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Original Article

Association between peri-operative angiotensin-converting enzyme inhibitors and angiotensin-2 receptor blockers and acute kidney injury in major elective non-cardiac surgery: a multicentre, prospective cohort study

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Summary

The peri-operative use of angiotensin-converting enzyme inhibitors or angiotensin-2 receptor blockers is thought to be associated with an increased risk of postoperative acute kidney injury. To reduce this risk, these agents are commonly withheld during the peri-operative period. This study aimed to investigate if withholding angiotensin-converting enzyme inhibitors or angiotensin-2 receptor blockers peri-operatively reduces the risk of acute kidney injury following major non-cardiac surgery. Patients undergoing elective major surgery on the gastrointestinal tract and/or the liver were eligible for inclusion in this prospective study. The primary outcome was the development of acute kidney injury within seven days of operation. Adjusted multi-level models were used to account for centre-level effects and propensity score matching was used to reduce the effects of selection bias between treatment groups. A total of 949 patients were included from 160 centres across the UK and Republic of Ireland. From this population, 573 (60.4%) patients had their angiotensin-converting enzyme inhibitors or angiotensin-2 receptor blockers withheld during the peri-operative period. One hundred and seventy-five (18.4%) patients developed acute kidney injury; there was no difference in the incidence of acute kidney injury between patients who had their angiotensin-converting enzyme inhibitors or angiotensin-2 receptor blockers continued or withheld (107 (18.7%) vs. 68 (18.1%), respectively; p = 0.914). Following propensity matching, withholding angiotensin-converting enzyme inhibitors or angiotensin-2 receptor blockers did not demonstrate a protective effect against the development of postoperative acute kidney injury (OR (95%CI) 0.89 (0.58–1.34); p = 0.567).

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Introduction

Acute kidney injury (AKI) following elective, non-cardiac surgery is increasingly recognised as an important postoperative complication. A recent meta-analysis demonstrated that one in six patients undergoing major abdominal surgery suffer AKI [1]. Despite most AKI being classified as 'mild' (a small increase in serum creatinine level, and returning to pre-operative baseline), sustaining AKI postoperatively is associated with a 12-fold increase in the unadjusted risk of in-hospital mortality and a three-fold increase in

one-year mortality [1–3]. There is concern that the stress response to surgery, which typically lowers serum creatinine in its early anabolic phase, may be masking the true severity of postoperative AKI, and overestimating renal recovery. In severe AKI, its impact is more apparent, when temporary renal replacement therapy may be required.

The development of AKI following elective surgery is a multifactorial process. Induction of general anaesthesia, intra-operative fluid depletion (including bleeding), systemic inflammatory responses and insensible fluid losses all contribute towards a reduction in end-organ perfusion and subsequent renal injury [2]. Nephrotoxic drugs and intravenous contrast dyes are also used commonly in the peri-operative setting, with risk of interstitial nephritis and acute tubular damage. Patient comorbidities, particularly cardiovascular disease, chronic renal disease and renal artery stenosis, further increase the risk of AKI in this cohort [3, 4]. Concerns exist regarding the mechanism of action of commonly used antihypertensive drugs and the risk of postoperative AKI [5]. Angiotensin-converting enzyme inhibitors (ACEi) and angiotensin-2 receptor blockers (ARBs) may increase the risk of AKI through a range of mechanisms, including systemic hypotension, renal artery constriction and interstitial nephritis [6]. Withholding these agents in the peri-operative period may be an effective means of reducing the burden of postoperative AKI.

When multiple antihypertensive drugs are used concurrently, the risk of AKI may be even more significant [7]. In patients aged < 55 years, ACEi or ARBs are recommended as first-line treatment of hypertension before elective surgery [8] and offer long-term benefits to patients with significant cardiovascular and renal disease [9]. In patients with chronic kidney disease (CKD) and diabetes, ACEi/ARBs are recommended by the National Institute of Health and Care Excellence, due to their renoprotective effect [10, 11]. In cardiac surgery, the peri-operative administration of ACEi/ARBs has been associated with a lower-risk of AKI [12, 13]. There is currently a paucity of data to support the routine continuation or withholding of ACEi/ARBs peri-operatively in non-cardiac surgery, with no large cohort or randomised studies examining the impact on the incidence of AKI.

