Risk factors associated with biochemically detected and hospitalised acute kidney injury in patients prescribed renin angiotensin system inhibitors

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What is already known about this subject:

- Therapeutic inhibition of the renin angiotensin system (RAS) has led to improvements in survival in patients with heart failure.
- RAS inhibition has been associated with increased risk of acute kidney injury (AKI).
- Patients at highest cardiovascular risk may be at higher risk of AKI due to additional comorbid factors.

What this study adds:

- We found risk factors for AKI in >60,000 patients prescribed RAS inhibitors were age, heart failure, diabetes, chronic kidney disease and comorbidity
- Patients with greatest benefit from RAS inhibition are also at risk of AKI.
- This association does not suggest causation; awareness of AKI is required in these patients.

Abstract

Aims Therapy with angiotensin converting enzyme inhibitors (ACEi) and angiotensin receptor blockers (ARB) is a mainstay of treatment for heart failure (HF), diabetes mellitus (DM) and chronic kidney disease (CKD). These agents have been associated with development of acute kidney injury (AKI) during intercurrent illness. Risk factors for AKI in patients prescribed ACEi/ARB therapy are not well described.

Methods We the incidence of AKI in patients commencing ACEi/ARB during 2009-2015 using anonymised patient records. Hospital-coded AKI was defined from hospital episode statistics; biochemical AKI was ascertained from laboratory data. Risk factors for biochemically detected and hospitalised AKI were investigated.

Results Of 61,318 patients prescribed ACEi/ARB, with 132,885 person years (py) follow up, there were 1,070 hospitalisations with AKI as a diagnoses recorded and a total of 4,645 AKI events, including AKI episodes indicated by biochemical KDIGO-based creatinine change criteria. Incidence of any AKI event was 35.0 per 1000- py, hospital-coded AKI was 7.8 per 1000-py and biochemical AKI was 33.7 per 1000-py. Independent risk factors in a multivariable model for hospital-coded AKI events were age, male gender, HF, diabetes, cerebrovascular disease, lower estimated glomerular filtration rate, socioeconomic deprivation, diuretic or non-steroidal anti-inflammatory use (all $p<0.001$).

Conclusion In patients prescribed ACEi/ARB, the highest risk of AKI is associated with conditions which are considered strong evidence-based indications for their prescription. Socio-economic status is an under-reported risk factor for AKI with these agents. Strategies targeted at prevention of AKI may be of benefit, such as enhanced awareness based on higher risk comorbidities.

Introduction

Therapeutic inhibition of the renin angiotensin system with angiotensin converting enzyme inhibitor (ACEi) and angiotensin receptor blocker (ARB) drugs is a mainstay of therapy for conditions associated with increased cardiovascular risk including hypertension, heart failure (HF), diabetes mellitus (DM) and proteinuric chronic kidney disease (CKD). This approach has been established following landmark clinical trials demonstrating efficacy of these agents in improving outcomes[1-8].

There is evidence that patients taking renin angiotensin system inhibitors (RASi) with ACEi/ARB in combination with non-steroidal anti-inflammatory drugs (NSAIDs) and diuretics are at increased risk of AKI[9, 10]. In addition, it is commonly reported that RASi are associated with acute kidney injury (AKI), particularly in the setting of impaired renal perfusion[9, 10]. A commonly described scenario for this is when a patient becomes dehydrated e.g. due to a diarrhoeal illness[11] and background RASi treatment leads to failure of regulation of angiotensin II-dependent glomerular perfusion and renal hypoperfusion leading to AKI. However, the degree to which RASi are causal for AKI in this setting are debated[12] . AKI in association with RASi therapy is common and the incidence is rising, either due to more widespread prescribing of these agents in patients at risk of AKI, or alternatively due to better awareness of AKI, including coding AKI as a diagnosis during hospitalisation[13, 14].

AKI is common and when severe may be life threatening, often requiring hospitalisation and potentially acute dialysis. The overall mortality for acute kidney injury is high, with 1-year survival less than 50% even in mild AKI[15]. In patients who recover, it is common (but not invariable) for renal function not to return to the baseline level, especially in the presence of pre-existing CKD[16, 17]. Nevertheless, longer term studies show very poor survival up to one year after discharge[16]. Strategies that can identify people with high risk of AKI or poor outcomes are needed.

AKI defined by the KDIGO criteria for diagnosis of AKI, based on small changes in creatinine, is associated with poor short and long term outcomes, irrespective of hospitalisation[18]. Electronic alerts (e-alerts) for biochemical AKI have been proposed as a mechanism for improving detection and management of AKI, although e-alerts need to be combined with education and clinical support to alter outcomes[19, 20].

By linking demographic, clinical, prescribing and biochemical sources of patient data from both primary and secondary care, it is possible to ascertain the incidence of, and risk factors for AKI, including biochemical-only AKI detected by blood tests, and episodes of AKI requiring hospitalisation. The aim of this study, using novel linkage of electronic patient data in an area of social deprivation and high rates of cardiovascular disease[21], was to describe the incidence and risk factors for AKI among patients prescribed RASi therapy.

Methods

Cohort

Greater Glasgow and Clyde National Health Service (NHS) provides healthcare to a population of approximately 1.2million. The NHS Greater Glasgow and Clyde 'Safe Haven', is a secure environment whereby health data from different sources can be linked together and made available in de-identified form for analysis. It has been ethically approved by the ethics committee of NHS Greater Glasgow and Clyde. This specific project was approved Local Privacy Advisory Committee of the Safe Haven.

All health episodes in Scotland are linked by the Community Health Index (CHI), a unique identifier for all patients. In this study, we used data related to NHS care, including patient records, prescribing, hospitalisations and laboratory testing. We defined patients included in the cohort as those incident users of RASi encashing at least one prescription for ACEi or ARB from the prescription information system (PIS), which captures data of all 'cashed' prescriptions in NHS Greater Glasgow and Clyde from Jan 2009-Dec 2015[22]. We excluded patients with prevalent use of RASi prior to 1/9/2009 and patients with a prior diagnosis of cancer (excluding non-melanoma skin cancer) at the time of commencement of RASi therapy. Patients entered the cohort at the date of their first prescription, and exited the cohort at death, at the last prescription date plus 30 days, to allow for a washout period, or at the end of the data extract from PIS. The makeup of the cohort is shown in Figure 1.

