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Renin–angiotensin system blocker use and the risk of acute kidney injury after colorectal cancer surgery: a population-based cohort study

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ABSTRACT

Objectives It is unknown whether preoperative use of ACE inhibitors (ACE-I) or angiotensin receptor blockers (ARBs) affects the risk of acute kidney injury (AKI) after colorectal cancer (CRC) surgery. We assessed the impact of preoperative ACE-I/ARB use on risk of AKI after CRC surgery.

Design Observational cohort study. Patients were divided into three exposure groups—current, former and non-users—through reimbursed prescriptions within 365 days before the surgery. AKI within 7 days after surgery was defined according to the current Kidney Disease Improving Global Outcome consensus criteria.

Setting Population-based Danish medical databases.

Participants A total of 9932 patients undergoing incident CRC surgery during 2005–2014 in northern Denmark were included through the Danish Colorectal Cancer Group Database.

Outcome measure We computed cumulative incidence proportions (risk) of AKI with 95% CIs for current, former and non-users of ACE-I/ARB, including death as a competing risk. We compared current and former users with non-users by computing adjusted risk ratios (aRRs) using log-binomial regression adjusted for demographics, comorbidities and CRC-related characteristics. We stratified the analyses of ACE-I/ARB users to address any difference in impact within relevant subgroups.

Results Twenty-one per cent were ACE-I/ARB current users, 6.4% former users and 72.3% non-users. The 7-day postoperative AKI risk for current, former and non-users was 26.4% (95% CI 24.6% to 28.3%), 25.2% (21.9% to 28.6%) and 17.8% (17.0% to 18.7%), respectively. The aRRs of AKI were 1.20 (1.09 to 1.32) and 1.16 (1.01 to 1.34) for current and former users, compared with non-users. The relative risk of AKI in current compared with non-users was consistent in all subgroups, except for higher aRR in patients with a history of hypertension.

Conclusions Being a current or former user of ACE-I/ARBs is associated with an increased risk of postoperative AKI compared with non-users. Although it may not be a drug effect, users of ACE-I/ARBs should be considered a risk group for postoperative AKI.

Strengths and limitations of this study

- First study on risk of acute kidney injury (AKI) after undergoing colorectal cancer surgery in current/former users of renin–angiotensin system blockers.
- We used Danish population-based administrative medical and clinical quality databases.
- Participants had uniform access to healthcare and virtually complete follow-up.
- We defined AKI according to current guidelines (Kidney Disease Improving Global Outcome).
- Residual and unmeasured confounding cannot be ruled out in this observational study.

INTRODUCTION

ACE inhibitors (ACE-I) and angiotensin receptor blockers (ARBs) are widely prescribed drugs targeting the regulation of water and salt retention in the kidneys leading to haemodynamic effects.[1] ACE-I/ARBs are primarily prescribed to treat hypertension and heart failure as well as to preserve kidney function in patients with chronic kidney disease, and to delay and inhibit the development of diabetic nephropathy.[1–3] Unfortunately, they may increase the risk of acute kidney injury (AKI) through their inhibition of angiotensin II leading to renal vasodilatation and consequently decreased glomerular filtration rate (GFR).[4] AKI is defined as a sudden decline in the excretory function of the kidneys and occurs in around 20% of patients undergoing colorectal cancer (CRC) surgery.[5] AKI may arise as a result of prerenal, intrarenal or postrenal causes, as well as a combination of these. Along with increased severity of AKI, the ability of the kidneys to maintain homeostasis, acidity levels and blood pressure within the autoregulatory range declines.[6 7] In the most severe stages of AKI, renal replacement therapy (RRT) may be required and the damages can

be irreversible.[6] Since approximately 30% of the Danish population above 40 years of age redeemed a prescription on ACE-I/ARBs during 2015 and the median age at CRC diagnosis is 72 years, the prevalence of ACE-I/ARB use is expected to be high in patients with CRC.[8]

Thus, despite the beneficial long-term effects of ACE-I/ARBs, the potential short-term effects in surgical patients need consideration. At present, the literature on the potential consequences of preoperative use of ACE-I/ARB on the risk of postoperative AKI is limited. Consequently, recommendations regarding the care of this subgroup of patients undergoing CRC surgery as well as whether to discontinue ACE-I/ARBs preoperatively are based on institutional policies and guidelines without strong recommendations.[9–11]

We hypothesise that current use of ACE-I/ARB before CRC surgery is associated with an increased risk of AKI. Prior studies have been limited by inconsistency in staging of AKI, definition of ACE-I/ARB use and the inclusion of heterogeneous surgical populations.[12–14] Also, prior studies have not specifically examined patients undergoing CRC surgery, who may be a particular high-risk group due to advanced age and comorbidities.[12 15–19]

Thus, in the current study, we examined whether preoperative use of ACE-I/ARBs was associated with an increased risk of postoperative AKI in patients undergoing colorectal surgery.