This study aimed to identify whether withholding ACEi/ARBs pre-operatively reduces the incidence of post-operative AKI following major, elective gastro-intestinal and liver surgery.

Methods

In this prospective, observational, multicentre study, data were collected from patients undergoing elective gastrointestinal or liver surgery between 23 September and 18 November 2015. Any hospital in the UK and Republic of Ireland providing elective surgery was eligible to participate. Data were collected according to a previously published study protocol [14]. A UK research ethics committee determined that this project did not require ethical approval as the variables collected were routine clinical data and no change or intervention was made to patient care. However, each participating centre was responsible for local registration of the study as service evaluation/clinical audit and gaining Caldicott guardian approval. Data were collected across a collaborative student audit and research network, which has been described previously [14]. Briefly, data collection in each unit was performed by teams consisting of two to three medical students, with a supervising junior doctor and consultant providing oversight and guidance. This study is reported according to STROBE guidelines [15].

Each participating centre collected data on consecutive patients during predefined two-week intervals. Consecutive patients aged ≥ 18 years undergoing elective bowel resection, liver resection, or reversal of ileostomy or colostomy were eligible for inclusion. All operative approaches were eligible for inclusion, including open, laparoscopic and robotic procedures. Bowel resection was defined as complete transection and removal of a continuous section of bowel. The following were not studied: cholecystectomy and hernia repair with no resection of the liver or bowel; gynaecological, urological, vascular or transplant procedures; patients on renal replacement therapy (RRT) pre-operatively; and patients who had previously received a renal transplant.

The primary outcome of this study was the incidence of AKI within seven days of surgery. The Kidney Disease Improving Global Outcomes (KDIGO) serum creatinine-based criteria for AKI were used (26.5 μmol.l^{-1} rise in serum creatinine within 48 h or > 50% rise in serum creatinine within seven days) [16]. Serial measurements were used to calculate increases in serum creatinine. Since urine output is often measured and documented poorly, the KDIGO urine output criteria for AKI were not used within this observational study. Secondary outcome measures were the requirement for RRT (defined as a new postoperative requirement of dialysis (haemodialysis, peritoneal dialysis or haemofiltration) and mortality within 30 days after surgery.

To analyse the association between the peri-operative use of ACEi/ARBs and the incidence of postoperative AKI, patients taking ACEi/ARB pre-operatively were classified into two cohorts: 1. ACEi/ARBs

therapy continued peri-operatively; and 2. ACEi/ARB medication withheld ≥ 24 h before surgery.

The peri-operative administration of other medications was defined within the study protocol [14]. For diuretics, all loop, thiazide, thiazide-like and potassium-sparing diuretics were considered together and could have been administered before or after the operation. Peri-operative non-steroidal anti-inflammatory drug (NSAID) administration was defined as intra-operative administration or if the patient was taking them before or following the operation. Owing to the complex nature of aminoglycoside pharmacokinetics, peri-operative aminoglycoside administration was defined as either at least one intra-operative dose, or dosing in the first seven postoperative days. The day of surgery was defined as postoperative day 0. Pre-operative was defined as up to 7 days before surgery and postoperative was considered within 7 days after surgery.

Additional data collected included: age (in completed years); sex; ASA physical status; ethnicity; smoking status; intra-operative aminoglycoside administration; history of cardiovascular disease; estimated glomerular filtration rate (eGFR)/chronic kidney disease stage; operative approach; history of diabetes mellitus; and intra-operative contamination. Estimated glomerular filtration rate was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation with an upper bound of 120 $ml.min^{-1}.1.73\ m^{-2}$ due to the formula's bounds of sensitivity [17]. This was then equated to a pre-operative CKD stage using the KDIGO classification [16].

