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

3

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17

18 **Short title:** AKI in patients prescribed RAS inhibition

19 **Key words:** Acute kidney injury, angiotensin converting enzyme inhibitor, angiotensin
20 receptor blocker, heart failure, chronic kidney disease

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22 Patrick Mark

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26 conflict of interest statements)

27

28

29 **What is already known about this subject:**

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

36

37 **What this study adds:**

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

43

44

45 **Abstract**

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

51 **Methods** We the incidence of AKI in patients commencing ACEi/ARB during 2009-
52 2015 using anonymised patient records. Hospital-coded AKI was defined from hospital
53 episode statistics; biochemical AKI was ascertained from laboratory data. Risk factors
54 for biochemically detected and hospitalised AKI were investigated.

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

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

69

70

71 **Introduction**

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

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

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

97 AKI defined by the KDIGO criteria for diagnosis of AKI, based on small changes
98 in creatinine, is associated with poor short and long term outcomes, irrespective of
99 hospitalisation[18]. Electronic alerts (e-alerts) for biochemical AKI have been
100 proposed as a mechanism for improving detection and management of AKI, although
101 e-alerts need to be combined with education and clinical support to alter outcomes[19,
102 20].

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

110

111 **Methods**

112 **Cohort**

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

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

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

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

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

149

150 **Definition of acute kidney injury (AKI)**

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

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

- 170 1. Serum creatinine ≥ 1.5 times higher than the median of all creatinine values 8–
171 365 days ago
- 172 2. Serum creatinine ≥ 1.5 times higher than the lowest creatinine within 7 days
- 173 3. Serum creatinine $> 26 \mu\text{mol/L}$ higher than the lowest creatinine within 48 h

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

- 179 • Stage 1: Serum creatinine ≥ 1.5 and < 2.0 times AKI baseline or $\geq 26.0 \mu\text{mol/l}$
180 increase above AKI baseline
- 181 • Stage 2: Serum creatinine ≥ 2.0 and < 3.0 times AKI baseline
- 182 • Stage 3: Serum creatinine 3.0 times AKI baseline or $\geq 354 \mu\text{mol/l}$ increase
183 above AKI baseline

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

189
190
191

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

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

220

221 **Results**

222

223 **Demographics of cohort and Incidence of AKI**

224 Figure 1 summarises how the cohort of incident RASi users was generated. During
225 the study period 61,318 patients were prescribed ACEi/ARB. The mean age of the
226 cohort was 59.8 years (SD 13.9), and 51.9% were male. 3,302 (5.4%) had HF, 8,807
227 (14.4%) had diabetes, and the mean eGFR was 86.1ml/min/1.73m² (SD 18.2). There
228 were 7993 deaths during follow-up.

229 During a median follow up of 1.92 yrs there were 1,070 hospital-coded AKI events,
230 and 4,483 biochemical AKI episodes. In total, 4,645 patients had at least one AKI
231 event during 132,885 person years (py) of follow up. Hospital-coded AKI and
232 biochemical AKI overlapped, but were not mutually exclusive, as 162 patients had a
233 hospital-coded AKI, without confirmatory biochemistry, where the patient had no
234 available baseline kidney function tests. The incidence of all AKI events was 35.0 per
235 1000-py, hospital-coded AKI was 7.8 per 1000-py and biochemical AKI was 33.7 per
236 1000-py.

237

238 **Risk factors associated with AKI**

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

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

250 Risk of AKI was highest in three distinct (though overlapping) groups. Patients with
251 heart failure had an incidence of hospital-coded AKI of 29.4 per 1000-py and
252 biochemical AKI of 122.4 per 1000-py. Similar figures were observed for patients with
253 CKD with hospital-coded AKI incidence of 40.9 and biochemical AKI incidence of
254 117.6 per 1000-py. Using Charlson index of 3 or more as a measure of greatest
255 comorbidity identified a group of extremely high risk of both hospital-codeAKI and
256 biochemical AKI (40.1 and 166.8 per 1000-py respectively, Tables 2 and 3).

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

263

264

265

266 **Discussion**

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

278

279 **Risk factors for both biochemical and hospital-coded AKI**

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

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

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

318

319

320 **Multi-morbidity and AKI risk**

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

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

341

342 **Strengths and limitations of this study**

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

347 give a consistent message. We do not have a control group so the incidence of AKI
348 in patients with these comorbid conditions not prescribed ACEi/ARB is unknown.
349 Defining the most appropriate patients to study as a control group is challenging. There
350 would be biases in selecting a group of patients commenced on an alternative class
351 of antihypertensive medication such as calcium channel blockers. This has been
352 explored in other studies with only small increases of AKI incidence with ACEi/ARB in
353 comparison to patients exposed to antihypertensive regimes not including
354 ACEi/ARB¹⁴. In the case of HF, it would be unusual not to be treated with ACEi/ARB
355 therapy.

