures of drug use and baseline covariates, we required that all participants had at least one year of continuous registration in CPRD before the first recorded antihypertensive drug prescription. We calculated the length of each prescription using the quantity of medication prescribed and the daily dose recorded, excluding patients for whom dosing information was inadequate to obtain a robust duration of exposure. Exposure to medications was assumed to start on the date of the prescription. We identified continuous courses of therapy by allowing for a 60-day gap between the end date of one prescription and the start of the next consecutive prescription (to allow for stock piling of medications).

Drug exposure status was time updated based on continuous courses of therapy. We defined exposure status using four time-varying, binary indicator variables to indicate exposure to each antihypertensive, with exposure status ‘switching on’ when an individual was prescribed a drug and ‘off’ when their prescription ended (example scenarios illustrating the assignment of indicator

variables are included in **Supplementary Text S1** and **Figure S1**). This allowed us to maximise the available follow-up time, control for exposure to other antihypertensives, allowed drug combinations to be investigated through interaction terms, and more closely modelled real life prescribing patterns.

Follow-up started at first prescription for the first of any of the antihypertensive drugs and ended at either occurrence of the outcome or the earliest of: i) end of final prescription; ii) death; iii) left GP practice; iv) last data collection; or v) diagnosis of end-stage renal disease (ESRD) (**Supplementary Text S2**). We excluded patients with ESRD prior to cohort entry.

We defined the outcome as the first episode of AKI identified within 28 days of the start of a hospital admission identified using ICD-10 morbidity coding in HES (**Supplementary Table S1**), to capture cases of AKI that were present at hospital admission but may have not been immediately diagnosed, without excluding cases that resulted in a prolonged admission. The actual number of AKI cases is likely to be higher than that captured by ICD-10 coding as less severe cases may not result in hospitalisation or may not be coded in hospital records.

Covariates

Due to the complex and overlapping potential risk factors for AKI, we used a directed acyclic graph (DAG) approach to visualise our *a priori* assumptions about the potential biological mechanisms between exposure and outcome and to guide adjustment for confounding in sequentially adjusted regression models (**Supplementary Figure S2**).[22] By asking researchers to produce an illustration of the *a priori* paths between exposure, outcome and potential confounders, causal diagrams offer a "starting point for identifying variables that must be measured and controlled [for] to obtain unconfounded effect estimates".[23] We identified potential confounders based on clinical knowledge and previous research investigating predictors of AKI.[6,7,9,10]

We adjusted for baseline CKD stage, established by calculating eGFR using the CKD-EPI equation.[24] We used serum creatinine results recorded in the 12 months before first prescription to calculate eGFR, using either the highest eGFR from the most recent two serum creatinine results, separated by a minimum of three months or, if only one creatinine result was available, the single most recent serum creatinine recorded prior to first prescription. Serum creatinine measurements were not routinely IDMS-standardised until 2013. We therefore assumed that all creatinine results were unstandardised and multiplied results with a correction factor of 0.95 before calculating eGFR without regard to ethnicity.[25] To avoid selection bias, we included an absent CKD category for those with no recorded serum creatinine result in the 12 months prior to first antihypertensive prescription.

Other chronic comorbidities included as confounders were: diabetes mellitus, hypertension, cardiac failure, cardiac arrhythmia, and ischaemic heart disease, identified both from CPRD and HES data. In regression analyses these comorbidities were recorded as time-varying variables representing "ever diagnosed," whose status changed with the first recorded code for each specific condition. Age group was entered as a time-updating variable. We adjusted for time-varying exposure to loop and potassium sparing diuretics in addition to antihypertensive drugs.[7]

We used existing morbidity code lists and algorithms for ethnicity,[19] smoking status, alcohol intake, BMI,[20] and chronic comorbidities.[26–30] Socioeconomic status was defined using quintiles of index of multiple deprivation scores for 2004.

We included calendar period as a covariate to adjust for the many changes in clinical, diagnostic and administrative practices over the study period that may influence the measurement of baseline renal function and number of reported AKI cases.

Statistical analysis

When variables (such as drug exposure, age, and comorbidities) did not remain constant over time we defined them as a time-varying variables. We did this by splitting the data for each study subject into several observations, each observation started on the date of a change in that subject's status (for example, the prescription of a new drug, the diagnosis of a new comorbidity, or a change in age). In the main analysis we classified exposure status using a time-varying binary indicator variable for person-time prescribed an ACEI/ARB. Rather than comparing a group of individual patients prescribed a particular class of drugs to another group prescribed a different class, we compared person-time taking one drug to person-time taking another. To avoid immortal time bias we excluded all time when patients were not taking any antihypertensive drugs. We estimated rate ratios associated with time exposed to antihypertensive treatment *including* an ACEI/ARB, compared to time exposed to antihypertensive treatment that *did not include* an ACEI/ARB, adjusting for potential confounders using Poisson regression. We used robust standard errors to account for clustering by general practice. We initially adjusted for age and sex only, and then fitted an adjusted model including DAG-informed time-varying confounders (age, sex, chronic comorbidities, other antihypertensive drugs, loop and potassium-sparing diuretics, and calendar period). Further adjustments were for smoking, alcohol, BMI and socioeconomic status. All data management and analyses were performed using Stata version 13 (StataCorp, Texas).

We have made code lists for all covariates available in online repository at: https://clinicalcodes.rss.mhs.man.ac.uk/.[31]

Sensitivity analyses

To determine the impact of including individuals with unknown baseline renal function, we repeated the main analysis in the subgroup of the cohort with known baseline renal function. Next, we repeated the main analysis in new entrants to the cohort, who had ethnicity recorded in CPRD or HES, after 2006 when recording of ethnicity was rewarded in primary care leading to improvements in CPRD data completeness.[19] We included ethnicity both in the equation used to calculate eGFR and as a covariate in the analysis. Finally, we tested the robustness of the definition of AKI in a range of sensitivity analyses including limiting the defining ICD-10 code to just N17, which has a high positive predictive value for AKI.[32]

Additional analyses

We conducted three additional analyses. Firstly, we investigated the impact of including interaction terms between treatment with loop diuretics and, separately, potassium-sparing diuretics and ACEI/ARB – as concurrent use of ACEI/ARB and diuretics has been linked to increased risk of AKI.[6,7] In our second additional analysis, renal function was time updated to examine how the relationship between AKI and ACEI/ARB exposure was related to renal function at the time that AKI occurred, rather than at entry to the cohort. To minimize misclassification of CKD stage by renal function measured during an AKI episode we excluded all measurements of kidney function that occurred within one week of an admission with AKI.[33] Finally, we investigated whether there was any difference in rate of AKI during time exposed to ACEI compared to ARB, and during combination therapy.[12,13]

RESULTS

Study population and baseline characteristics

Of 1,373,441 individuals aged 18 years or older with a new prescription for an ACEI/ARB, beta-blocker, calcium channel blocker or thiazide diuretic identified in the Clinical Practice Research Datalink (CPRD) between April 1997 and March 2014, 570,445 were included in the final cohort (**Figure 1**). Of these, 303,763 (53%) were prescribed an ACEI/ARB during follow-up. Total follow-up time for the whole cohort was over 2.3 million person years and 56% (1,320,001/2,345,098) of that was time exposed to ACEI/ARB. Follow-up ended a mean of 4.1 years (SD 4.1) after first antihypertensive drug prescription. 14,907 people developed AKI. The characteristics of the overall cohort, and the cohort during time exposed to antihypertensive treatment regimens that either included or excluded an ACEI/ARB are presented in **Table 1**. Those exposed to ACEI/ARB were more likely to be male with cardiac comorbidities, and to have had renal function measured prior to starting an antihypertensive. Fifty-three percent of time exposed to antihypertensive treatment

including an ACEI/ARB was between 2009 and 2014 compared to 38% of time exposed to antihypertensive treatment *excluding* an ACEI/ARB.

Table 1. Person-time under follow-up broken down by patient-level characteristics and ACEI/ARB exposure status. Data are person years unless otherwise stated. Numbers in brackets are column percentages unless otherwise specified.