Local investigators uploaded data to a secure online website, provided using the Research Electronic Data Capture (REDCap) system [18]. The submitted data were checked centrally. Investigators who submitted entries with incomplete or incorrect data were contacted to ensure data integrity. Where data were missing over 5% of predictor variables, it was intended to impute this using a Markov chain Monte Carlo multiple imputation approach. Before undertaking the study, collaborators were invited to investigator meetings and required to complete training modules on outcome assessment and data security. On completion of the study, data points were validated for accuracy and case ascertainment by investigators who were independent from the teams collecting data at each centre. Data accuracy was calculated by the number of correct individual data fields per centre divided by the total number of data points collected at that given centre. Case ascertainment was calculated by dividing the number of correctly included cases by the number of cases eligible for inclusion within the given data collection period.

There is a paucity of high-quality non-randomised data on the effects of ACEi/ARB on the incidence of AKI, which thus precluded formal sample size calculation. We hypothesised 12% of patients would develop AKI post-operatively and that withholding ACEi/ARBs would be associated with an absolute risk reduction of 7%. Given these assumptions, we required 332 patients in each group, given a power of 0.90 and a two-sided α of 0.05, with an allocation ratio of 1:1.

Due to the influence of selection bias on patients receiving ACEi/ARBs and cardiovascular risk factors, careful adjustment for these factors was required. Baseline characteristics and outcome data were summarised using basic counts and percentages to create summary tables. Testing between treatment groups in summary tables was done using the Chi-squared test, or in the case of continuous variables, independent sample t-tests or Kruskal–Wallis test. Univariable logistic regression models were used to identify factors associated with the subsequent development of AKI. From these univariable models, clinically plausible variables, including cardiovascular risk factors, were entered into multilevel models, to account for individual patient-level risk (at level 1) and centre-level random effects (at level 2) across treatment groups. A nearest-neighbour propensity score matching algorithm was then used to further account for factors implicated with ACEi/ARB administration in an approximate 1:1 ratio. This propensity-matched model aimed to account for selection bias present between treatment groups to provide more accurate effects estimates, thus reducing selection bias. A calliper was set at 0.1 SD to select the closest matched patients. No with or without replacement was performed. Once the propensity-matched models had been designed to consider clinically-relevant variables, they were checked for balance using univariable statistical comparison. Propensity models were then rebalanced to account for any variables which were not accounted for adequately on the initial match. We also adjusted for confounding factors in subsequent logistic regression models used on the matched data. This is known as a 'doubly robust' approach as it combines two methods to reduce the effects of selection bias and is less sensitive to mis-specification. All second-order interactions were explored using multiplicative models. Model fit was guided using the Akaike information criterion (AIC), with a lower AIC indicative of a better fit. Effect estimates are presented as OR, alongside their 95%CI. Statistical significance was set at the level $p < 0.05$. All statistical analyses were performed using the R 3.2.1 software package (R Foundation for Statistical Computing, Vienna, Austria).

Results

Over the study period, 949 patients undergoing elective surgery on ACEi/ARB therapy were included from 160 centres in the UK and Republic of Ireland (Fig. 1). This was a planned subset analysis of a prospective cohort study investigating the incidence of AKI after surgery [14]. In this study, 949 out of 4423 patients (21.5%) were prescribed ACEi/ARBs before admission (Fig. 1.). Out of 4423 patients, ACEi/ARB prescription data were missing for 37 (0.8%). Independent validation of 12,096 data points from 1008 patients from the study that these data were obtained from, demonstrated the data accuracy to be 98.0%, with a case ascertainment rate of 92.2%. Baseline data were similar for the two study cohorts (Table 1).