Comorbidities at baseline were defined by the presence of a diagnosis of hypertension, heart failure (HF), diabetes mellitus (DM), cardiovascular disease (CVD), or cerebrovascular disease (CeVD), from general practitioner (GP) electronic records (termed 'local enhanced service' (LES)) data, as well as from ICD-10 codes from prior hospital admission records at cohort entry. A Charlson co-morbidity index was calculated for all patients[23]. PIS records for all patients were used to identify additional treatment with diuretics (loop, thiazide and potassium sparing) and non-

steroidal anti-inflammatory drugs (NSAID). Patients were also classified as having chronic kidney disease (CKD) based on this being recorded by their GP within LES coding. We defined baseline kidney function as the mean estimated glomerular filtration rate (eGFR) calculated using the CKD-EPI formula in the year prior to cohort entry[24]. Serum creatinine measures were isotope dilution mass spectrometry aligned.

The Scottish Government provide online calculators allowing use of patient postcode to generate divisions of socioeconomic deprivation, the Scottish Index of Multiple Deprivation (SIMD) (http://www.gov.scot/Topics/Statistics/SIMD). Using patient postcode, deprivation quintiles of deprivation status were calculated and categorised into most deprived (quintile 1) to least deprived (quintile 5).

Definition of acute kidney injury (AKI)

Hospital-coded AKI was defined as a hospital admission with ICD-10 code N17 in any diagnostic position on hospital discharge coding in the Scottish Morbidity Records 01 (SMR01). SMR01 collects data on all non-obstetric, non-psychiatric hospital discharges since 1968. Since 1989 SMR01 has been used to plan financial management of hospitals in order to ensure high completion rate. Internal audit of this data supports overall 89% accuracy for main condition diagnosis and similar or greater accuracy has been demonstrated in AKI in the United Kingdom[25, 26]. As a secondary event of interest, we captured the incidence, stage and severity of AKI episodes not associated with a hospitalisation episode, based on all creatinine measurements for individual patients from the laboratory database during the period of exposure. These were categorised as ‘community-based AKI’, where the creatinine measure used to define AKI was taken from a blood sample which during a period which did not coincide with any hospital admission and ‘all AKI’ which encompassed hospital-coded AKI, community-based AKI and ‘other AKI events’ i.e. AKI episodes

occurring during a hospital admission but were not coded by hospital coding data on hospital discharge. Biochemical AKI was defined using an algorithm aligned to the NHS e-alert AKI warning system currently implemented in NHS England for routine health care and as previously reported[27, 28]. AKI was diagnosed from the following criteria:

1. Serum creatinine ≥1.5 times higher than the median of all creatinine values 8–365 days ago
2. Serum creatinine ≥1.5 times higher than the lowest creatinine within 7 days
3. Serum creatinine >26 μmol/L higher than the lowest creatinine within 48 h

If one or more of these criteria were met, AKI was attributed to that date / measurement. Our sources only resolved measurements to the level of date. When more than one value was recorded on a given day, the highest value was considered. Severity of AKI was based on the KDIGO definition applied to this algorithm[29].For every AKI identified above a staging was assigned per the following rules:

- Stage 1: Serum creatinine ≥1.5 and < 2.0 times AKI baseline or >=26.0 μmol/l increase above AKI baseline
- Stage 2: Serum creatinine >=2.0 and < 3.0 times AKI baseline
- Stage 3: Serum creatinine 3.0 times AKI baseline or >=354 μmol/l increase above AKI baseline

To avoid confounding by early changes in serum creatinine following instigation of ACEi/ARB therapy, we discounted serum creatinine measured <14 days following commencement of therapy. E-alerts were not used in the laboratory systems during the period of this study. We identified deaths and date of death by linkage to the National Records Scotland death certificates (NRS).

192 **Statistical analyses**

193 The primary outcome was defined as the incidence of first AKI – either biochemical
194 AKI detected in the community, or hospitalisation for AKI. Patients who died during
195 follow-up without experiencing an AKI event were censored at death. Kaplan Meier
196 survival curves were generated for time to first AKI in relation to: age, sex, SIMD,
197 eGFR, diuretics use at baseline, NSAID use at baseline, use of diuretics or NSAID at
198 baseline, prescription groups at baseline and history of co-morbidities, namely:
199 hypertension, heart failure, diabetes, CKD, cerebrovascular disease and Charlson
200 Index of co-morbidities. Univariable Cox proportional hazard models were fitted to
201 obtain estimates of the association between each covariate and incident AKI, reported
202 as hazard ratios with 95% confidence intervals. The proportional hazards assumption
203 was assessed using Schoenfeld residuals, and the assumption was not met for several
204 variables in each model. However, visual inspection of Kaplan-Meier plots suggested
205 that these deviations were quite subtle, and the hazard ratios may be interpreted as
206 giving the average association over the follow-up period.
207 Multivariable Cox regression models were fitted to further analyse the associations
208 between covariates and incident AKI. A manual backwards selection procedure was
209 used, with all covariates (except for the Charlson Index excluded on the basis it is
210 comprised of multiple co-morbidities being tested in the Cox model) considered in the
211 starting model. Covariates were sequentially excluded based on the p-value, to obtain
212 a final model with all predictors making a significant contribution (at a 5% significance
213 level) to the model. All other predictors were categorical. No adjustments were made
214 for multiple comparisons. All analyses were carried out using the statistical software
215 package R[30].
216 The data that support the findings of this study are not publicly available due to privacy
217 or ethical restrictions. Further information on the handling of electronic health record

data used in this study are available here https://www.nhsggc.org.uk/about-us/professional-support-sites/nhsggc-safe-haven/about-the-safe-haven/.

Results

Demographics of cohort and Incidence of AKI

Figure 1 summarises how the cohort of incident RASi users was generated. During the study period 61,318 patients were prescribed ACEi/ARB. The mean age of the cohort was 59.8 years (SD 13.9), and 51.9% were male. 3,302 (5.4%) had HF, 8,807 (14.4%) had diabetes, and the mean eGFR was 86.1ml/min/1.73m^2 (SD 18.2). There were 7993 deaths during follow-up.

During a median follow up of 1.92 yrs there were 1,070 hospital-coded AKI events, and 4,483 biochemical AKI episodes. In total, 4,645 patients had at least one AKI event during 132,885 person years (py) of follow up. Hospital-coded AKI and biochemical AKI overlapped, but were not mutually exclusive, as 162 patients had a hospital-coded AKI, without confirmatory biochemistry, where the patient had no available baseline kidney function tests. The incidence of all AKI events was 35.0 per 1000-py, hospital-coded AKI was 7.8 per 1000-py and biochemical AKI was 33.7 per 1000-py.