		Whole cohort	Cohort during time exposed to antihypertensive treatment *including* an ACEI/ARB	Cohort during time exposed to antihypertensive treatment *excluding* an ACEI/ARB
	Total person years at risk	2,345,098	1,320,001	1,025,097
	Median person years at risk (IQR)	2.8 (0.4–7)	3.6 (1.1–6.9)	0.8 (0.2–3.4)
	Range of person years at risk	0.0–17.0	0.0–17.0	0.0–17.0
AKI	Number of events	14,907	10,157	4,750
Sex	Female	1,152,897 (49.2)	577,957 (43.8)	574,940 (56.1)
Age (years)	18–44	151,515 (6.5)	73,332 (5.6)	78,183 (7.6)
	45–54	350,170 (14.9)	211,576 (16.0)	138,593 (13.5)
	55–59	274,706 (11.7)	161,826 (12.3)	112,881 (11.0)
	60–64	324,416 (13.8)	188,097 (14.2)	136,319 (13.3)
	65–69	326,139 (13.9)	184,344 (14.0)	141,795 (13.8)
	70–74	308,156 (13.1)	171,103 (13.0)	137,053 (13.4)
	75–84	467,754 (19.9)	255,577 (19.4)	212,178 (20.7)
	85+	142,242 (6.1)	74,146 (5.6)	68,096 (6.6)
CKD stage (eGFR in ml/ min/1.73m^2)	No CKD (eGFR >=60)	934,070 (39.8)	580,871 (44.0)	353,199 (34.5)
	CKD stage 3a (eGFR 45–59)	113,238 (4.8)	68,074 (5.2)	45,163 (4.4)
	CKD stage 3b (eGFR 30–44)	18,435 (0.8)	10,873 (0.8)	7,562 (0.7)
	CKD stage 4 (eGFR 15–29)	1,926 (0.1)	1,036 (0.1)	890 (0.1)
	Baseline CKD status absent	1277429 (54.5)	659,145 (49.9)	618,283 (60.3)
Comorbidities	Diabetes mellitus	504,053 (21.5)	371,423 (28.1)	132,630 (12.9)
	Ischaemic heart disease	735,949 (31.4)	437,433 (33.1)	298,516 (29.1)
	Cardiac failure	152,904 (6.5)	116,449 (8.8)	36,456 (3.6)
	Arrhythmia	281,141 (12.0)	156,555 (11.9)	124,586 (12.2)
	Hypertension	2,036,050 (86.8)	1,194,641 (90.5)	841,409 (82.1)
Other antihypertensive drugs	Beta blockers	764,584 (32.6)	289,190 (21.9)	475,394 (46.4)
	Calcium channel blockers	732,628 (31.2)	331,429 (25.1)	401,199 (39.1)
	Thiazides	742,535 (31.7)	328,679 (24.9)	413,855 (40.4)
Non-thiazide diuretic drugs	Loop diuretics	155,911 (6.6)	118,565 (9.0)	37,346 (3.6)
	Potassium sparing diuretics	42,047 (1.8)	25,015 (1.9)	17,033 (1.7)
Ethnicity	White	982,377 (41.9)	569,946 (43.2)	412,431 (40.2)
	South Asian	26,933 (1.1)	17,647 (1.3)	9,286 (0.9)
	Black	14,8301 (0.6)	6,723 (0.5)	8,108 (0.8)
	Other	7,832 (0.3)	4,792 (0.4)	3,041 (0.3)
	Mixed heritage	2,553 (0.1)	1,490 (0.1)	1,063 (0.1)
	Not stated or missing	1,310,572 (55.9)	719,403 (54.5)	591,169 (57.7)
Calendar period	1997–2000	93,628 (4.0)	26,446 (2.0)	67,182 (6.6)
	2001–2004	418,412 (17.8)	170,465 (12.9)	247,947 (24.2)
	2005–2008	742,558 (31.7)	422,466 (32.0)	320,092 (31.2)
	2009–2011	646,221 (27.6)	416,685 (31.6)	229,535 (22.4)
	2012–2014	444,280 (18.9)	283,938 (21.5)	160,342 (15.6)

[#]note numbers exposed to antihypertensive treatment regimens *including* an ACEI/ARB and *excluding* an ACEI/ARB do not total the whole cohort number as individuals may be included in both columns.
ACEI/ARB: Angiotensin converting enzyme inhibitor/angiotensin receptor blocker
IQR: Interquartile range
CKD: Chronic kidney disease
eGFR: Estimated glomerular filtration rate

Association of ACEI or ARB prescription with rate of AKI

The association between covariates including age and comorbidities is shown in **Supplementary Table S2.** In the fully-adjusted model, age above 70 years, baseline CKD stage 3B and above, loop diuretic treatment and cardiac failure were all associated with a greater than doubling of AKI risk. Over the whole study period, the age and sex adjusted incidence rate ratio (RR) for first AKI comparing time exposed to antihypertensive treatment *including* an ACEI/ARB to that *excluding* an ACEI/ARB was 1.69 (95% CI 1.63–1.76), which fell to 1.12 (95% CI 1.07–1.17) after full adjustment (**Supplementary Table S2**). Further adjustment for lifestyle covariates and socioeconomic status made marginal difference to all results (**Supplementary Table S3**). Among subgroups with the highest absolute rates of AKI such as those with cardiac failure and chronic kidney disease (CKD) stage 4 there was no measurable association (or an apparent protective effect) of AKI with ACEI/ARB treatment (**Figure 2**).

Sensitivity analyses

Inclusion of only those with known baseline CKD stage, adjustment for ethnicity, and varying the way that AKI was defined from ICD-10 coding made minimal differences to the RR for AKI comparing time exposed to antihypertensive treatment including an ACEI/ARB to that excluding an ACEI/ARB (**Supplementary Table S3**).

Interaction between diuretics and ACEI/ARB treatment

There was an interaction between loop diuretics and ACEI/ARB treatment; there was no apparent increase in risk of AKI associated with ACEI/ARB exposure during periods of treatment with loop diuretic. Among people exposed to loop diuretics the RR for AKI during time exposed to treatment including an ACEI/ARB compared to that excluding an ACEI/ARB was 0.98 (95% CI 0.91–1.24) while among those not requiring loop diuretics the RR was 1.18 (95% CI 1.13–1.24) ($p<0.001$). Absolute rates of AKI stratified by ACEI/ARB treatment and comorbidity, modelled with inclusion of the interaction term, highlight the higher rates of AKI among people taking loop diuretics within each stratum (**Supplementary Table S4 and Figure S4**). There was no evidence for an interaction between potassium-sparing diuretics and ACEI/ARB treatment (RR for AKI among those prescribed potassium-sparing diuretics during time exposed to ACEI/ARB compared to time unexposed 1.09 (95% CI 0.96–1.24) while among those not requiring potassium-sparing diuretics the RR was 1.12 (95% CI 1.08–1.17: p=0.667)).

Impact of change in renal function on rate of AKI

When renal function was time updated, the RR for AKI during time exposed to antihypertensive treatment including and excluding an ACEI/ARB was attenuated to 1.02 (95% CI 0.98–1.07) (**Supplementary Table S2**). Among people who developed AKI, the median number of days between last measurement of estimated glomerular filtration rate (eGFR) and admission with the AKI episode was 116 days (IQR 44–258 days).

Rate of AKI in users of ACEI compared to ARB, or both combined

Compared to time not exposed to either drug, exposure to an ACEI was associated with an adjusted RR for AKI of 1.14 (95% CI 1.09–1.19), while exposure to an ARB was associated with a RR of 1.06 (95% CI 1.00–1.12). Dual therapy with both an ACEI and an ARB with associated with nearly twice the rate of AKI compared to time unexposed to either drug (RR 1.83 95% CI 1.53–2.17).

DISCUSSION

Among antihypertensive users we found a 12% (95% CI 1.07–1.17) increase in the rate of AKI during time exposed to ACEI/ARB compared to time unexposed (after adjustment for comorbidities, additional drug exposure, and calendar period). However, this relative risk varied markedly among different subgroups, and was highest among those with the lowest absolute risk of acute kidney injury. There was no evidence of increased AKI risk for ACEI/ARB users among those at greatest absolute risk of AKI (e.g. those with comorbidities or those also prescribed loop diuretics). Adjustment for most recent renal function further attenuated the risk of AKI due to ACEI/ARB exposure. We have shown that treatment with ACEI is associated with a similar magnitude of risk of AKI as ARB, but there is a near doubling of risk of AKI during time exposed to both ACEI and ARB. In addition to examining the effect of antihypertensives on AKI risk, we have calculated absolute rates of AKI in a general population cohort and the impact of important comorbidities and age upon these rates.

To illustrate our results, it is useful to consider the number of cases of AKI associated with ACEI/ARB use within different subgroups. Assuming that differences in AKI rates were directly attributable to ACEI/ARB exposure, in a low risk group – such as those with normal renal function – despite a 17% increase in relative risk of AKI during ACEI/ARB treatment, for 1,000 people, removal of the drug would reduce the number of AKI cases from 10 to 8 per year. In contrast, in a group at high absolute risk of AKI – such as those with cardiac failure treated with loop diuretics – exposure to ACEI/ARB has minimal impact. Among 1000 such people there are 76 cases of AKI in those treated with ACEI/ARB and 78 cases among those not treated.

Strengths and limitations

This is the largest study of this topic to date, it examines an inclusive population-based cohort from primary care and reflects routine clinical use of these medications. By comparing ACEI/ARB use to other antihypertensives, we were able to reduce confounding by indication compared to previous case-control studies. We were able to clearly define and adjust for covariates including renal function prior to starting the medication. The time-updated analysis reduced residual confounding, while restriction to only incident users reduced adherence bias.

However, there are a number of important limitations. Our assessment of drug exposure was based on prescriptions so we cannot be certain that people prescribed the drug were taking the medication; importantly we were unable to take into account any temporary discontinuation in medication use during acute illness or hospitalisation. We did not have inpatient biochemical data so could only use ICD-10 coding to define AKI. Therefore, we have captured only a proportion of the cases defined by current biochemical definitions of AKI (although this includes a greater proportion of more severe cases [34,35]) and we were not able to grade the severity of AKI. We examined first episode of AKI only. We cannot be certain that AKI was present at the time of hospital admission, or developed while in hospital although we have conducted several sensitivity analyses to address this. It is possible that there is bias in classification of the outcome. For example, due to awareness of an association, hospital staff may be more likely to recognise and code AKI in patients taking ACEI/ARB. Alternately, patients taking these drug may have more frequent monitoring of renal function and therefore be more likely to have AKI detected. However, these sources of bias would lead to an overestimate of the association between ACEI/ARB and AKI. We did not examine the additional effects of NSAIDs because these have been examined in previous studies.[6–8] There is limited and selective data on proteinuria from primary care records so we were not able to adjust for this potentially important covariate. Finally, this study is limited to NHS patients in England, which may restrict its generalisability.