Patients who had their ACEi/ARBs therapy continued peri-operatively did not have a higher incidence of postoperative AKI compared with those who had these drugs withheld (68 (18.1%) vs. 107 (18.7%), respectively; $p = 0.914$). Furthermore, for patients who did sustain AKI, this was comparable in severity across both study cohorts (Table 2). At the univariable level, withholding ACEi/ARBs over the peri-operative period was not associated with a reduction in risk of AKI (Table 3). Following adjustment for explanatory variables which included: age; sex; ASA physical status; CKD stage; smoking; hypertension; congestive cardiac failure; diabetes; and peri-operative aminoglycoside administration, there remained no association (Table 3). To reduce the influence of selection bias, patients in both study cohorts were matched using

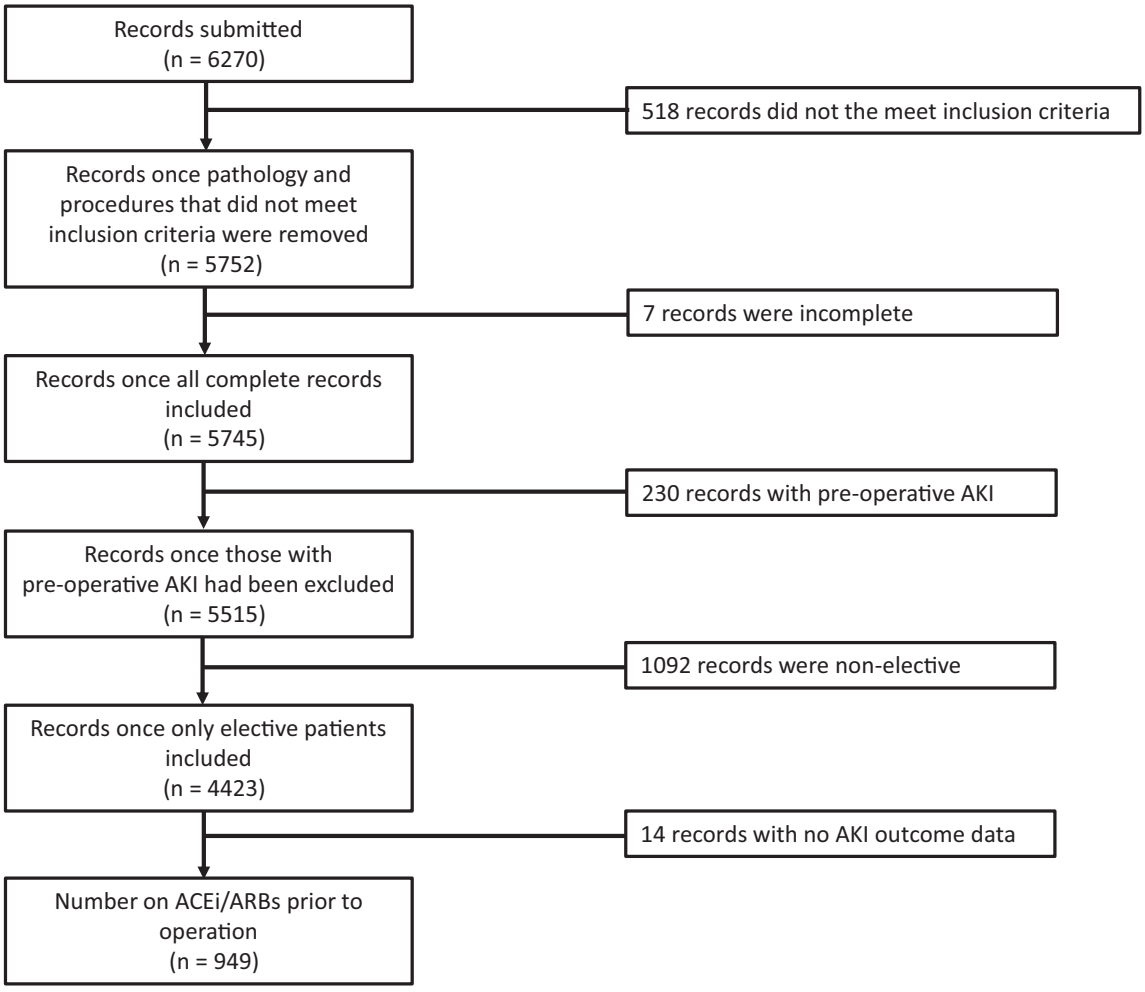

Figure 1 Study flow. AKI, acute kidney injury; ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin-2 receptor blocker.