Risk factors associated with AKI

The patients at highest risk of AKI were those with most comorbidities. Data are presented on all AKI events in Table 1 (biochemical or hospital-coded AKI) as the overall pattern of risk factors associated with AKI were similar for both biochemical and hospital-coded AKI. Data on hospital-coded and biochemical AKI are presented separately in Tables 2 and 3. On univariable analyses of the association between baseline characteristics and incident AKI, the risk of AKI events increased with

increasing age, socioeconomic deprivation (Figure 2), lower eGFR, diuretic use, heart failure, diabetes, a diagnosis of CKD, cerebrovascular disease, or increasing Charlson co-morbidity index. On univariable analysis there was no association with NSAID use in isolation (Table 2 and 3), and combined NSAID and diuretic use did not confer higher risk than diuretic use alone.

Risk of AKI was highest in three distinct (though overlapping) groups. Patients with heart failure had an incidence of hospital-coded AKI of 29.4 per 1000-py and biochemical AKI of 122.4 per 1000-py. Similar figures were observed for patients with CKD with hospital-coded AKI incidence of 40.9 and biochemical AKI incidence of 117.6 per 1000-py. Using Charlson index of 3 or more as a measure of greatest comorbidity identified a group of extremely high risk of both hospital-codeAKI and biochemical AKI (40.1 and 166.8 per 1000-py respectively, Tables 2 and 3).

Using a multivariable Cox proportional hazards model, independent predictors of AKI were male gender, increasing age, increasing socioeconomic deprivation, diuretic use, NSAID use, history of heart failure, diabetes mellitus, eGFR, and history of cerebrovascular disease, as presented in Table 4. It is notable that male gender was associated with higher risk of AKI based on multivariable analysis, despite female gender being higher risk on univariable analysis.

Discussion

This is one of the first reports using routine clinical data to quantify risk factors for AKI in ACEi/ARB users. Patients with increasing comorbidity were at highest risk of AKI, with many conditions associated with increased risk of AKI, including HF, DM, and CKD – conditions where there is high grade evidence for using these drugs in accordance with national guidelines[31-33]. Patients concomitantly prescribed diuretics and NSAIDSs are at greater risk of AKI, as observed by others[9, 10]. Amongst incident patients prescribed ACEi/ARB medication, we found a similar rate of AKI episodes associated with a hospital admission to a previous cohort of ACEi/ARB users[14]. The incidence of biochemical AKI based on internationally recognised creatinine change criteria was approximately two-fold higher than has previously been reported for the general population in the Grampian region[34].

Risk factors for both biochemical and hospital-coded AKI

The recognition of association of AKI with prescription of ACEi/ARB therapy in the setting of relative hypovolaemia is well established[11, 35]. However, using observational prescribing data combined with biochemical flagging and hospitalisation coding records for AKI, we identify patients at highest risk of AKI whilst prescribed these agents. Caution is required in interpreting any association between ACEi/ARB therapy and AKI as causal. Recent studies using national primary care data did not demonstrate higher risk of hospitalisation with AKI overall, or following common infections including gastroenteritis, among users of ACEi/ARB compared to other antihypertensives[36]. Our data demonstrate that patients with the most compelling evidence-based indications for prescription of ACEi/ARB therapy are those at highest risk of subsequent AKI. These indications include HF, CKD and/or DM with proteinuria where there are data from high quality randomised controlled trials (RCTs) suggesting benefit with these agents[1, 4-6, 8, 37, 38]. The evidence for benefits of ACEi are most

compelling in patients with HF and reduced left ventricular ejection fraction[8, 38]. These agents are strongly recommended in the recent European Society of Cardiology (ESC) and American Heart Association (AHA) guidelines for management of HF[31, 32]. However, despite our observation that AKI is common among those with HF on ACEi/ARB, AKI is described as 'rare' in HF patients in the ESC guidelines[31] and monitoring of renal function is seen as 'good practice' with no mention of AKI in the AHA guidelines[32]. Biochemically detected AKI events may represent natural fluctuations in serum creatinine occurring in patients with HF talking RASi often in combination with diuretic therapy. These changes may not represent 'AKI' with any intrinsic renal damage and may simply reflect changes in serum creatinine in the setting of haemodynamic perturbation as glomerular perfusion pressure responds to changes in hydration status. Nevertheless, greater rises in serum creatinine in patients requiring ACEi/ARB therapy highlights a group of patients at greater mortality risk during follow up[39]. Therefore, we would simply state that increased awareness of AKI in patients with HF is required and sensitivity is needed in interpreting AKI alerts in these patients.

There is evidence that these agents delay progression of proteinuric CKD and/or improve outcomes in patients with diabetes and albuminuria [5, 40]. These results suggest that the groups potentially deriving most benefit from these agents are at highest risk of being hospitalised with AKI, albeit in observational data with no control group. The clinical significance of these biochemically detected AKI events is unclear, and further studies are required to determine if these events confer any longer-term risk of decline in renal function. Whilst hospitalised AKI increases risk of subsequent CKD[41, 42], it is less clear whether subtler acute, transient declines in renal function lead to longer term renal risk.

Multi-morbidity and AKI risk

In an ageing population with increasing comorbidity, the association of Charlson index and AKI episodes is concerning. These patients in this cohort were prescribed ACEi/ARBs based on evidence from randomised controlled trials, which were performed over 15 years ago. It should be recognised that in an aging society where multi-morbidity is more common, these RCTs may no longer be representative of many contemporary patients prescribed these agents. This was highlighted in a report from a similar population as our study, whereby 23.2% were classified as 'multi-morbid'[43]. On the other hand, undertreatment of multimorbid patients with HF is likely to be associated with poor survival. Multi-morbidity is common in patients from a socially deprived background[43]. We observed that social deprivation status was associated with increased AKI risk. Therefore, AKI risk in patients prescribed ACEi/ARB therapy is associated with a cluster of interrelated risk factors including number of comorbid conditions, concomitant therapy and socioeconomic deprivation.

The optimal strategy to address the risk of AKI in the community in patients taking ACEi/ARB is unknown. General practitioners should be aware that that the most comorbid patients are most at risk and need close monitoring, particularly during acute illness. Initiatives to tackle this problem are currently being investigated such as 'sick day rules' where patients taking these drugs are advised to stop them during acute illness. This strategy requires resources for patient education and to date is not supported by clinical evidence of efficacy[44, 45].

Strengths and limitations of this study

The strength of these analyses include a large sample size, with excellent coverage of the population studied, avoiding sampling biases. The results demonstrating similar risk factors for hospital coded and biochemical AKI suggest that our analysis methods for assessing influence of comorbid variables were robust and

give a consistent message. We do not have a control group so the incidence of AKI in patients with these comorbid conditions not prescribed ACEi/ARB is unknown. Defining the most appropriate patients to study as a control group is challenging. There would be biases in selecting a group of patients commenced on an alternative class of antihypertensive medication such as calcium channel blockers. This has been explored in other studies with only small increases of AKI incidence with ACEi/ARB in comparison to patients exposed to antihypertensive regimes not including ACEi/ARB[14]. In the case of HF, it would be unusual not to be treated with ACEi/ARB therapy.