MATERIALS AND METHODS

Study design and setting

This cohort study was conducted in northern Denmark (North and Central Denmark Regions, with ~1.8 million inhabitants) based on prospectively collected data from medical and administrative databases. CRC surgeries were performed at nine different hospitals in the study area. All Danish residents are provided with tax-supported healthcare through the Danish National Health Service. Since 1968, all residents have been assigned a unique 10-digit civil registration number (CPR) that allows for unambiguous individual-level linkage among medical and administrative databases.[20]

Study population

The study included all patients registered in the Danish Colorectal Cancer Group (DCCG.dk) database (reported patient completeness of 98%–99%),[21] who underwent surgery for incident CRC from 1 January 2005 to 31 December 2014. The DCCG database, a clinical quality database established in May 2001, contains information on, for example, demographics, treatments, postoperative complications (<31 days) and mortality.[21] Postoperative surgical and non-surgical complications within 30 days after surgery were registered in the DCCG database.

To ensure availability of baseline laboratory data for identifying AKI outcome and preoperative chronic kidney disease, we required residency in the study regions for at least 1 year before surgery. Laboratory data were retrieved from the clinical laboratory information system (LABKA) research database at Aarhus University.[22] Registration of laboratory results from general practice and hospitals in northern Denmark was initiated in the 1990s. Data completeness of creatinine was above 90% in most hospitals after 2004. Two hospitals started reporting to LABKA at later time points; to ensure data completeness of at least 90%, we included patients undergoing surgery only after 2005 for one hospital and after 2009 at the other hospital.[22]

We excluded patients with chronic RRT within 30 days before surgery, undergoing an explorative-only procedure or if no follow-up data were available.

ACE-I and ARB use

Preoperative ACE-I/ARB use was identified through the National Health Service Prescription Database (NHSPD) and defined as current, former and non-users according to figure 1.[23] The NHSPD contains data on all dispensed prescriptions for reimbursable drugs in community pharmacies in Denmark since 2004 (online supplementary table S1).

Acute kidney injury

AKI was defined by applying the creatinine criteria of the Kidney Disease Improving Global Outcome (KDIGO) consensus criteria.[6] Data on plasma creatinine (equivalent to serum creatinine)[24] were retrieved from the LABKA database.[22] Patients were defined as having AKI if they met one of the following four criteria within 7 days after surgery: (1) an increase in creatinine of 50% or more from baseline, (2) an increase in creatinine of ≥0.3 mg/dL (26.4 µmol/L) within 48 hours, (3) creatinine ≥4.0 mg/dL (353.6 µmol), with an acute increase of at least 0.5 mg/dL (44 µmol/L), or (4) initiation of RRT.

Baseline creatinine was defined as either the mean outpatient creatinine within 7–365 days before surgery or, if unavailable, the lowest creatinine value within the last 7 days.[25] If neither measurement was available, it was estimated using the Modification of Diet in Renal Disease formula as recommended by the RIFLE, AKIN and KDIGO consensus criteria.[6 26]

Mortality

We obtained data on mortality from date of CRC surgery to 7 days post surgery from the Danish Civil Registration System (CRS). The CRS has maintained complete information on all changes in vital status and migration for the entire Danish population since 1968 and is electronically updated daily.[20]

Potential confounders

Age and gender were determined from the CPR number provided by the CRS.[20] Pre-existing comorbidities were chosen based on their potential association with use of ACE-I/ARBs and risk of AKI.[6 12 27] The following covariates were identified through the Danish National Patient Registry (DNPR) based on inpatient or outpatient hospital contacts within 10 years before CRC surgery: obstructive