Table 1 Patient characteristics of the study cohort. Values are mean (SD) or number (proportion).

	ACEi/ARB continued n = 376	ACEi/ARB withheld n = 573
Age; years	70.5 (10.4)	69.9 (10.5)
Female sex	140 (37%)	192 (34%)
ASA physical status		
1	13 (3.5%)	13 (2.3%)
2	175 (47%)	285 (50%)
3	155 (41%)	227 (40%)
4	6 (1.6%)	13 (2.3%)
5	–	1 (0.2%)
Missing	27 (7.2%)	34 (5.9%)
Ethnicity		
Caucasian or Asian	370 (98%)	565 (99%)
Missing	1 (0.3%)	1 (0.2%)
CKD stage		
0/1	100 (27%)	178 (31%)
2	167 (44%)	246 (43%)
3	94 (25%)	133 (23%)
4/5	7 (1.9%)	5 (0.9%)
Missing	8 (2.1%)	11 (1.9%)
Type of surgery		
Laparoscopic	172 (46%)	286 (50%)
Missing	1 (0.3%)	2 (0.3%)
Smoking status		
Current smoker	40 (11%)	72 (13%)
Missing	–	1 (0.2%)
Comorbid conditions		
Ischaemic heart disease	98 (26%)	143 (25%)
Hypertension	326 (87%)	499 (87%)
Congestive cardiac failure	18 (4.8%)	22 (3.8%)
Diabetes mellitus	115 (31%)	180 (31%)
Cerebrovascular disease	25 (6.6%)	52 (9.1%)
Peri-operative drugs administered		
Diuretic	98 (26%)	133 (23%)
Aminoglycoside	97 (26%)	208 (36%)
NSAID	47 (13%)	100 (18%)
Intra-operative contamination		
Clean-contaminated	371 (99%)	547 (96%)
Dirty/contaminated	4 (1.1%)	26 (4.5%)
Missing	1 (0.3%)	–

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin-2 receptor blocker; CKD, chronic kidney disease; NSAID, non-steroidal anti-inflammatory drug.

a propensity score matching algorithm. After the matching algorithm was applied there were no significant differences between cohorts (see Appendix S1). After propensity score matching, the lack of observed effect between withholding ACEi/ARB therapy and AKI remained (Table 4).

Table 2 Postoperative outcomes according to continuation or withholding of angiotensin-converting enzyme inhibitor (ACEi) or angiotensin II receptor blocker (ARB) therapy.

	ACEi/ARB continued n = 376	ACEi/ARB withheld n = 573	p value
Acute kidney injury			
Stage 1	47 (13%)	71 (12%)	0.914
Stage 2	10 (2.7%)	20 (3.5%)	
Stage 3	11 (2.9%)	16 (2.8%)	
Renal replacement therapy	5 (1.3%)	9 (1.6%)	0.446
Missing	1 (0.3%)	0 (0.0%)	
30-day mortality	4 (1.1%)	8 (1.4%)	0.865
Missing	1 (0.3%)	1 (0.2%)	

There was no significant difference between 30-day mortality and requirement for renal replacement therapy between the study cohorts. At the univariable level, there were no associations between withholding ACEi/ARBs and postoperative mortality at 30 days (Table 5). When this was adjusted for the effects of explanatory variable, there remained no association between withholding ACEi/ARBs and the risk of death within 30 postoperative days (Table 5).

Discussion

This large, prospective study found that withholding ACEi/ARB therapy peri-operatively was not associated with a lower incidence of AKI after major, non-cardiac surgery. When we accounted for the use of other medications with known nephrotoxicity, such as diuretics and aminoglycoside antibiotics, there was still no association between withholding ACEi/ARBs peri-operatively and the subsequent development of AKI.