Comparison to other studies

Previous high quality evidence regarding the association between ACEI/ARB and AKI is scarce. Estimates of the increase in AKI risk associated with use of ACEI/ARB from randomised trials are limited.[5] Many commonly cited observational studies are cross-sectional or address the risk of AKI in relation to specific diseases or interventions.[8–10] Two recent nested case-control studies using UK primary care data reported only relative risks for AKI among users of NSAIDS in addition to ACEI/ARB and diuretics.[6,7] Only one population-based study has examined the relative risk of AKI among ACEI/ARB users compared to non-users. This study, despite limited data quality, found similar

results to our own with a fully adjusted OR of 1.11 (95% CI 1.02–1.20) comparing those prescribed and not prescribed ACEI/ARB.[36]

However, strong evidence does exist in relation to the risks of AKI associated with combined ACEI and ARB therapy. Here, recent clinical trials using this regime have reported hazard ratios for renal adverse events ranging from 1.20 (95% CI 0.96–1.50) to 2.19 (95% CI 1.13–4.22), compared to single agent treatment alone.[12,13] Our results, showing a near doubling of rate for AKI with dual blockade, are similar to these findings and strongly support the validity of our study.

Finally, similar to other recent studies, we show that the rate of AKI detected by ICD-10 coding has increased markedly over the time period of this study. This is well documented and likely to be multifactorial, attributable to better hospital coding, increased recognition of AKI and possibly a true increase in incidence.[37]

Possible explanations and implications for clinicians and policymakers

Although surprising, we believe that this study has provided the most accurate estimates of the strength of the association between ACEI/ARB use and AKI to date. One alternate explanation for the small effect size is that we have compared time exposed to ACEI/ARB to other antihypertensives, with no untreated comparison group. While this design reduces confounding by indication, it is possible that all antihypertensives increase AKI risk during acute illness. In addition, among those at the highest absolute risk of AKI (e.g. those with additional comorbidities), we found rates of AKI for ACEI/ARB users were lower than for non-users. The probable explanation for these findings is that, in patients with multiple comorbidities that are indications for ACEI/ARB treatment, not being treated with ACEI or ARB is a marker of unmeasured poor health status or frailty. For example, an individual may have stopped ACEI/ARB treatment when they became unwell, perhaps due to worsening renal function, and the reason for stopping ACEI/ARB places them at higher risk of AKI during subsequent follow-up. This is likely to have attenuated the estimate of the strength of association between ACEI/ARB and AKI over the whole study population, although the proportion of patients with multiple comorbidities is small. Finally, our results do not exclude that AKI among users of ACEI/ARB is more severe compared to users of other antihypertensives. However, even when the AKI definition was restricted to code positions representing the primary diagnosis, ACEI/ARB treatment was only associated with a 21% (95% CI 11–33%) increase in AKI rate.

We have also shown that patients taking loop diuretics have higher rates of AKI than similar patients not prescribed the drugs. This may be causal, due to salt and water depletion during acute illness, or additional loop diuretic treatment may be a marker of severity of comorbidities. We anticipated that

pharmacological interaction between loop diuretics and ACEI/ARB would be associated with an increased risk of AKI compared to treatment with loop diuretics alone but we have shown the converse. Again, this is likely to be explained by confounding by underlying health status where the most severely unwell patients at highest risk of AKI are not treated with both diuretics and ACEI/ARB. Finally, we have shown that when adjusted for most recent renal function, there was no measurable association between ACEI/ARB use and AKI. The findings of this analysis have to be considered in light of possible misclassification of CKD stage by renal function measured during an AKI episode, although we excluded all measurements of kidney function that occurred before of an admission with AKI.

Treatment with ACEI and ARB are widely believed to be risk factors for AKI, particularly during acute illness. This underlies the 'sick-day rules' recommendation for patients to stop taking these drugs when they become acutely unwell with symptoms of gastroenteritis or fever.[17] This study was not designed to examine the effect of temporary cessation of these drugs on the development of AKI. However, we have demonstrated that patient comorbidities are much stronger risk factors for the development of AKI than these drugs, and that there is no measurable effect of the drugs among those at highest risk of AKI. This reinforces the importance of assessing overall risk of AKI in planning potential interventions aimed at lowering hospital admissions with AKI. Patients with multiple risk factors but not taking ACEI/ARB may be those who would benefit most from close review of fluid balance and intensive monitoring during acute illness, but they may be overlooked if the clinical focus is on drug cessation.

Conclusions

In conclusion, our results show that treatment with ACEI/ARB appears to be associated with only a small increase in AKI risk while patient characteristics (such as age and comorbidities) are much more strongly associated with the rate of AKI. While people may benefit from optimised medicines management during acute illness, our results suggest that these interventions should be targeted at individuals at highest risk of AKI rather than focussing on users of ACEI/ARB.

FUNDING

LT is funded by a Wellcome Trust intermediate clinical fellowship (101143/Z/13/Z). KB is funded by a Wellcome Trust/Royal Society Sir Henry Dale fellowship (107731/Z/15/Z). LS is supported by a Wellcome Trust Senior Research Fellowship in Clinical Science (098504/Z/12/Z). The funders had no role in study design; collection, analysis, and interpretation of data; writing the report; and the decision to submit the report for publication.

CONTRIBUTIONS

LT had the original idea for the study. All authors were involved in the study design. KM undertook the data management, primary analysis and wrote the first draft. All authors contributed to further drafts and approved the final manuscript. KM and LT had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

COMPETING INTERESTS

All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years, no other relationships or activities that could appear to have influenced the submitted work.

ETHICAL APPROVAL

This study was approved by the LSHTM Research Ethics Committee (reference 6536) and by the CPRD independent scientific advisory committee (ISAC protocol number: 14-208).

DATA SHARING

No additional data available.

REFERENCES

1 Chertow GM, Burdick E, Honour M, *et al.* Acute kidney injury, mortality, length of stay, and costs in hospitalized patients. *J Am Soc Nephrol* 2005;**16**:3365–70. doi:10.1681/ASN.2004090740

2 Think Kidneys. Acute Kidney injury: The NHS campaign to improve the care of people at risk of, or with, acute kidney injury. [internet]. 2016. Available from: https://www.thinkkidneys.nhs.uk/aki/ (accessed Jan 2016)

3 Mehta RL, Cerdá J, Burdmann EA, *et al.* International Society of Nephrology's 0by25 initiative for acute kidney injury (zero preventable deaths by 2025): a human rights case for nephrology. *Lancet* 2015;**6736**:1–28. doi:10.1016/S0140-6736(15)60126-X

4 Schoolwerth AC, Sica DA, Ballermann BJ, *et al.* Renal considerations in angiotensin converting enzyme inhibitor therapy: a statement for healthcare professionals from the Council on the Kidney in Cardiovascular Disease and the Council for High Blood Pressure Research of the American Heart Association. *Circulation* 2001;**104**:1985–91. doi:10.1161/hc4101.096153

5 Palmer SC, Mavridis D, Navarese E, *et al.* Comparative efficacy and safety of blood pressure-lowering agents in adults with diabetes and kidney disease: a network meta-analysis. *Lancet* 2015;**385**:2047–56. doi:10.1016/S0140-6736(14)62459-4

6 Lapi F, Azoulay L, Yin H, *et al.* Concurrent use of diuretics, angiotensin converting enzyme inhibitors, and angiotensin receptor blockers with non-steroidal anti-inflammatory drugs and risk of acute kidney injury: nested case-control study. *Br Med J* 2013;**346**:8525. doi:10.1136/bmj.e8525

7 Dreischulte T, Morales DR, Bell S, *et al.* Combined use of nonsteroidal anti-inflammatory drugs with diuretics and/or renin–angiotensin system inhibitors in the community increases the risk of acute kidney injury. *Kidney Int* 2015;:1–8. doi:10.1038/ki.2015.101

8 Loboz KK, Shenfield GM. Drug combinations and impaired renal function – the ' triple whammy '. *B J Pharmacol* 2004;**59**:239–43. doi:10.1111/j.1365-2125.2004.02188.x

9 Plataki M, Kashani K, Cabello-Garza J, *et al.* Predictors of acute kidney injury in septic shock patients: an observational cohort study. *Clin J Am Soc Nephrol* 2011;**6**:1744–51. doi:10.2215/CJN.05480610

10 Arora P, Rajagopalam S, Ranjan R, *et al.* Preoperative use of angiotensin-converting enzyme inhibitors/angiotensin receptor blockers is associated with increased risk for acute kidney injury after cardiovascular surgery. *Clin J Am Soc Nephrol* 2008;**3**:1266–73. doi:10.2215/CJN.05271107

11 Chaumont M, Pourcelet A, van Nuffelen M, *et al.* Acute Kidney Injury in Elderly Patients With Chronic Kidney Disease: Do Angiotensin-Converting Enzyme Inhibitors Carry a Risk? *J Clin Hypertens* 2016;**18**:1–8. doi:10.1111/jch.12795

12 Fried LF, Emanuele N, Zhang JH, *et al.* Combined angiotensin inhibition for the treatment of diabetic nephropathy. *N Engl J Med* 2013;**369**:1892–903. doi:10.1056/NEJMoa1303154

13 Mann JFE, Schmieder RE, McQueen M, *et al.* Renal outcomes with telmisartan, ramipril, or both, in people at high vascular risk (the ONTARGET study): a multicentre, randomised, double-blind, controlled trial. *Lancet* 2008;**372**:547–53.http://www.ncbi.nlm.nih.gov/pubmed/18707986 (accessed 1 May2014).

14 European Medicines Agency. Combined use of medicines affecting the renin-angiotensin system (RAS) to be restricted – CHMP endorses PRAC recommendation. 2014.http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2014/05/news_detail_002107.jsp&mid=WC0b01ac058004d5c1 (accessed 18 Sep2015).