We acknowledge further limitations with these analyses. AKI without clinical symptoms may be diagnosed more frequently in patients having frequent blood samples (ascertainment bias). We are unaware of the indication for taking the blood sample leading to a record in the laboratory database. The incidence of biochemical AKI in untested patients is unknowable. Whilst we use the term 'hospital-coded AKI', it is possible and indeed likely, that AKI was one of a number of diagnoses coded during a hospitalisation episode, rather than the sole diagnosis. There may be coding bias in either direction with hospital-coded AKI, where AKI is added as a diagnosis in the absence of biochemical evidence, or where AKI was present but not recorded as a diagnosis on hospital discharge. The incidence of biochemically diagnosed AKI was particularly high in patients with CKD. Whilst these patients are likely to be at high risk of AKI, the use of an algorithm based on serum creatinine, may lead to a higher incidence of AKI related to how the algorithm diagnoses patients with an AKI event. It is possible that some of the co-morbid conditions have not been coded in the health care records, leading to an under-reporting of the Charlson co-morbidity index. This This can be seen with chronic kidney disease, where only 1989 subjects have been coded as having CKD by their general practitioner despite 4553 patients having a recorded GFR <59ml/min/m^2 (which is likely to be consistent with CKD).

The prescribing records indicate that a patient collected a prescription, rather than took the prescribed medication. Although we describe CKD as an 'indication' for therapy, we do not have proteinuria data and therefore it is unclear how strong this indication was for ACEi/ARB therapy and or whether proteinuria alters risk of AKI.

Conclusion

We describe associations of various clinical variables with increased risk of AKI in patients prescribed ACEi/ARB therapy. However, we do not describe these relationships as causal. The overwhelming evidence demonstrates that these medicines have heralded remarkable improvements in survival in patients with HF, in particular[8, 38]

We demonstrate that older patients with heart failure, diabetes, CKD, lower socioeconomic status and prior stroke are at highest risk of AKI, both hospital-coded and biochemically detected in the community. Biochemical AKI may serve as a risk marker for future adverse events. Further work is required to identify strategies to minimise risk of hospital-coded and/or biochemical AKI in patients receiving therapy with these agents.

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Conflict of Interest

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The results presented in this article have not been published previously in whole or part, except in abstract format.

Authors' Contributions

P.B.M, L.A.T, C.B. and C.M conceived the study. N.R., R.P. and A.M analysed the data. All authors interpreted the data, drafted and approved the final manuscript.

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References

1. Parving HH, Lehnert H, Brochner-Mortensen J, Gomis R, Andersen S, Arner P, Irbesartan in Patients with Type D, Microalbuminuria Study G. The effect of irbesartan on the development of diabetic nephropathy in patients with type 2 diabetes. N Engl J Med 2001; 345: 870-8.
2. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JG, Coats AJ, Falk V, Gonzalez-Juanatey JR, Harjola VP, Jankowska EA, Jessup M, Linde C, Nihoyannopoulos P, Parissis JT, Pieske B, Riley JP, Rosano GM, Ruilope LM, Ruschitzka F, Rutten FH, van der Meer P, Authors/Task Force M. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC)Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur Heart J 2016; 37: 2129-200.
3. KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. Kidney Int Suppl 2013; 3: 1-150.
4. Heart Outcomes Prevention Evaluation Study I, Yusuf S, Sleight P, Pogue J, Bosch J, Davies R, Dagenais G. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. N Engl J Med 2000; 342: 145-53.
5. Brenner BM, Cooper ME, de Zeeuw D, Keane WF, Mitch WE, Parving HH, Remuzzi G, Snapinn SM, Zhang Z, Shahinfar S, Investigators RS. Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. N Engl J Med 2001; 345: 861-9.
6. Pfeffer MA, Swedberg K, Granger CB, Held P, McMurray JJ, Michelson EL, Olofsson B, Ostergren J, Yusuf S, Pocock S, Investigators C, Committees. Effects of candesartan on

mortality and morbidity in patients with chronic heart failure: the CHARM-Overall programme. Lancet 2003; 362: 759-66.
7. Board JBS. Joint British Societies' consensus recommendations for the prevention of cardiovascular disease (JBS3). Heart 2014; 100 Suppl 2: ii1-ii67.
8. Investigators S, Yusuf S, Pitt B, Davis CE, Hood WB, Cohn JN. Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. N Engl J Med 1991; 325: 293-302.
9. Lapi F, Azoulay L, Yin H, Nessim SJ, Suissa S. 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. BMJ 2013; 346: e8525.
10. Dreischulte T, Morales DR, Bell S, Guthrie B. 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; 88: 396-403.
11. Stirling C, Houston J, Robertson S, Boyle J, Allan A, Norrie J, Isles C. Diarrhoea, vomiting and ACE inhibitors:--an important cause of acute renal failure. J Hum Hypertens 2003; 17: 419-23.
12. Perazella MA, Coca SG. Three feasible strategies to minimize kidney injury in 'incipient AKI'. Nat Rev Nephrol 2013; 9: 484-90.
13. Tomlinson LA, Abel GA, Chaudhry AN, Tomson CR, Wilkinson IB, Roland MO, Payne RA. ACE inhibitor and angiotensin receptor-II antagonist prescribing and hospital admissions with acute kidney injury: a longitudinal ecological study. PLoS One 2013; 8: e78465.
14. Mansfield KE, Nitsch D, Smeeth L, Bhaskaran K, Tomlinson LA. Prescription of renin-angiotensin system blockers and risk of acute kidney injury: a population-based cohort study. BMJ Open 2016; 6: e012690.
15. Linder A, Fjell C, Levin A, Walley KR, Russell JA, Boyd JH. Small acute increases in serum creatinine are associated with decreased long-term survival in the critically ill. Am J Respir Crit Care Med 2014; 189: 1075-81.
16. Sawhney S, Mitchell M, Marks A, Fluck N, Black C. Long-term prognosis after acute kidney injury (AKI): what is the role of baseline kidney function and recovery? A systematic review. BMJ Open 2015; 5: e006497.
17. Stoumpos S, Mark PB, McQuarrie EP, Traynor JP, Geddes CC. Continued monitoring of acute kidney injury survivors might not be necessary in those regaining an estimated glomerular filtration rate >60 mL/min at 1 year. Nephrol Dial Transplant 2017; 32: 81-88.
18. Palevsky PM, Liu KD, Brophy PD, Chawla LS, Parikh CR, Thakar CV, Tolwani AJ, Waikar SS, Weisbord SD. KDOQI US commentary on the 2012 KDIGO clinical practice guideline for acute kidney injury. Am J Kidney Dis 2013; 61: 649-72.
19. Selby NM, Crowley L, Fluck RJ, McIntyre CW, Monaghan J, Lawson N, Kolhe NV. Use of electronic results reporting to diagnose and monitor AKI in hospitalized patients. Clin J Am Soc Nephrol 2012; 7: 533-40.
20. Selby NM, Hill R, Fluck RJ, Programme NHSETKA. Standardizing the Early Identification of Acute Kidney Injury: The NHS England National Patient Safety Alert. Nephron 2015; 131: 113-7.
21. Velupillai YN, Packard CJ, Batty GD, Bezlyak V, Burns H, Cavanagh J, Deans K, Ford I, McGinty A, Millar K, Sattar N, Shiels P, Tannahill C. Psychological, social and biological determinants of ill health (pSoBid): study protocol of a population-based study. BMC Public Health 2008; 8: 126.
22. Alvarez-Madrazo S, McTaggart S, Nangle C, Nicholson E, Bennie M. Data Resource Profile: The Scottish National Prescribing Information System (PIS). Int J Epidemiol 2016; 45: 714-15f.
23. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis 1987; 40: 373-83.