Controversy remains surrounding the peri-operative use of ACEi/ARBs as they have traditionally been thought to contribute towards the development of AKI [3, 7, 18–21]. The proposed mechanisms behind this include lower systemic blood pressure, contributing towards intra-operative hypotension, and renal artery vasoconstriction, both of which result in renal hypoperfusion and ischaemia [4, 22].

A recent large cohort study [19] has investigated the use of ACEi/ARBs peri-operatively and found that withholding ACEi/ARBs for 24 h before non-cardiac surgery

Table 3 Unmatched multilevel model for postoperative acute kidney injury. Values are number (proportion) or mean (SD).

	No AKI n = 774	AKI n = 175	Univariable OR (95%CI)	p value	Multi-level OR (95%CI)	p value
Peri-operative ACEi/ARB therapy withheld	466 (60%)	107 (61%)	1.04 (0.74–1.46)	0.819	0.96 (0.67–1.39)	0.840
Age; years (centred)	6.9 (10.6)	8.2 (9.7)	1.01 (1.00–1.03)	0.132	1.02 (1.00–1.04)	0.126
Male sex	491 (63%)	126 (72%)	1.48 (1.04–2.14)	0.033	1.55 (1.05–2.28)	0.027
ASA physical status ≥ 3	321 (45%)	81 (49%)	1.17 (0.84–1.64)	0.595	1.02 (0.71–1.49)	0.899
CKD stage 2	342 (45%)	71 (41%)	1.05 (0.70–1.58)	0.825	1.10 (0.70–1.72)	0.691
CKD stage 3–5	183 (24%)	56 (32%)	1.54 (1.00–2.39)	0.051	1.46 (0.86–2.48)	0.158
Non-smoker	687 (89%)	149 (85%)	0.72 (0.45–1.17)	0.169	0.63 (0.37–1.06)	0.082
Ischaemic heart disease	205 (27%)	36 (21%)	0.72 (0.48–1.06)	0.106	–	–
Hypertension	672 (87%)	153 (87%)	1.06 (0.66–1.77)	0.830	1.05 (0.61–1.79)	0.864
Diabetes mellitus	234 (30%)	61 (35%)	1.23 (0.87–1.74)	0.233	1.16 (0.79–1.70)	0.453
Congestive cardiac failure	34 (4.4%)	6 (3.4%)	0.77 (0.29–1.74)	0.567	0.64 (0.23–1.72)	0.373
Cerebrovascular disease	61 (7.9%)	16 (9.1%)	1.18 (0.64–2.05)	0.581	0.98 (0.52–1.84)	0.953
Peri-operative aminoglycoside administration	234 (30%)	71 (41%)	1.58 (1.12–2.21)	0.008	1.69 (1.16–2.48)	0.007
Pre-operative diuretic administration	197 (26%)	34 (19%)	0.71 (0.46–1.05)	0.093	–	–
Peri-operative NSAID administration	126 (16%)	21 (12%)	0.70 (0.42–1.13)	0.165	–	–
Intra-operative contamination; dirty/ contaminated	24 (3.1%)	6 (3.4%)	1.11 (0.41–2.59)	0.825	–	–

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; CKD, chronic kidney disease; NSAID, non-steroidal anti-inflammatory drug.

Table 4 Propensity-matched model for postoperative acute kidney injury. Values are number (proportion) or mean (SD).

	No AKI n = 541	AKI n = 115	Univariable OR (95%CI)	p value	Matched OR (95%CI)	p value
Peri-operative ACEi/ARB therapy withheld	275 (51%)	53 (46%)	0.83 (0.55–1.24)	0.356	0.89 (0.58–1.34)	0.567
Age; years (centred)	5.9 (10.6)	8.2 (9.5)	1.02 (1.00–1.04)	0.027	1.03 (1.00–1.05)	0.031
Male sex	328 (61%)	79 (69%)	1.43 (0.93–2.21)	0.107	1.71 (1.09–2.71)	0.021
ASA physical status ≥ 3	249 (46%)	62 (54%)	1.37 (0.92–2.06)	0.125	1.36 (0.88–2.11)	0.169
CKD stage 2	260 (48%)	51 (44%)	1.06 (0.65–1.75)	0.819	0.93 (0.56–1.57)	0.782
CKD stage 3–5	119 (22%)	34 (30%)	1.54 (0.90–2.67)	0.119	1.23 (0.67–2.25)	0.505
Ischaemic heart disease	151 (28%)	27 (24%)	0.79 (0.49–1.25)	0.332	0.59 (0.35–0.97)	0.041
Hypertension	473 (87%)	103 (90%)	1.23 (0.67–2.47)	0.526	1.22 (0.65–2.49)	0.550
Diabetes mellitus	156 (29%)	37 (32%)	1.17 (0.75–1.79)	0.476	1.12 (0.70–1.75)	0.639
Congestive cardiac failure	21 (3.9%)	5 (4.3%)	1.13 (0.37–2.83)	0.816	0.87 (0.28–2.26)	0.789