15 Feehally J, Gilmore I, Barasi S, *et al.* RCPE UK Consensus Conference Statement Management of acute kidney injury: the role of fluids, e-alerts and biomarkers. *JR Coll Physicians* 2013;**43**:37–8.http://www.lumison.co.uk/~rcpe/journal/issue/journal_43_1/acutekidneyinjury.pdf (accessed 4 Sep 2014).

16 National Institute for Health and Care Excellence. NICE clincal guideline 169: Acute kidney injury - Prevention, detection and management of acute kidney injury up to the point of renal replacement therapy. [internet] 2013. Available from: http://www.nice.org.uk/nicemedia/live/14258/65056/65056.pdf (accessed 14 Aug 2015)

17 Scottish Patient Safety Programme. Medicine Sick Day Rules Card. Healthc. Improv. Scotl. 2015.Available from: http://www.scottishpatientsafetyprogramme.scot.nhs.uk/programmes/primary-care/medicine-sick-day-rules-card (accessed 16 Jun2015).

18 Herrett E, Gallagher AM, Bhaskaran K, *et al.* Data Resource Profile: Clinical Practice Research Datalink (CPRD). *Int J Epidemiol* 2015;**44**:1–10. doi:10.1093/ije/dyv098

19 Mathur R, Bhaskaran K, Chaturvedi N, *et al.* Completeness and usability of ethnicity data in UK-based primary care and hospital databases. *J Public Health (Oxf)* 2013;**36**:684–92. doi:10.1093/pubmed/fdt116

20 Bhaskaran K, Forbes HJ, Douglas I, *et al.* Representativeness and optimal use of body mass index (BMI) in the UK Clinical Practice Research Datalink (CPRD). *BMJ Open* 2013;**3**:e003389. doi:10.1136/bmjopen-2013-003389

21 HSCIC. Hospital Episode Statistics. http://www.hscic.gov.uk/hes (accessed 25 Jun2015).

22 Hernán MA, Hernández-Díaz S, M.Werler M, *et al.* Causal Knowledge as a Prerequisite for Confounding Evaluation: An Application to Birth Defects Epidemiology. *Am J Epidemiol* 2002;**155**:176–84. doi:10.1093/aje/155.2.176

23 Greenland S, Pearl J, Robins3 JM. Causal Diagrams for Epidemiologic Research. *Epidemiology* 1999;**10**:37–48. doi:10.1097/00001648-199901000-00008

24 Levey AS, Stevens LA, Schmid CH, *et al.* A new equation to estimate glomerular filtration rate. *Ann Intern Med* 2009;**150**:604–12.http://annals.org/article.aspx?articleid=744469 (accessed 28 Mar2014).

25 Fox CS, Matsushita K, Woodward M, *et al.* Associations of kidney disease measures with mortality and end-stage renal disease in individuals with and without diabetes: a meta-analysis. *Lancet* 2012;**380**:1662–73. doi:10.1016/S0140-6736(12)61350-6

26 McDonald HI, Thomas SL, Millett ERC, *et al.* CKD and the Risk of Acute, Community-Acquired Infections Among Older People With Diabetes Mellitus: A Retrospective Cohort Study Using Electronic Health Records. *Am J Kidney Dis* 2015;**66**:60–8. doi:doi:10.1053/j.ajkd.2014.11.027

27 Quint JK, Herrett E, Bhaskaran K, *et al.* Effect of β blockers on mortality after myocardial infarction in adults with COPD: population based cohort study of UK electronic healthcare records. *BMJ* 2013;**347**:f6650. doi:10.1136/bmj.f6650

28 Brauer R, Smeeth L, Anaya-Izquierdo K, *et al.* Antipsychotic drugs and risks of myocardial infarction: a self-controlled case series study. *Eur Heart J* 2014;:ehu263. doi:10.1093/eurheartj/ehu263

29 Herrett E, Shah AD, Boggon R, *et al.* Completeness and diagnostic validity of recording hospital care disease registry and national mortality. *Br Med J* 2013;**346**. doi:10.1136/bmj.f2350

30 Douglas IJ, Evans SJW, Hingorani AD, *et al.* Clopidogrel and interaction with proton pump inhibitors: comparison between cohort and within person study designs. *BMJ* 2012;**345**:e4388. doi:10.1136/bmj.e4388

31 Springate DA, Kontopantelis E, Ashcroft DM, *et al.* ClinicalCodes: an online clinical codes repository to improve the validity and reproducibility of research using electronic medical records. *PLoS One* 2014;**9**:e99825. doi:10.1371/journal.pone.0099825

32 Tomlinson LA, Riding AM, Payne RA, *et al.* The accuracy of diagnostic coding for acute kidney injury in England - a single centre study. *BMC Nephrol* 2013;**14**:58. doi:10.1186/1471-2369-14-58

33 Siew ED, Ikizler TA, Matheny ME, *et al.* Estimating baseline kidney function in hospitalized patients with impaired kidney function. *Clin J Am Soc Nephrol* 2012;**7**:712–9. doi:10.2215/CJN.10821011

34 Sawhney S, Fluck N, Marks A, *et al.* Acute kidney injury - How does automated detection perform? *Nephrol Dial Transplant* 2015;**30**:1853–61. doi:10.1093/ndt/gfv094

35 Grams ME, Waikar SS, Macmahon B, *et al.* Performance and Limitations of Administrative Data in the Identification of AKI. *Clin J Am Soc Nephrol* 2014;:1–8. doi:10.2215/CJN.07650713

36 Bedford M, Farmer CK, Irving J, *et al.* Acute kidney injury: an acceptable risk of treatment with renin-angiotensin system blockade in primary care? *Can J Kidney Heal Dis* 2015;**2**:14. doi:10.1186/s40697-015-0044-y

37 Tomlinson LA, Abel GA, Chaudhry AN, *et al.* ACE inhibitor and angiotensin receptor-II antagonist prescribing and hospital admissions with acute kidney injury: a longitudinal ecological study. *PLoS One* 2013;**8**:e78465. doi:10.1371/journal.pone.0078465

FIGURE LEGENDS

Figure 1. Flow diagram showing the creation of the cohort and reasons for exclusion.

<<Insert Figure 1>>

ACEI/ARB: Angiotensin converting enzyme inhibitor/angiotensin receptor blocker
BB: Beta blocker
CCB: Calcium channel blocker
CPRD: Clinical Practice Research Datalink
HES: Hospital Episode Statistics
ESRD: End stage renal disease

Figure 2. Modelled rates* of AKI (during the calendar period 2012–2014) per 1,000 person years at risk for AKI during time exposed to antihypertensive treatment including ACEI/ARB compared to time exposed to antihypertensive treatment excluding ACEI/ARB, stratified by characteristics and comorbidities.

<<Insert Figure 2>>

*Absolute rates (unless otherwise stated) are for men, aged 75–84, with CKD stage 3a, and no comorbidities – chosen as a large, clinically important, high risk group.
**Adjusted using Poisson regression for: age, sex, chronic comorbidities (CKD, hypertension, diabetes mellitus, cardiac failure, ischaemic heart disease, and arrhythmia), time exposed to other antihypertensive drugs (beta-blockers, calcium channel blockers, and thiazides), time exposed to loop and potassium-sparing diuretics, and calendar period.
AKI: Acute kidney injury
ACEI/ARB: Angiotensin converting enzyme inhibitor/angiotensin receptor blocker
pyar: Person years at risk
CKD: Chronic kidney disease
ACEI/ARB exposed: Antihypertensive treatment including ACEI/ARB
ACEI/ARB unexposed: Antihypertensive treatment excluding ACEI/ARB
IRR: Incidence rate ratio
CI: Confidence interval

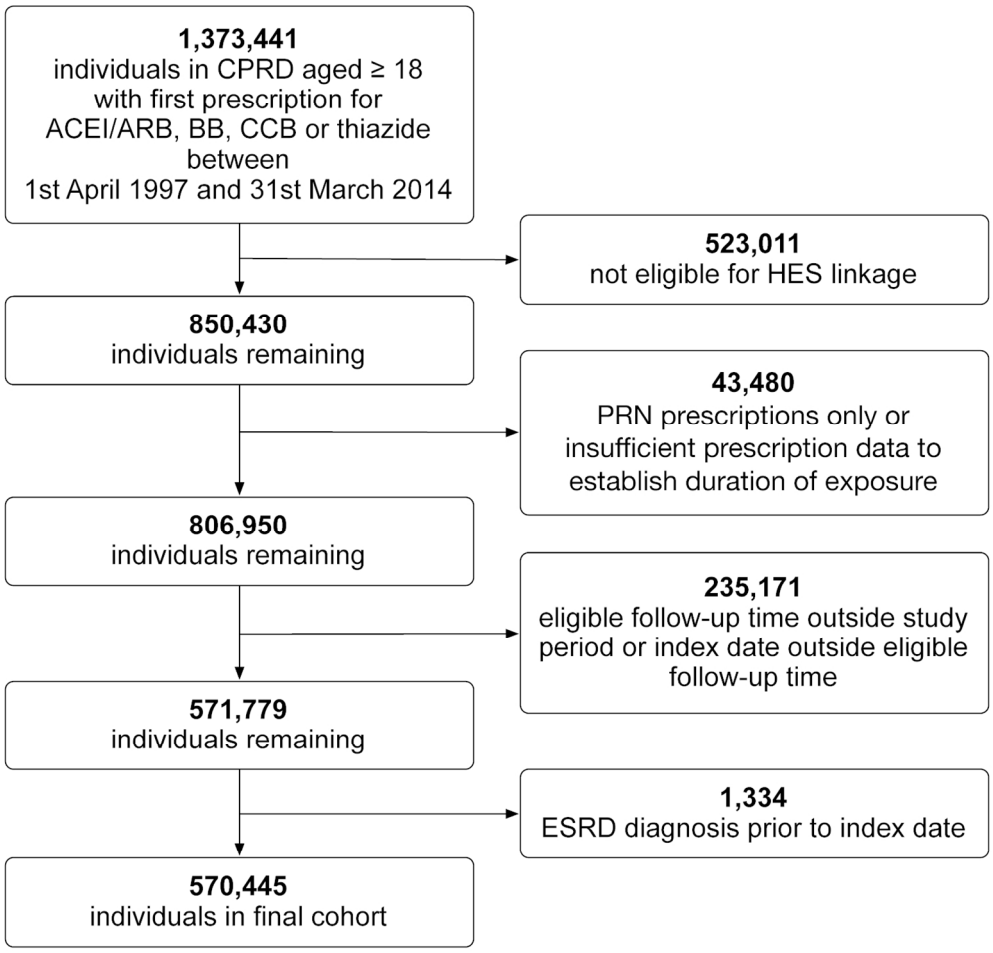


Figure 1. Flow diagram showing the creation of the cohort and reasons for exclusion.
Figure 1
129x124mm (300 x 300 DPI)