493 24. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF, 3rd, Feldman HI, Kusek
494 JW, Eggers P, Van Lente F, Greene T, Coresh J. A new equation to estimate glomerular
495 filtration rate. Ann Intern Med 2009; 150: 604-12.
496 25. ISD. Information Divisions Scotland (ISD). SMR Datasets | SMR01 - General / Acute
497 Inpatient and Day Case | ISD Scotland | Data Dictionary. 2017.
498 26. Tomlinson LA, Riding AM, Payne RA, Abel GA, Tomson CR, Wilkinson IB, Roland
499 MO, Chaudhry AN. The accuracy of diagnostic coding for acute kidney injury in England - a
500 single centre study. BMC Nephrol 2013; 14: 58.
501 27. Sawhney S, Fluck N, Marks A, Prescott G, Simpson W, Tomlinson L, Black C. Acute
502 kidney injury-how does automated detection perform? Nephrol Dial Transplant 2015; 30:
503 1853-61.
504 28. NHS-England. Patient safety alert on standardising the early identification of Acute
505 Kidney Injury. 2014.
506 29. KDIGO. KDIGO clinical practice guideline for acute kidney injury. Kidney Int Suppl
507 2012; 2: 1-138.
508 30. R: A language and environment for statistical computing. R Foundation for Statistical
509 Computing, Vienna, Austria. In, 2017.
510 31. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JG, Coats AJ, Falk V,
511 Gonzalez-Juanatey JR, Harjola VP, Jankowska EA, Jessup M, Linde C, Nihoyannopoulos P,
512 Parissis JT, Pieske B, Riley JP, Rosano GM, Ruilope LM, Ruschitzka F, Rutten FH, van der
513 Meer P, Authors/Task Force M, Document R. 2016 ESC Guidelines for the diagnosis and
514 treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of
515 acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with
516 the special contribution of the Heart Failure Association (HFA) of the ESC. Eur J Heart Fail
517 2016; 18: 891-975.
518 32. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE, Jr., Colvin MM, Drazner MH,
519 Filippatos GS, Fonarow GC, Givertz MM, Hollenberg SM, Lindenfeld J, Masoudi FA,
520 McBride PE, Peterson PN, Stevenson LW, Westlake C. 2017 ACC/AHA/HFSA Focused
521 Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure: A Report of
522 the American College of Cardiology/American Heart Association Task Force on Clinical
523 Practice Guidelines and the Heart Failure Society of America. Circulation 2017; 136: e137-
524 e61.
525 33. Stevens PE, Levin A, Kidney Disease: Improving Global Outcomes Chronic Kidney
526 Disease Guideline Development Work Group M. Evaluation and management of chronic
527 kidney disease: synopsis of the kidney disease: improving global outcomes 2012 clinical
528 practice guideline. Ann Intern Med 2013; 158: 825-30.
529 34. Sawhney S, Robinson HA, van der Veer SN, Hounkpatin HO, Scale TM, Chess JA,
530 Peek N, Marks A, Davies GI, Fraccaro P, Johnson MJ, Lyons RA, Nitsch D, Roderick PJ,
531 Halbesma N, Miller-Hodges E, Black C, Fraser S. Acute kidney injury in the UK: a replication
532 cohort study of the variation across three regional populations. BMJ Open 2018; 8: e019435.
533 35. Thadhani R, Pascual M, Bonventre JV. Acute renal failure. N Engl J Med 1996; 334:
534 1448-60.
535 36. Mansfield KE, Douglas IJ, Nitsch D, Thomas SL, Smeeth L, Tomlinson LA. Acute
536 kidney injury and infections in patients taking antihypertensive drugs: a self-controlled case
537 series analysis. Clin Epidemiol 2018; 10: 187-202.
538 37. Ruggenenti P, Perna A, Gherardi G, Garini G, Zoccali C, Salvadori M, Scolari F,
539 Schena FP, Remuzzi G. Renoprotective properties of ACE-inhibition in non-diabetic
540 nephropathies with non-nephrotic proteinuria. Lancet 1999; 354: 359-64.
541 38. Pfeffer MA, Braunwald E, Moye LA, Basta L, Brown EJ, Jr., Cuddy TE, Davis BR,
542 Geltman EM, Goldman S, Flaker GC, et al. Effect of captopril on mortality and morbidity in
543 patients with left ventricular dysfunction after myocardial infarction. Results of the survival
544 and ventricular enlargement trial. The SAVE Investigators. N Engl J Med 1992; 327: 669-77.