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; CKD, chronic kidney disease.

was associated with a reduction in a composite end-point of mortality and cardiovascular events. Although the authors suggested that withholding ACEi/ARBs may be beneficial, they did not study the relationship between withholding ACEi/ARBs and postoperative AKI. As data on this key clinical outcome were not collected, we believe that our study is the only large prospective cohort analysis that examines the effects of withholding ACEi/ARBs in a non-cardiac surgical population on the incidence of AKI.

Randomised controlled trials of withholding ACEi/ARBs in the peri-operative setting have largely focussed on physiological end-points (e.g. intra-operative hypotension) rather than clinical end-points (e.g. subsequent renal function or death) [19, 24]. Despite these shortcomings, studies have found that patients on long-term ACEi/ARB therapy were more likely to have episodes of post-induction hypotension and require inotropic support intra-operatively [22–24]. Conversely, in cardiothoracic surgery, the use of ACEi/ARBs has been shown to

Table 5 Unmatched multilevel model for 30-day postoperative mortality. Values are number (proportion) or mean (SD).

	Alive n = 935	Died n = 12	Univariable OR (95%CI)	p value	Multi-level OR (95%CI)	p value
Peri-operative ACEi/ARB therapy withheld	564 (60%)	8 (67%)	1.32 (0.41–4.96)	0.656	0.88 (0.24–3.20)	0.849
Age; years (centred)	7.1 (10.5)	6.7 (7.1)	1.00 (0.95–1.05)	0.880	1.03 (0.96–1.10)	0.425
Male sex	606 (65%)	10 (83%)	2.71 (0.71–17.73)	0.199	2.05 (0.42–9.99)	0.375
ASA physical status ≥ 3	395 (45%)	6 (55%)	1.46 (0.44–5.09)	0.536	0.93 (0.25–3.47)	0.913
CKD stage 2	410 (45%)	3 (25%)	0.28 (0.06–1.02)	0.069	0.31 (0.07–1.41)	0.129
CKD stage 3–5	236 (26%)	2 (17%)	0.33 (0.05–1.37)	0.166	0.28 (0.04–1.86)	0.189
Non-smoker	825 (88%)	9 (75%)	0.40 (0.12–1.81)	0.170	0.33 (0.08–1.45)	0.142
Hypertension	815 (87%)	8 (67%)	0.29 (0.09–1.12)	0.049	0.26 (0.07–0.97)	0.045
Diabetes mellitus	288 (31%)	6 (50%)	2.25 (0.70–7.24)	0.164	2.69 (0.74–9.78)	0.134
Congestive cardiac failure	38 (4%)	2 (17%)	4.72 (0.71–18.71)	0.050	8.33 (1.44–48.22)	0.018
Peri-operative aminoglycoside administration	299 (32%)	6 (50%)	2.13 (0.66–6.85)	0.194	2.76 (0.77–9.84)	0.118
Pre-operative diuretic administration	230 (25%)	1 (8.3%)	0.28 (0.02–1.44)	0.222	–	–
Peri-operative NSAID administration	144 (15.4%)	2 (16.7%)	1.10 (0.17–4.21)	0.907	–	–

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin-2 receptor blocker; CKD, chronic kidney disease; NSAID, non-steroidal anti-inflammatory drug.

decrease the rate of postoperative atrial fibrillation and has been implicated with a reduction in postoperative cardiovascular events, although this remains controversial [12].