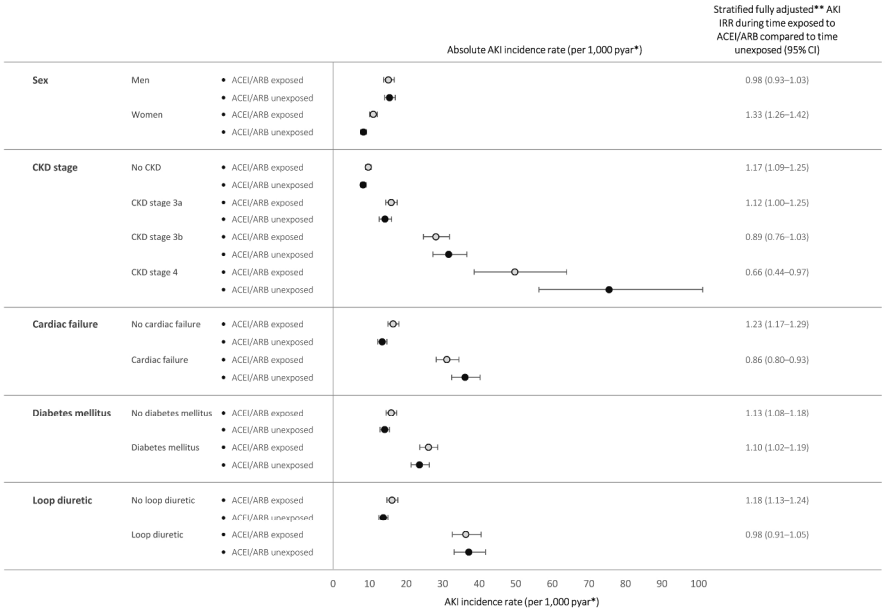


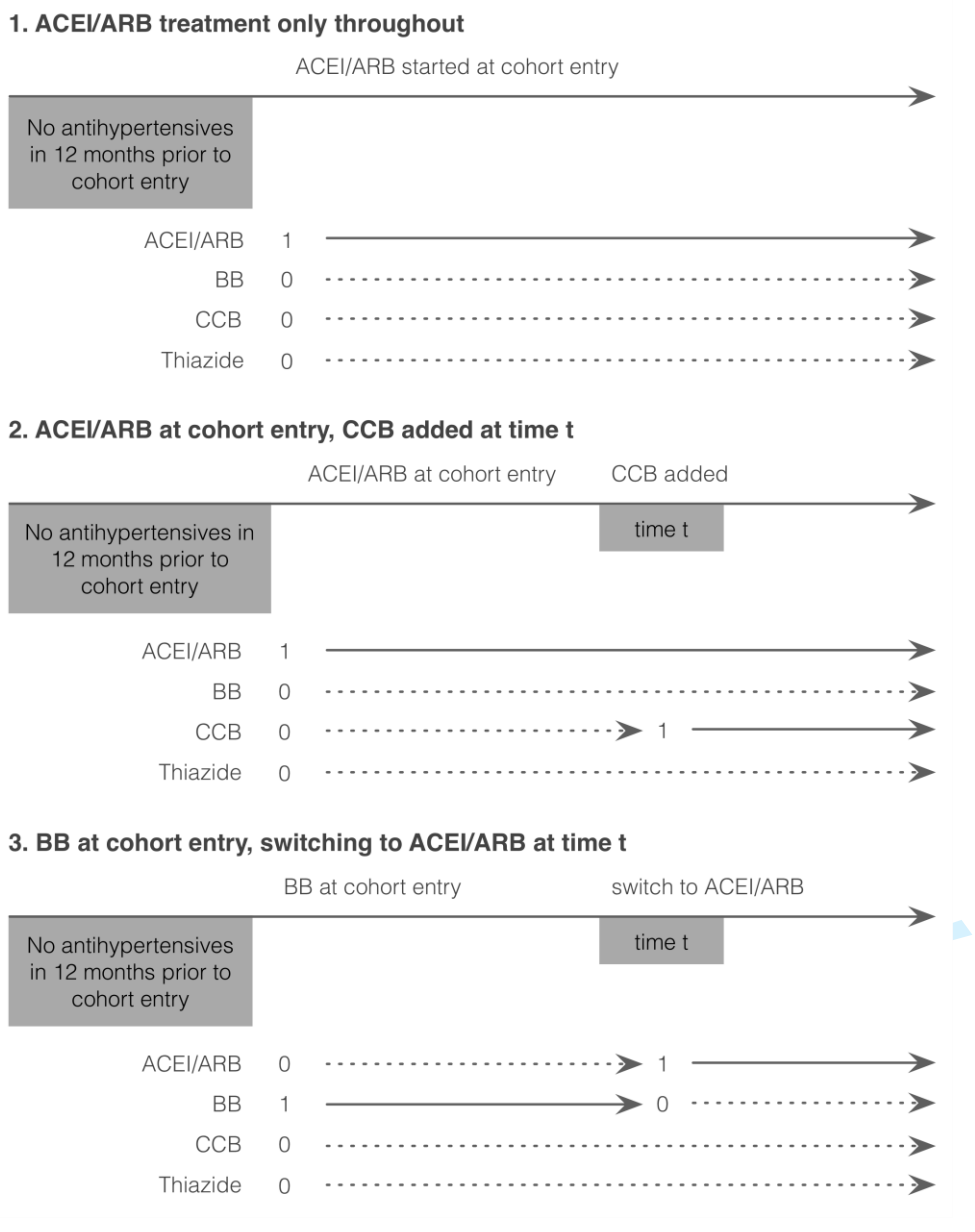
Figure 2. Modelled rates* of AKI (during the calendar period 2012–2014) per 1,000 person years at risk for AKI during time exposed to ACEI/ARBs compared to time unexposed, stratified by characteristics and comorbidities

Figure 2
271x169mm (300 x 300 DPI)

Text S1: Antihypertensive drug exposure defined by multiple binary indicators

Rather than a single variable representing time exposed to a single class of antihypertensive, we used four time-updating, binary indicator variables to indicate antihypertensive exposure status. Defining exposure status in this way allowed patients to be exposed to more than one class of antihypertensive at a time. Each indicator variable identified whether the associated period of time at risk was exposed (1) or unexposed (0) to a specific class of antihypertensive. Figure S1 illustrates how the indicator variables would be assigned in three example scenarios. In scenario one, the patient remains exposed to only one agent for the duration of the study. In scenario two, a second antihypertensive is added. In scenario three, the patient switches from one class of drug to a different class of drug.

Figure S1: Assignment of time-varying exposure status during follow-up using multiple binary indicator exposure variables under three example scenarios.



0=indicator variable 'switched off' (drug not prescribed); 1=indicator variable 'switched on' (drug prescribed).
ACEI/ARB: Angiotensin converting enzyme inhibitor/angiotensin receptor blocker
BB: Beta-blocker
CCB: Calcium channel blocker

Table S1. Definition of acute kidney injury: ICD-10 codes used to define of acute kidney injury in HES data.