39. Schmidt M, Mansfield KE, Bhaskaran K, Nitsch D, Sorensen HT, Smeeth L, Tomlinson LA. Serum creatinine elevation after renin-angiotensin system blockade and long term cardiorenal risks: cohort study. BMJ 2017; 356: j791.
40. Lewis EJ, Hunsicker LG, Bain RP, Rohde RD. The effect of angiotensin-converting-enzyme inhibition on diabetic nephropathy. The Collaborative Study Group. N Engl J Med 1993; 329: 1456-62.
41. Sawhney S, Marks A, Fluck N, Levin A, McLernon D, Prescott G, Black C. Post-discharge kidney function is associated with subsequent ten-year renal progression risk among survivors of acute kidney injury. Kidney Int 2017; 92: 440-52.
42. Heung M, Chawla LS. Predicting progression to chronic kidney disease after recovery from acute kidney injury. Curr Opin Nephrol Hypertens 2012; 21: 628-34.
43. Barnett K, Mercer SW, Norbury M, Watt G, Wyke S, Guthrie B. Epidemiology of multimorbidity and implications for health care, research, and medical education: a cross-sectional study. Lancet 2012; 380: 37-43.
44. Morris RL, Ashcroft D, Phipps D, Bower P, O'Donoghue D, Roderick P, Harding S, Lewington A, Blakeman T. Preventing Acute Kidney Injury: a qualitative study exploring 'sick day rules' implementation in primary care. BMC Fam Pract 2016; 17: 91.
45. Whiting P, Morden A, Tomlinson LA, Caskey F, Blakeman T, Tomson C, Stone T, Richards A, Savovic J, Horwood J. What are the risks and benefits of temporarily discontinuing medications to prevent acute kidney injury? A systematic review and meta-analysis. BMJ Open 2017; 7: e012674.

		N Eligible	N events	Person years follow-up	Event rate (per 1000-py)	HR (95% CI);p-value
All		61318	4645	132885.0	35.0	-
	Female	29468	2302	62080.5	37.1	-
	Male	31850	2343	70804.5	33.1	0.90(0.85,0.95);p<0.001
Age	≤50	15603	517	35424.9	14.6	-
	51-60	16554	752	37818.5	19.9	1.36(1.22,1.52);p<0.001
	61-70	13984	1027	31116.5	33.0	2.25(2.03,2.50);p<0.001
	≥ 71	15177	2349	28525.1	82.3	5.50(5.00,6.05);p<0.001
SIMD Quintile	1(Most deprived)*	21087	1895	45699.5	41.5	1.61(1.46,1.76);p<0.001
	2	10203	872	22126.9	39.4	1.53(1.38,1.70);p<0.001
	3	7848	618	17327.9	35.7	1.39(1.24,1.55);p<0.001
	4	6829	458	15261.7	30.0	1.17(1.03,1.32);p=0.014
	5(Least deprived)	10065	581	22614.7	25.7	-
	Missing	5286	221	9854.3	22.4	0.84(0.72,0.98);p=0.026
baseline eGFR (ml/min)*	≤ 29	281	91	361.4	251.8	7.61(6.18,9.37);p<0.001
	30-59	4271	973	7673.9	126.8	3.97(3.70,4.27);p<0.001
	> 59	45408	3147	101000.3	31.2	-
	Missing	11358	434	23849.3	18.2	0.58(0.52,0.64);p<0.001
Diuretics	No	45862	2683	100391.6	26.7	-
	Yes	15456	1962	32493.3	60.4	2.25(2.12,2.38);p<0.001
NSAID	No	37672	3067	87595.3	35.0	-
	Yes	23646	1578	45289.7	34.8	0.96(0.90,1.02);p=0.188
Prescription groups	None	28534	1772	67136.8	26.4	-
	NSAID only	17328	911	33254.8	27.4	1.00(0.92,1.08);p=0.991
	Diuretics only	9138	1295	20458.5	63.3	2.39(2.22,2.56);p<0.001
	Diuretic + NSAID	6318	667	12034.8	55.4	2.02(1.85,2.21);p<0.001
Hypertension	No	46939	2978	100661.3	29.6	-
	Yes	14379	1667	32223.7	51.7	1.76(1.66,1.87);p<0.001
Heart failure	No	58016	3840	126568.0	30.3	-
	Yes	3302	805	6316.9	127.4	4.12(3.81,4.44);p<0.001
Diabetes	No	52511	3702	113698.8	32.6	-
	Yes	8807	943	19186.2	49.1	1.51(1.40,1.62);p<0.001
CKD	No	59330	4169	129127.3	32.3	-
	Yes	1988	476	3757.6	126.7	3.86(3.51,4.25);p<0.001
Cerebrovascular disease	No	58567	4226	127671.1	33.1	-
	Yes	2751	419	5213.9	80.4	2.37(2.15,2.62);p<0.001
Charlson index	0	44429	2200	99182.5	22.2	-
	1	10477	1117	21975.7	50.8	2.27(2.11,2.44);p<0.001
	2	4013	668	7910.3	84.4	3.74(3.43,4.08);p<0.001
	3+	2399	660	3816.5	172.9	7.43(6.81,8.11);p<0.001

Table 1 Patient demographics and incidence of all AKI events with associated hazard ratios for each variable on univariable analysis

		N Eligible	N events	Person years follow-up	Event rate (per 1000-py)	HR (95% CI);p-value
All		61318	1070	137874.6	7.8	-
	Female	29468	515	64508.1	8.0	-
	Male	31850	555	73366.4	7.6	0.95(0.84,1.07);p=0.373
Age	≤50	15603	94	36166.1	2.6	-
	51-60	16554	147	38790.8	3.8	1.46(1.12,1.89);p=0.004
	61-70	13984	211	32339.4	6.5	2.51(1.97,3.21);p<0.001
	≥ 71	15177	618	30578.2	20.2	7.86(6.32,9.76);p<0.001
SIMD Quintile	1(Most deprived)	21087	431	47760.9	9.0	-
	2	10203	214	23030.1	9.3	1.03(0.87,1.21);p=0.729
	3	7848	141	18018.9	7.8	0.87(0.72,1.05);p=0.141
	4	6829	106	15740.6	6.7	0.75(0.60,0.92);p=0.007
	5(Least deprived)	10065	128	23242.0	5.5	0.61(0.50,0.74);p<0.001
	Missing	5286	50	10082.1	5.0	0.56(0.42,0.75);p<0.001
baseline eGFR (ml/min)	≤ 29	281	35	429.7	81.5	-
	30-59	4271	311	8509.1	36.5	0.45(0.31,0.63);p<0.001
	> 59	45408	620	104633.5	5.9	0.07(0.05,0.10);p<0.001
	Missing	11358	104	24302.2	4.3	0.05(0.04,0.08);p<0.001
Diuretics	No	45862	558	103495.5	5.4	-
	Yes	15456	512	34379.0	14.9	2.76(2.45,3.11);p<0.001
NSAID	No	37672	729	90829.8	8.0	-
	Yes	23646	341	47044.8	7.2	0.91(0.80,1.04);p=0.170
Prescription groups	None	28534	375	69202.2	5.4	-
	NSAID only	17328	183	34293.3	5.3	1.00(0.83,1.19);p=0.971
	Diuretics only	9138	354	21627.5	16.4	3.02(2.61,3.49);p<0.001
	Diuretic + NSAID	6318	158	12751.5	12.4	2.31(1.92,2.79);p<0.001
Hypertension	No	46939	637	103767.6	6.1	-
	Yes	14379	433	34107.0	12.7	2.06(1.83,2.33);p<0.001
Heart failure	No	58016	861	130763.7	6.6	-
	Yes	3302	209	7110.8	29.4	4.50(3.87,5.23);p<0.001
Diabetes	No	52511	828	117630.7	7.0	-
	Yes	8807	242	20243.9	12.0	1.70(1.47,1.96);p<0.001
CKD	No	59330	897	133647.4	6.7	-
	Yes	1988	173	4227.2	40.9	6.09(5.18,7.17);p<0.001
Cerebrovascular disease	No	58567	961	132322.9	7.3	-
	Yes	2751	109	5551.7	19.6	2.72(2.23,3.31);p<0.001
Charlson index	0	44429	446	101681.2	4.4	-
	1	10477	262	23213.8	11.3	2.58(2.22,3.01);p<0.001
	2	4013	185	8567.4	21.6	4.97(4.18,5.90);p<0.001
	3+	2399	177	4412.1	40.1	9.29(7.81,11.06);p<0.001