Future research is required to further define the role of postoperative ACEi/ARB in non-cardiac surgery. Large cohort studies including ours and others [19] have separately identified potential benefits and harms to routinely withholding ACEi/ARBs peri-operatively. Observational studies are limited due to a high risk of selection bias; therefore, a large randomised trial would provide greater clarity. Any such trial should take into consideration the drug elimination time for ACEi/ARBs which varies between agents. It should also aim to capture outcomes on both cardiovascular, renal and postoperative outcomes (including intra-operative hypotension), in addition to conducting a follow-up to elucidate the long-term consequences of withholding ACEi/ARB therapy. Outside of a trial, future research should focus on discovering treatments and biomarkers which could prevent and detect postoperative AKI.

At present, there are randomised trials underway in orthopaedics and cardiac surgery which will contribute to the ongoing debate [25–27].

A key strength of our study is the use of accurate, validated data from a prospective, multicentre cohort study. In this context, it makes the findings widely generalisable. Collection of prospective data on patients undergoing major gastro-intestinal surgery allowed for creatinine levels to be recorded to detect AKI according to the KDIGO classification [16], although this should be considered with the caveat that collection of the urine output criteria was not feasible. This clear and objective outcome assessment enabled this study to identify a higher incidence of AKI than previously reported in other studies [2, 28, 29]. Furthermore, this study collected data on other variables thought to contribute towards AKI (including medications), which enabled us to explore multiple variables as opposed to ACEi/ARBs use in isolation.

Our study has several limitations to consider. As an observational study, it is subject to selection bias. We attempted to minimise this through careful risk-adjustment and using methods for causal inference to provide a robust sensitivity analysis. It is important to consider that clinical decisions are not random and, in our study, patients who had their ACEi/ARB withheld before surgery may have been considered to be at higher risk of developing AKI. Furthermore, ACEi/ARBs have a terminal serum half-life of up to 40 h. Our study and another [19] both defined withholding as "*stopping medications up to 24 h prior to surgery*"; thus, patients may still have had residual systemic levels of ACEi/ARBs. However, this timeframe may more accurately replicate clinical practice. In our study, we only included elective procedures, as emergency surgical patients were not likely to have had their ACEi/ARBs withheld. Another important factor to consider is the fluid balance status of the patient during the peri-operative period. Fluid balance is a major contributory

factor for AKI, and patients undergoing major gastrointestinal surgery may potentially experience substantial physiological disturbance to their volaemic status. Other factors include the presence of intra- and postoperative hypotension, which would impact upon renal perfusion. We did not collect haemodynamic or fluid balance data, as these are complex and intrinsically linked factors which have been studied in depth already [22]. Nevertheless, these factors may have influenced our study's findings. Our study relied on routinely collected blood samples for the measurement of serum creatinine. It is possible that some patients may have had a rise in creatinine which was undetected by routine sampling; therefore, we propose the incidence of AKI in this study is a conservative estimate. Furthermore, our study may have underestimated the incidence of AKI due to excluding the KDIGO urine output criteria for AKI diagnosis.

This study is the largest of its type investigating the effects of withholding ACEi/ARB therapy during the peri-operative period in major elective, non-cardiac surgical patients. Our data do not show that the routine withholding of ACEi/ARBs in peri-operative setting has any impact on the incidence of postoperative AKI. Policymakers should consider pursuing a definitive answer to the research question through a well-conducted, randomised trial.

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Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Appendix S1. Patient characteristics of those undergoing surgery who had ACEi/ARB therapy continued or withheld following propensity score matching. Values are number (%), unless otherwise indicated. All tests are Chi-square, except when indicated by *, where test is Kruskall–Wallis. ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; ASA, American Society of Anesthesiologists; CKD, chronic kidney disease.

Appendix S2. Members of the STARSurg collaborative.

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