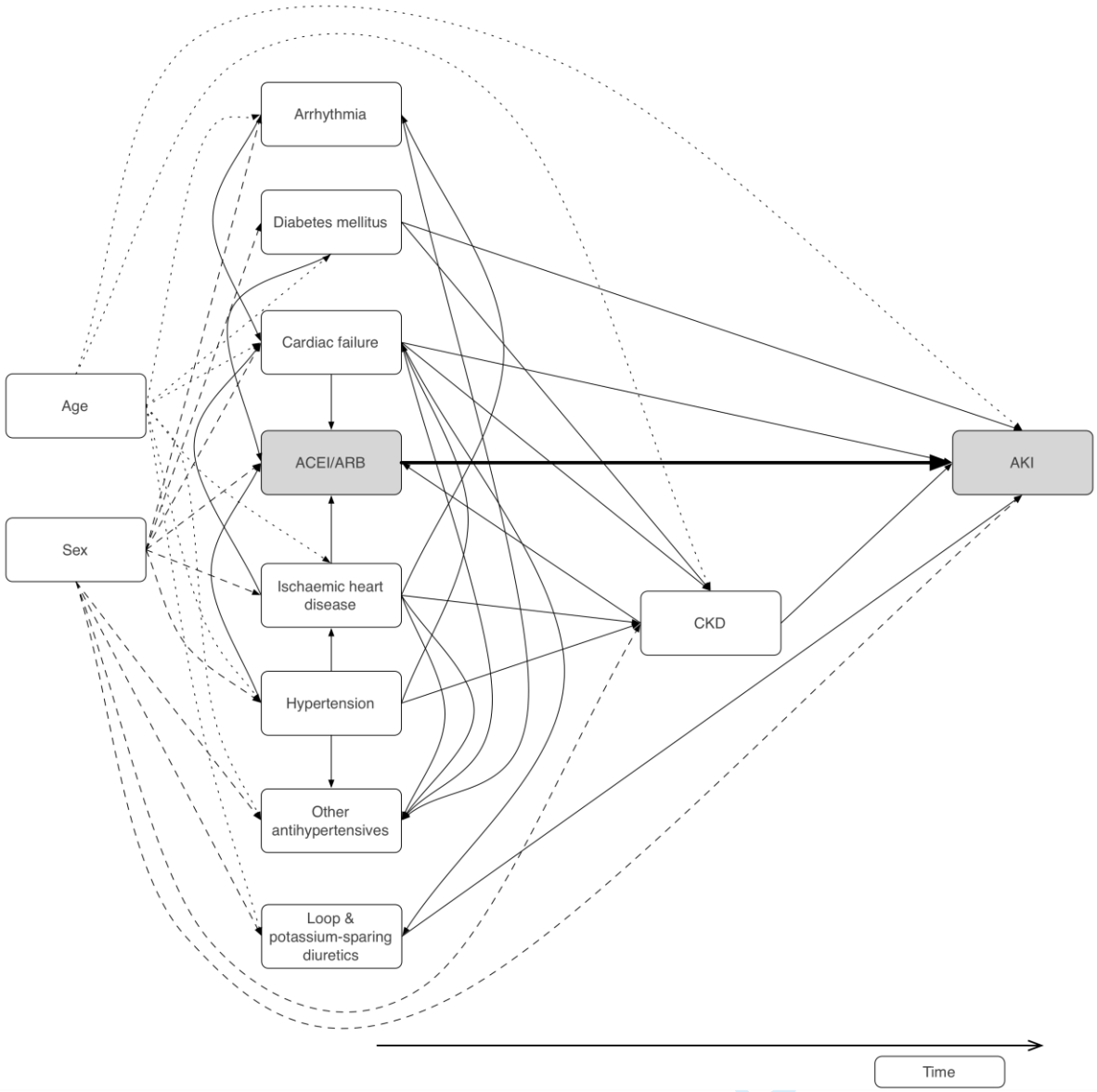
ICD-10 code	Clinical term	% of cases of AKI cases defined by code
N14.1	Nephropathy induced by other drugs, medicaments and biological substances	0.12
N14.2	Nephropathy induced by unspecified drug, medicament or biological substance	0.03
N17.0	Acute renal failure with tubular necrosis	0.78
N17.1	Acute renal failure with acute cortical necrosis	0.04
N17.2	Acute renal failure with medullary necrosis	0.03
N17.8	Other acute renal failure	0.28
N17.9	Acute renal failure, unspecified	70.14
N19	Unspecified kidney failure	25.31
N99.0	Post procedural renal failure	1.29
R34	Anuria and oliguria	0.90
R94.4	Abnormal results of kidney function studies	0.99

Text S2. Definition of end-stage renal disease

ESRD was defined using hospital and primary care morbidity coding, and hospital procedure coding as the presence of:

i) An ESRD morbidity code.
ii) A code for renal transplant.
iii) A code for peritoneal or haemodialysis.
iv) Stage 5 chronic kidney disease (identified using morbidity coding and estimated glomerular filtration rate (eGFR).
v) Stage 4 CKD with a fistula, suggesting ESRD is anticipated.

Figure S2. Simplified directed acyclic graph (DAG) illustrating implicitly assumed causal structure underlying our adjusted models.



➔ Represents causal path of interest

Under this assumed framework, adjusting for all measured variables blocks confounding pathways.

AKI: Acute kidney injury
ACEI/ARB: Angiotensin converting enzyme inhibitor/angiotensin receptor blocker
CKD: Chronic kidney disease

Table S2. Age and sex, and fully adjusted* incidence rate ratios (95% CIs) for AKI in sequentially adjusted models.

	AKI incidence rate ratio (95% CI)		
	Age & sex adjusted	Fully adjusted*	Fully adjusted* with CKD stage as a time-updated variable
	n=570,445	n=570,445	n=570,445
Exposure of interest			
ACEI/ARB	1.69 (1.63–1.76)	1.12 (1.07–1.17)	1.02 (0.98–1.07)
Sex			
Female	0.61 (0.59–0.63)	0.66 (0.64–0.68)	0.63 (0.61–0.65)
Age			
18–44	reference	reference	reference
45–54	0.85 (0.74–0.97)	0.81 (0.71–0.93)	0.89 (0.77–1.02)
55–59	1.08 (0.94–1.23)	0.97 (0.85–1.12)	1.07 (0.93–1.22)
60–64	1.41 (1.24–1.61)	1.18 (1.03–1.35)	1.25 (1.09–1.42)
65–69	2.11 (1.86–2.38)	1.59 (1.41–1.80)	1.55 (1.36–1.76)
70–74	3.15 (2.80–3.55)	2.17 (1.92–2.45)	1.84 (1.62–2.09)
75–84	6.03 (5.37–6.78)	3.34 (2.96–3.76)	2.26 (2.00–2.56)
85+	15.06 (13.34–17.01)	5.54 (4.87–6.30)	2.98 (2.61–3.41)
Comorbidity			
CKD stage			
No CKD	N/A	reference	reference
CKD stage 3a	N/A	1.67 (1.57–1.77)	2.60 (2.46–2.75)
CKD stage 3b	N/A	3.19 (2.91–3.51)	5.77 (5.42–6.15)
CKD stage 4	N/A	6.69 (5.57–8.03)	13.44 (12.45–14.51)
Baseline CKD status absent	N/A	1.18 (1.13–1.23)	1.90 (1.74–2.08)
Diabetes mellitus	N/A	1.65 (1.59–1.72)	1.52 (1.46–1.58)
Ischaemic heart disease	N/A	1.14 (1.09–1.19)	1.12 (1.07–1.17)
Cardiac failure	N/A	2.09 (1.97–2.20)	1.92 (1.82–2.03)
Arrhythmia	N/A	1.42 (1.36–1.48)	1.45 (1.38–1.51)
Hypertension	N/A	1.09 (1.04–1.15)	1.01 (0.96–1.06)
Other antihypertensive drugs			
Beta-blocker	N/A	0.99 (0.95–1.03)	0.90 (0.87–0.94)
Calcium channel blocker	N/A	0.97 (0.93–1.01)	0.93 (0.90–0.97)
Thiazide	N/A	0.99 (0.95–1.04)	0.91 (0.87–0.96)
Non-thiazide diuretics			
Loop	N/A	2.36 (2.23–2.50)	1.77 (1.67–1.88)
Potassium sparing	N/A	1.86 (1.74–1.98)	1.67 (1.56–1.79)
Calendar period			
1997–2000	N/A	reference	reference
2001–2004	N/A	1.17 (1.03–1.34)	1.14 (0.99–1.32)
2005–2008	N/A	1.62 (1.42–1.85)	1.61 (1.39–1.86)
2009–2011	N/A	2.26 (1.99–2.57)	2.38 (2.06–2.75)
2012–2014	N/A	3.29 (2.89–3.74)	3.62 (3.12–4.19)

*Adjusted using Poisson regression for: age, sex, chronic comorbidities (CKD, hypertension, diabetes mellitus, cardiac failure, ischaemic heart disease, and arrhythmia), time exposed to other antihypertensive drugs (beta-blockers, calcium channel blockers and thiazides), time exposed to loop and potassium-sparing diuretics, and calendar period

AKI: Acute kidney injury

ACEI/ARB: Angiotensin converting enzyme inhibitor/angiotensin receptor blocker

CKD: Chronic kidney disease

eGFR: Estimated glomerular filtration rate

Table S3. Incidence rate ratios (95% CIs) for AKI during time exposed to ACEI/ARB compared to time exposed to other antihypertensives in the main analysis and additional sensitivity analyses.

	Number of individuals	Number of AKI cases identified	AKI incidence rate ratio (95% CI) for ACEI/ARB therapy (compared to time exposed to other antihypertensives)	
			Age and sex adjusted	Fully adjusted*
Main analysis: AKI defined using all ICD-10 codes in any position and any episode within 28 days of the start of a hospital admission.	570,445	14,907	1.69 (1.63–1.76)	1.12 (1.07–1.17)
AKI defined using only code N17 in any position and any episode within 28 days of the start of a hospital admission.	570,445	11,174	1.76 (1.68–1.84)	1.12 (1.06–1.17)
AKI defined using all ICD-10 codes in any diagnostic position in the 1st or 2nd episode for episodes that occur within 7 days of admission.	570,445	14,377	1.70 (1.64–1.77)	1.13 (1.09–1.18)
AKI defined using all ICD-10 codes in the 1st diagnostic position of the 1st or 2nd episode for episodes that start within 7 days of admission.	570,445	3,009	1.83 (1.69–1.97)	1.21 (1.11–1.33)
Restricted to those with known baseline CKD status.	268,456	7,312	1.56 (1.47–1.65)	1.09 (1.02–1.16)
Including time-updated CKD stage rather than baseline CKD stage.	570,445	14,907	1.69 (1.63–1.76)	1.02 (0.98–1.07)
Additionally adjusting for smoking status, alcohol intake, and BMI.	485,139	12,583	N/A	1.17 (1.12–1.22)
Additionally adjusting for smoking status, alcohol intake, BMI, and socioeconomic status.	484,525	12,559	N/A	1.18 (1.12–1.23)
Restricted to those entering the cohort from 2006 with known ethnicity.**	132,847	1,944	1.37 (1.24–1.52)	1.07 (0.95–1.21)

*Adjusted using Poisson regression for: age, sex, chronic comorbidities (CKD, hypertension, diabetes mellitus, cardiac failure, ischaemic heart disease, and arrhythmia), time exposed to other antihypertensive drugs (beta-blockers, calcium channel blockers and thiazides), time exposed to loop and potassium sparing diuretics, and calendar period.
**Additionally adjusted for ethnicity and with race used to calculate eGFR
AKI: Acute kidney injury
ACEI/ARB: Angiotensin converting enzyme inhibitor/angiotensin receptor blocker
CKD: Chronic kidney disease
eGFR: Estimated glomerular filtration rate

Prescription for Renin-Angiotensin System Blockers and Risk of Acute Kidney Injury: A Population-Based Cohort Study
Kathryn E Mansfield, Dorothea Nitsch, Liam Smeeth, Krishnan Bhaskaran, Laurie A Tomlinson

Table S4. Descriptive table of modelled rates of AKI (during the calendar period 2012–2014) per 1000 person years at risk stratified by characteristics and comorbidities. This model includes an interaction term for loop diuretic use.