Table 2 Patient demographics and incidence of hospitalised AKI events with associated hazard ratios for each variable on univariable analysis

		N Eligible	N events	Person years follow-up	Event rate (per 1000-py)	HR (95% CI);p-value
All		61318	4483	133045.2	33.7	-
	Female	29468	2231	62153.8	35.9	-
	Male	31850	2252	70891.4	31.8	0.89(0.84,0.94);p<0.001
Age	≤50	15603	507	35432.1	14.3	-
	51-60	16554	738	37834.1	19.5	1.36(1.22,1.53);p<0.001
	61-70	13984	995	31170.9	31.9	2.22(2.00,2.47);p<0.001
	≥ 71	15177	2243	28608.1	78.4	5.33(4.84,5.87);p<0.001
SIMD Quintile	1(Most deprived)	21087	1837	45770.1	40.1	-
	2	10203	841	22143.5	38.0	0.95(0.87,1.03);p=0.183
	3	7848	597	17345.2	34.4	0.86(0.78,0.94);p=0.001
	4	6829	442	15273.6	28.9	0.72(0.65,0.80);p<0.001
	5(Least deprived)	10065	556	22645.9	24.6	0.61(0.56,0.68);p<0.001
	Missing	5286	210	9866.8	21.3	0.51(0.44,0.59);p<0.001
baseline eGFR (ml/min)	≤ 29	281	87	364.9	238.4	-
	30-59	4271	914	7742.4	118.1	0.51(0.41,0.64);p<0.001
	> 59	45408	3070	101061.2	30.4	0.14(0.11,0.17);p<0.001
	Missing	11358	412	23876.7	17.3	0.08(0.06,0.10);p<0.001
Diuretics	No	45862	2589	100478.2	25.8	-
	Yes	15456	1894	32567.0	58.2	2.25(2.12,2.38);p<0.001
NSAID	No	37672	2960	87714.4	33.7	-
	Yes	23646	1523	45330.8	33.6	0.96(0.90,1.02);p=0.181
Prescription groups	None	28534	1716	67199.4	25.5	-
	NSAID only	17328	873	33278.8	26.2	0.99(0.91,1.07);p=0.778
	Diuretics only	9138	1244	20515.0	60.6	2.36(2.20,2.54);p<0.001
	Diuretic + NSAID	6318	650	12052.0	53.9	2.03(1.86,2.22);p<0.001
Hypertension	No	46939	2890	100733.8	28.7	-
	Yes	14379	1593	32311.4	49.3	1.73(1.63,1.84);p<0.001
Heart failure	No	58016	3707	126706.9	29.3	-
	Yes	3302	776	6338.3	122.4	4.10(3.79,4.43);p<0.001
Diabetes	No	52511	3577	113820.9	31.4	-
	Yes	8807	906	19224.3	47.1	1.50(1.39,1.61);p<0.001
CKD	No	59330	4037	129251.1	31.2	-
	Yes	1988	446	3794.1	117.6	3.71(3.36,4.09);p<0.001
Cerebrovascular disease	No	58567	4083	127816.4	31.9	-
	Yes	2751	400	5228.8	76.5	2.34(2.11,2.59);p<0.001
Charlson index	0	44429	2132	99248.4	21.5	-
	1	10477	1078	22025.8	48.9	2.26(2.10,2.43);p<0.001
	2	4013	633	7933.0	79.8	3.64(3.34,3.98);p<0.001
	3+	2399	640	3838.0	166.8	7.38(6.76,8.07);p<0.001

Table 3 Patient demographics and incidence of biochemical AKI events with associated hazard ratios for each variable on univariable analysis