356 We acknowledge further limitations with these analyses. AKI without clinical
357 symptoms may be diagnosed more frequently in patients having frequent blood
358 samples (ascertainment bias). We are unaware of the indication for taking the blood
359 sample leading to a record in the laboratory database. The incidence of biochemical
360 AKI in untested patients is unknowable. Whilst we use the term 'hospital-coded AKI',
361 it is possible and indeed likely, that AKI was one of a number of diagnoses coded
362 during a hospitalisation episode, rather than the sole diagnosis. There may be coding
363 bias in either direction with hospital-coded AKI, where AKI is added as a diagnosis in
364 the absence of biochemical evidence, or where AKI was present but not recorded as
365 a diagnosis on hospital discharge. The incidence of biochemically diagnosed AKI was
366 particularly high in patients with CKD. Whilst these patients are likely to be at high risk
367 of AKI, the use of an algorithm based on serum creatinine, may lead to a higher
368 incidence of AKI related to how the algorithm diagnoses patients with an AKI event. It
369 is possible that some of the co-morbid conditions have not been coded in the health
370 care records, leading to an under-reporting of the Charlson co-morbidity index. This
371 This can be seen with chronic kidney disease, where only 1989 subjects have been
372 coded as having CKD by their general practitioner despite 4553 patients having a
373 recorded GFR <59ml/min/m² (which is likely to be consistent with CKD).

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

378

379 **Conclusion**

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

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

391

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394 Clyde Safe Haven for technical assistance with the project.

395

396 **Conflict of Interest**

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406 part, except in abstract format.

407

408 **Authors' Contributions**

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

411

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414

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567

		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

568

569

570 **Table 1** Patient demographics and incidence of all AKI events with associated

571 hazard ratios for each variable on univariable analysis

572

		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

574

575 **Table 2** Patient demographics and incidence of hospitalised AKI events with