	Rate of AKI in ACEI/ARB exposed per 1000 pyar*		Rate of AKI in ACEI/ARB unexposed per 1000 pyar*		Absolute rate difference per 1000 pyar	
	On loop	Not on loop	On loop	Not on loop	On loop	Not on loop
Sex (rates for each sex aged 75-84 with CKD stage 3A and no comorbidities)						
Men	36.3	16.1	37.1	13.7	1.8	2.4
Women	24.0	10.6	24.5	9.0	0.5	1.6
Age (rates for each age group for men with CKD stage 3A and no comorbidities)						
18–44	10.9	4.8	11.1	4.1	0.2	0.7
45–54	8.8	3.9	9.0	3.3	0.2	0.6
55–59	10.6	4.7	10.8	4.0	0.2	0.7
60–64	12.8	5.7	13.1	4.8	0.3	0.9
65–69	17.3	7.7	17.7	6.5	0.4	1.2
70–74	23.6	10.5	24.1	8.9	0.5	1.6
75–84	36.3	16.1	37.1	13.7	0.8	2.4
85+	60.1	26.7	61.5	22.6	1.4	4.1
CKD stage (rates for each CKD stage for men with no comorbidities)						
No CKD (eGFR >=60)	21.8	9.7	22.3	8.2	0.5	1.5
CKD stage 3a (eGFR 45–59)	36.3	16.1	37.1	13.7	0.8	2.4
CKD stage 3b (eGFR 30–44)	69.3	30.8	70.8	26.1	1.5	4.7
CKD stage 4 (eGFR 15–29)	144.3	64.1	147.5	54.3	3.2	9.8
Comorbidity (rates for men aged 75-84 with CKD stage 3A and only the specified comorbidity)						
Diabetes mellitus	59.9	26.6	61.2	22.5	1.3	4.1
Ischaemic heart disease	41.3	18.4	42.2	15.5	0.9	2.9
Cardiac failure	76.3	33.9	78.0	28.7	1.7	5.2
Risk group						
Lowest risk group [1]	4.3	1.9	4.4	1.6	0.1	0.3
Highest risk group [2]	648.7	288.3	663.1	244.1	14.4	44.2

[1] Low risk: women aged 18-44 without CKD and no comorbidities

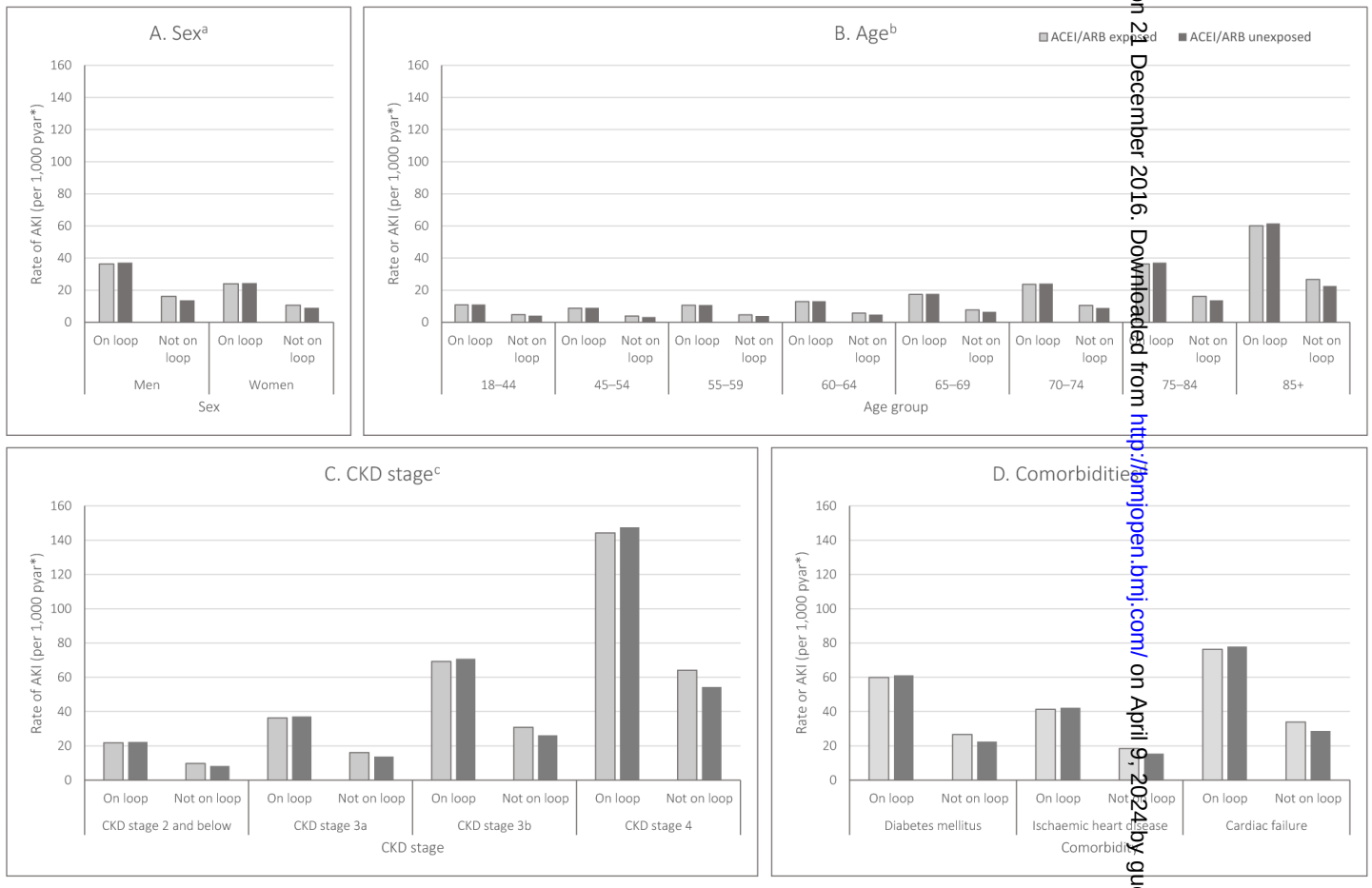
[2] High risk: men aged 85+ with CKD stage 4 and all of: ischaemic heart disease, cardiac failure and diabetes mellitus.

*Adjusted using Poisson regression for: age, sex, chronic comorbidities (CKD, hypertension, diabetes mellitus, cardiac failure, ischaemic heart disease, and arrhythmia), time exposed to other antihypertensive drugs (beta-blockers, calcium channel blockers and thiazides), time exposed to loop and potassium sparing diuretic, and calendar period. Also includes an interaction term for loop diuretic use.

Prescription for Renin-Angiotensin System Blockers and Risk of Acute Kidney Injury: A Population-Based Cohort Study

Kathryn E Mansfield, Dorothea Nitsch, Liam Smeeth, Krishnan Bhaskaran, Laurie A Tomlinson

Figure S4. Modelled rates of AKI (during the calendar period 2012–2014) per 1,000 person years at risk stratified by characteristics and comorbidities. This model includes an interaction term for loop diuretic use.



*Adjusted using Poisson regression for: age, sex, chronic comorbidities (CKD, hypertension, diabetes mellitus, cardiac failure, ischaemic heart disease, and arrhythmia), time exposed to other antihypertensive drugs (beta-blockers, calcium channel blockers and thiazides), time exposed to loop and potassium sparing diuretics, and calendar period. Also includes an interaction term for loop diuretic use.
Absolute rates (unless otherwise stated) are for men, aged 75–84, with CKD stage 3a, and no comorbidities – chosen as a large, clinically important, high risk group.
[a]rates for each sex aged 75-84 with CKD stage 3A and no comorbidities.
[b]rates for each age group for men with CKD stage 3A and no comorbidities.
[c]rates for each CKD stage for men with no comorbidities.
[d]rates for men aged 75-84 with CKD stage 3A and only the specified comorbidity.
ACEI/ARB: Angiotensin converting enzyme inhibitor/angiotensin receptor blocker.
AKI: Acute kidney injury
pyar: Person years at risk
CKD: Chronic kidney disease

The RECORD statement – checklist of items, extended from the STROBE statement, which should be reported in observational studies using routinely collected health data.