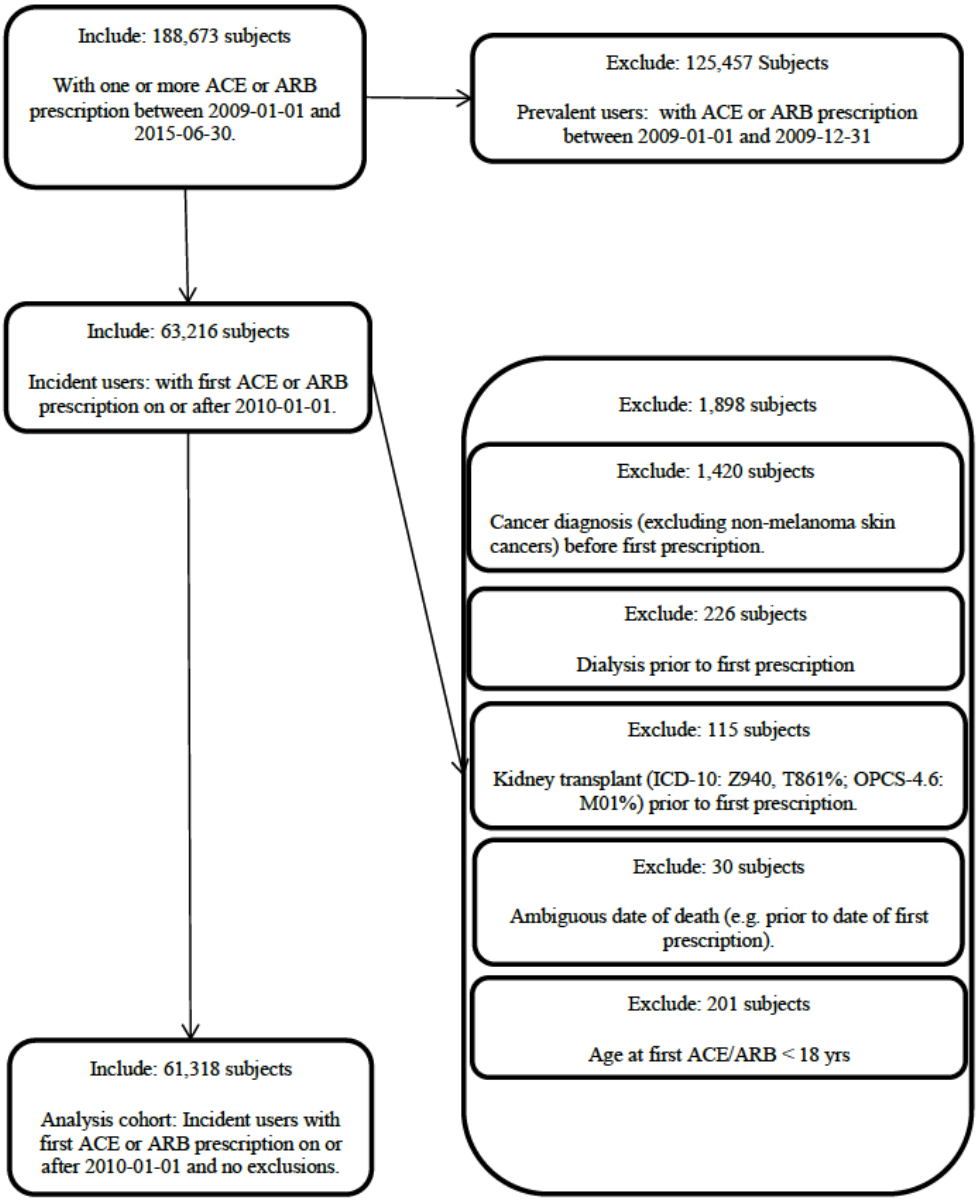
	Hazard Ratio	95% C.I	p-value
Gender (Male)	1.20	(1.13,1.29)	p<0.001
Age at entry (per 10 year increase)	1.31	(1.27,1.35)	p<0.001
SIMD 2	0.88	(0.81,0.96)	p=0.003
SIMD 3	0.82	(0.75,0.91)	p<0.001
SIMD 4	0.69	(0.62,0.77)	p<0.001
SIMD 5(Least deprived)	0.56	(0.51,0.62)	p<0.001
Diuretics (Yes)	1.32	(1.21,1.44)	p<0.001
NSAID (Yes)	1.16	(1.06,1.27)	p=0.001
History of heart failure (Yes)	2.57	(2.37,2.79)	p<0.001
eGFR at baseline (per 10 units increase)	0.80	(0.78,0.82)	p<0.001
History of diabetes (Yes)	1.35	(1.25,1.46)	p<0.001
History of CEVD (Yes)	1.46	(1.32,1.63)	p<0.001

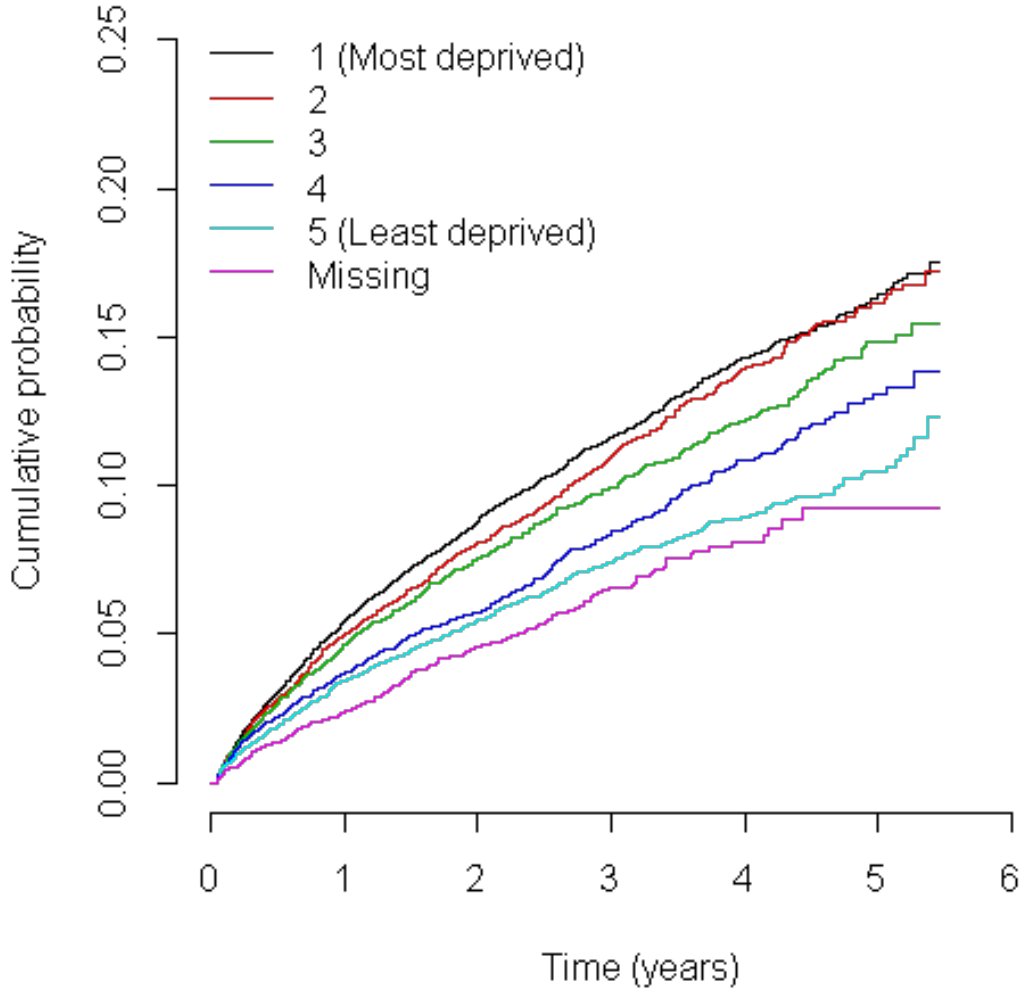
Table 4 Multivariable model for association between predictors and risk of any AKI event. Reference group for SIMD: SIMD 1(most deprived)

Legends to Figures

Figure 1 Flow diagram showing how cohort was generated for analysis from electronic patient records

Figure 2 Kaplan Meier curves for incidence of any AKI after first prescription of ACEi/ARB by SIMD Quintile




1 (Most deprived)
2
3
4
5 (Least deprived)
Missing
Cumulative probability
0.00
0.05
0.10
0.15
0.20
0.25
0
1
2
3
4
5
6
Time (years)

601