576 associated hazard ratios for each variable on univariable analysis

577

578

		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

580

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

583

585

586

	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

587

588

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

591

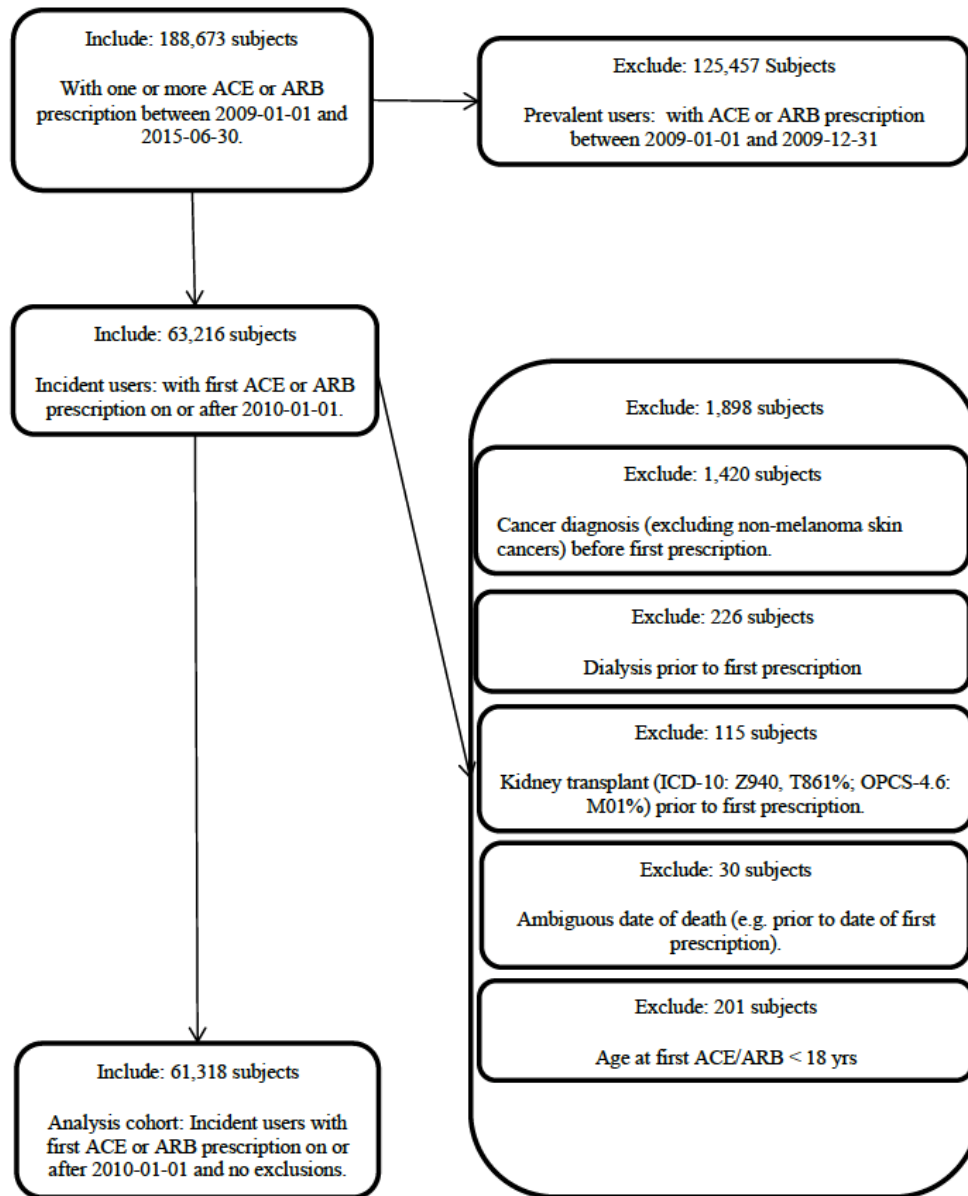
592

593 **Legends to Figures**

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

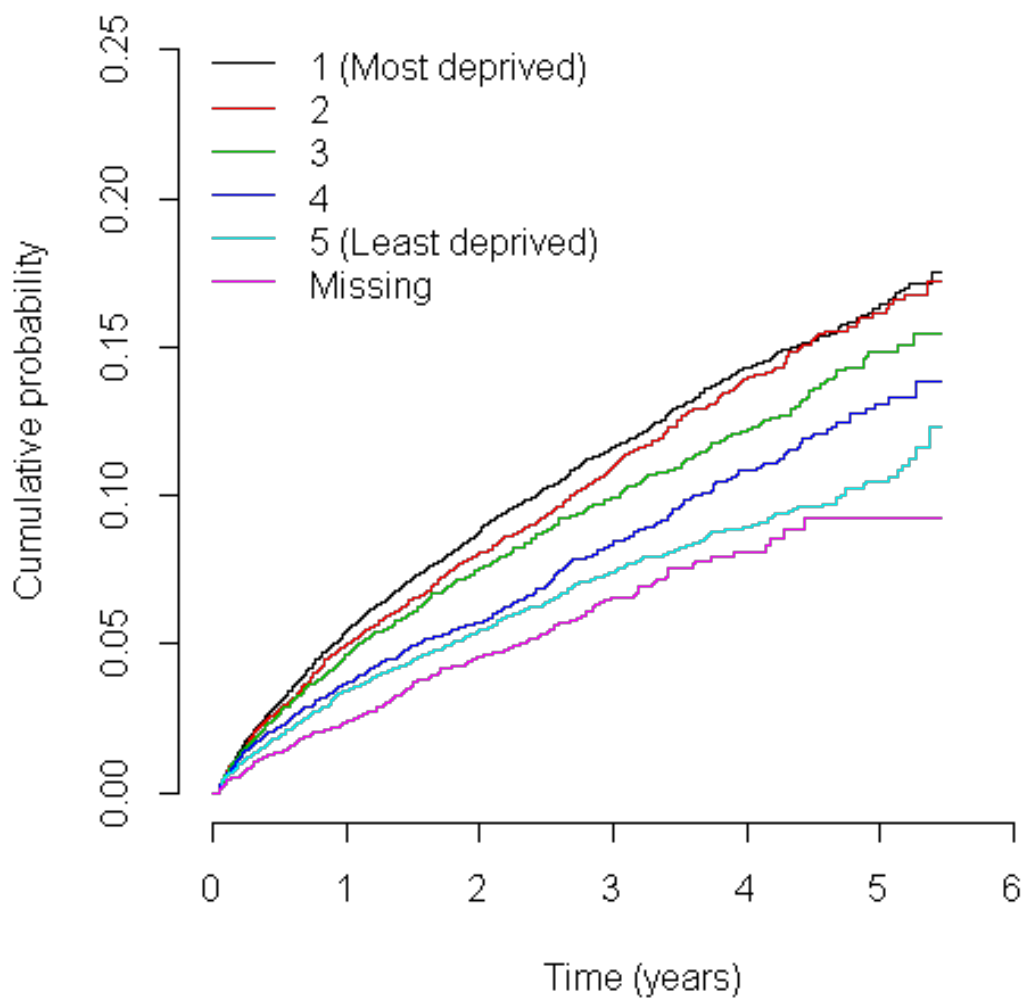
596 **Figure 2** Kaplan Meier curves for incidence of any AKI after first prescription of
597 ACEi/ARB by SIMD Quintile

598



599

600



601