	Item No.	STROBE items	Location in manuscript where items are reported	RECORD items	Location in manuscript where items are reported
Title and abstract					
	1	(a) Indicate the study's design with a commonly used term in the title or the abstract (b) Provide in the abstract an informative and balanced summary of what was done and what was found	(a) Reference made to cohort study design in title and abstract (p2) (b) Methods summarised in abstract (p2).	RECORD 1.1: The type of data used should be specified in the title or abstract. When possible, the name of the databases used should be included. RECORD 1.2: If applicable, the geographic region and timeframe within which the study took place should be reported in the title or abstract. RECORD 1.3: If linkage between databases was conducted for the study, this should be clearly stated in the title or abstract.	(1.1) Reference made to Clinical Practice Research Datalink (CPRD) and Hospital Episode Statistics (HES) made in abstract (p2). (1.2) Abstract outlines that study in UK between April 1997 and March 2014 (p2). (1.3) Use of linkage between HES and CPRD databases stated in the abstract (p2).
Introduction					
Background rationale	2	Explain the scientific background and rationale for the investigation being reported	Scientific background and rationale for study is presented in the Introduction section (p4).		
Objectives	3	State specific objectives, including any prespecified hypotheses	Specific aims of the study presented are in Introduction section (p4).		
Methods					
Study Design	4	Present key elements of study design early in the paper	Key elements of the study design are introduced in the Introduction section of the paper (p4) and expanded in the Methods section (p5).		
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Setting, locations, study dates are presented under the 'Study design and setting' subheading in the Methods section (p5).		

	Item No.	STROBE items	Location in manuscript where items are reported	RECORD items	Location in manuscript where items are reported
Participants	6	*(a) Cohort study* - Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study* - Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study* - Give the eligibility criteria, and the sources and methods of selection of participants *(b) Cohort study* - For matched studies, give matching criteria and number of exposed and unexposed *Case-control study* - For matched studies, give matching criteria and the number of controls per case	(a) Eligibility criteria, and cohort entry and exit criteria are presented under the 'Participants, exposures and outcomes' subheading in the Methods section (p5). (b) This study is not matched.	RECORD 6.1: The methods of study population selection (such as codes or algorithms used to identify subjects) should be listed in detail. If this is not possible, an explanation should be provided. RECORD 6.2: Any validation studies of the codes or algorithms used to select the population should be referenced. If validation was conducted for this study and not published elsewhere, detailed methods and results should be provided. RECORD 6.3: If the study involved linkage of databases, consider use of a flow diagram or other graphical display to demonstrate the data linkage process, including the number of individuals with linked data at each stage.	(6.1) A detailed explanation of how the study population were identified is presented in the Methods section under the 'Participants, exposures and outcomes' subheading (p5). (6.2) Codes used to identify the outcome definition (acute kidney injury) have been validated in another study referenced in the manuscript (p8 ref 32). Other code lists/algorithms have either been developed using those applied in other published studies (also referenced, p7). (6.3) The flow diagram presented in Figure 1 illustrates the number of individuals excluded from the study due to being ineligible for HES linkage.
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable.	Outcomes and exposures are defined under the 'Participants, exposures and outcomes' subheading of the Methods section (p5). Definitions for potential confounders are presented under the 'Covariates' subheading of the Methods section (p6).	RECORD 7.1: A complete list of codes and algorithms used to classify exposures, outcomes, confounders, and effect modifiers should be provided. If these cannot be reported, an explanation should be provided.	A complete list of codes and algorithms used to classify all variables is available for download from: https://clinicalcodes.rss.mhs.man.ac.uk/ An online clinical codes repository (p7).

	Item No.	STROBE items	Location in manuscript where items are reported	RECORD items	Location in manuscript where items are reported
Data sources/ measurement	8	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Each variable used is identified in CPRD or HES data. A clear definition of all variables used is presented in the appropriate sections of the Methods section (pp5-7). Variable definitions are the same for different groups of patients.		
Bias	9	Describe any efforts to address potential sources of bias	Covariates used are presented (p6). We present details of how study design was used to address possible selection bias and confounding by indication (under 'Participants, exposures and outcomes' subheading of Methods section, p5). In addition, we undertook a number of sensitivity analyses to test any variable definitions in order to address information and/or selection bias ('Sensitivity analysis' subheading of Methods section, p7).		
Study size	10	Explain how the study size was arrived at	The flow diagram presented in Figure 1 illustrates the creation of the cohort and reasons for exclusions. When developing the protocol we found that, based on a cautious estimate of a sample size (n= 102,524), we would have greater than 90% power (alpha 0.05) to detect a relative risk of 1.2 or more for incident AKI. The final sample size was nearly 5 x our cautious estimate (n=570,433).		

	Item No.	STROBE items	Location in manuscript where items are reported	RECORD items	Location in manuscript where items are reported
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why	Groupings for quantitative variables (age, eGFR) are presented in Tables 1 (p9) and S2 (Appendix)		
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding (b) Describe any methods used to examine subgroups and interactions (c) Explain how missing data were addressed (d) *Cohort study* - If applicable, explain how loss to follow-up was addressed *Case-control study* - If applicable, explain how matching of cases and controls was addressed *Cross-sectional study* - If applicable, describe analytical methods taking account of sampling strategy (e) Describe any sensitivity analyses	(a) Statistical methods used are presented under the 'Statistical analysis' subheading of the Methods section {p7). (b) Methods used to examine subgroups are presented under the 'Additional analyses' subheading of the Methods section (p8). (c) Missing data were addressed using sensitivity analyses (documented under the 'Sensitivity analysis' subheading of the Methods section, p8). (d) Loss to follow-up is not applicable to this design as patients are followed-up until no longer eligible. (e) Sensitivity analyses are described under the appropriate subheading in the Methods section (p8).		
Data access and cleaning methods		..		RECORD 12.1: Authors should describe the extent to which the investigators had access to the database population used to create the study population. RECORD 12.2: Authors should provide information on the data cleaning methods used in the study.	(12.1) Investigators had full access to the CPRD dataset – documented in declarations section at the end of the manuscript (p15). (12.2) Data cleaning methods are described in the Methods section (p5).

	Item No.	STROBE items	Location in manuscript where items are reported	RECORD items	Location in manuscript where items are reported
Linkage		..		RECORD 12.3: State whether the study included person-level, institutional-level, or other data linkage across two or more databases. The methods of linkage and methods of linkage quality evaluation should be provided.	(12.3) The study included person-level data linkage. Data linkage of CPRD and HES data is undertaken by a trusted third party: the Health and Social Care Information Centre (pp5-8).
Results					
Participants	13	(a) Report the numbers of individuals at each stage of the study (*e.g.*, numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed) (b) Give reasons for non-participation at each stage. (c) Consider use of a flow diagram	(a) The number of individuals at each stage of the study is presented in Figure 1. (b) Reasons for exclusions at each stage are also presented in Figure 1 (c) See Figure 1.	RECORD 13.1: Describe in detail the selection of the persons included in the study (*i.e.,* study population selection) including filtering based on data quality, data availability and linkage. The selection of included persons can be described in the text and/or by means of the study flow diagram.	See Figure 1.
Descriptive data	14	(a) Give characteristics of study participants (*e.g.*, demographic, clinical, social) and information on exposures and potential confounders (b) Indicate the number of participants with missing data for each variable of interest (c) *Cohort study* - summarise follow-up time (*e.g.*, average and total amount)	(a) See Table 1 (p9) (b) See Table 1 (p9) (c) See Table 1 (p9)		
Outcome data	15	*Cohort study* - Report numbers of outcome events or summary measures over time *Case-control study* - Report numbers in each exposure category, or summary measures of exposure *Cross-sectional study* - Report numbers of outcome events or summary measures	See Table 1 (p9)		

	Item No.	STROBE items	Location in manuscript where items are reported	RECORD items	Location in manuscript where items are reported
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (e.g., 95% confidence interval). Make clear which confounders were adjusted for and why they were included (b) Report category boundaries when continuous variables were categorized (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	(a) See Table S2 in the supplementary appendix and also presented in the text of the Results section (p10). (b) Age, CKD, and calendar period boundaries clearly presented in Tables 1 (p9) and S2 (Appendix). (c) Absolute risk presented in Figures 2 and S2 (Appendix), and Table S4 (Appendix).		
Other analyses	17	Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses	Results of sensitivity and secondary analyses presented in the Results section (p10) and Appendix Table S3.		
Discussion					
Key results	18	Summarise key results with reference to study objectives	Presented at beginning of Discussion section (p11).		
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Limitations discussed in the Discussion section (pp11-12).	RECORD 19.1: Discuss the implications of using data that were not created or collected to answer the specific research question(s). Include discussion of misclassification bias, unmeasured confounding, missing data, and changing eligibility over time, as they pertain to the study being reported.	Limitations related specifically to using routinely collected health data for research are discussed in the Discussion section (pp11-12).
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Overall interpretation of the results are presented in the Discussion section (pp11-14).		
Generalisability	21	Discuss the generalisability (external validity) of the study results	Generalisability of study results discussed in Discussion section (p12).		
Other Information					
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Source of funding acknowledged at the end of the manuscript under the 'Funding' subheading (p15).		

	Item No.	STROBE items	Location in manuscript where items are reported	RECORD items	Location in manuscript where items are reported
Accessibility of protocol, raw data, and programming code		..		RECORD 22.1: Authors should provide information on how to access any supplemental information such as the study protocol, raw data, or programming code.	Study protocol number provided. Due to CPRD guidelines on data sharing of patient level data we are unable to share raw data (p15).

*Reference: Benchimol EI, Smeeth L, Guttmann A, Harron K, Moher D, Petersen I, Sørensen HT, von Elm E, Langan SM, the RECORD Working Committee. The REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) Statement. *PLoS Medicine* 2015; in press.