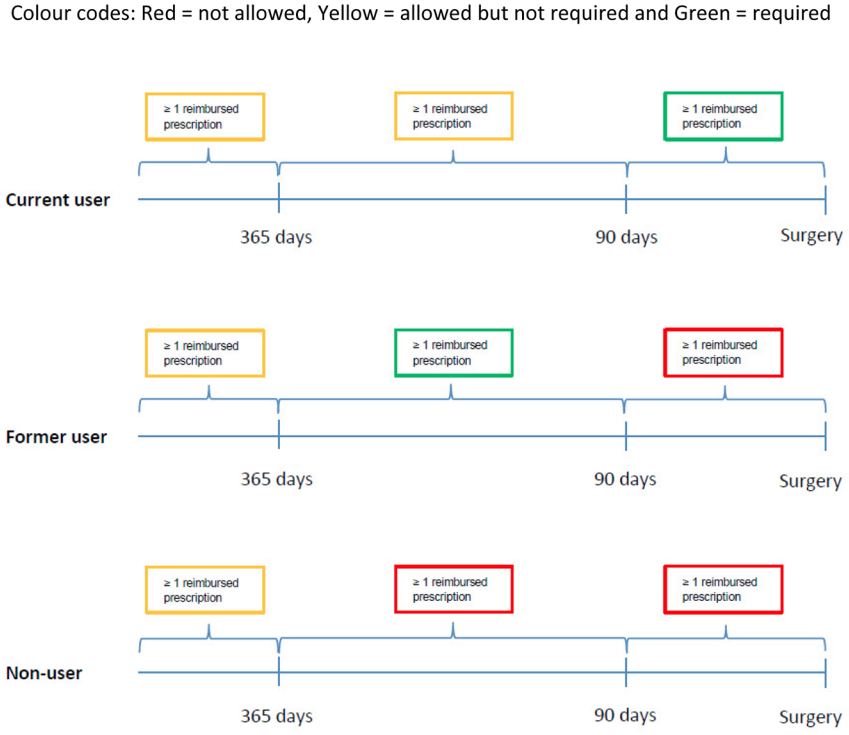


Figure 1 Definition of exposure to ACE inhibitors and/or angiotensin receptor blockers.

pulmonary disease (including chronic obstructive pulmonary disease and asthma), hypertension, diabetes, heart disease (myocardial infarction and congestive heart failure) and liver disease.[28] The DNPR contains information on all hospitalisations since 1977, outpatient visits since 1994 and emergency room visits since 1995. It includes among others information on diagnoses, procedures and admission/discharge (online supplementary table S1).

To improve the completeness of diabetes and obstructive pulmonary disease diagnoses in the study population, we searched the NHSPD for previous prescriptions (within a year before surgery) of medications used to treat these diseases.[23] Chronic kidney disease (CKD), a strong predictor for AKI,[6] was identified using creatinine measurements from LABKA[22] and defined as an estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2 lasting at least 3 months within 2 years before CRC surgery.[4] Data on smoking, weekly alcohol intake and body mass index (BMI, defined as 'underweight' if <18.5 kg/m^2, 'normal weight' if 18.5–25 kg/m^2 and 'overweight' if >25 kg/m^2) were retrieved from the DCCG database.[29]

Users of diuretics, statins, beta-blockers, calcium-channel blockers, acetylsalicylic acid, antibiotics and nitrates were identified according to the same definition as the ACE-I/ARB since these medications are likewise available in packages of 90–100 tablets in Denmark and are often taken once a day. Non-steroidal anti-inflammatory drugs (NSAIDs) are typically redeemed every 60 days. Therefore, NSAID current users were defined within 60 days before surgery.[30] These drugs were chosen based on their potential nephrotoxic role and frequent use in elderly patients for chronic conditions such as hypertension, heart disease, diabetes, CKD or for infection.[31]

Patient and public involvement

No patient involved.

Statistical methods

Baseline characteristics were tabulated by ACE-I/ARB user status, and discrete variables were reported as frequencies and proportions.

We computed 7-day postoperative cumulative incidence proportions (risk) of AKI with 95% CIs for patients with current, former and no use of ACE-I/ARBs, including death as a competing risk.[32 33]

Risk ratios (RRs) for current users compared with non-users, and for former users compared with non-users, were computed using log-binomial regression including the multiple imputed datasets. We controlled for potential confounders including age groups (0–59, 60–69, 70–79, >79), gender, BMI, alcohol, smoking, CKD, diabetes, obstructive pulmonary disease, hypertension, liver disease, heart disease, cancer type and urgency of surgery. To address any difference in impact between subgroups of patients with CRC, we repeated the analyses stratified by sex, age group, BMI, alcohol, smoking, CKD, diabetes, hypertension, heart disease, urgency of surgery, beta-blockers, acetylsalicylic acid, statins, antibiotics and NSAIDs, and diuretic use.

In 10% of our cohort, outcome data were missing. Based on two rationales, they were categorised as patients without AKI. First, the indication threshold for control creatinine is low. Second, the hospitals that contributed

the most patients lacking creatinine measurements followed a fast-track protocol. This protocol advises physicians and nurses to refrain from postoperative blood analyses and to maintain a zero fluid balance if the patient is healthy and recovering well.[34–36] The decision of categorising them as patients without AKI was validated with a sensitivity analysis (complete case).

Multiple imputations of the covariates (CKD, smoking, BMI, weekly alcohol intake) with missing data (~20%) were performed using the mi impute chained procedure in Stata V.13.1 to create five imputed datasets and included in the log-binomial regression.[37 38] We expected missing data to be missing at random since there would be some dependency between missing covariates and the risk of developing AKI.[38] We addressed the impact on our results of potential misclassification associated with missing covariates in a complete case analysis. Moreover, propensity score matched analyses were conducted. All analyses were conducted using the software package Stata, V.13.1 (StataCorp, College Station, Texas, USA). All data were obtained from Danish registries and, according to Danish law, their use does not require ethics approval or informed consent.

RESULTS

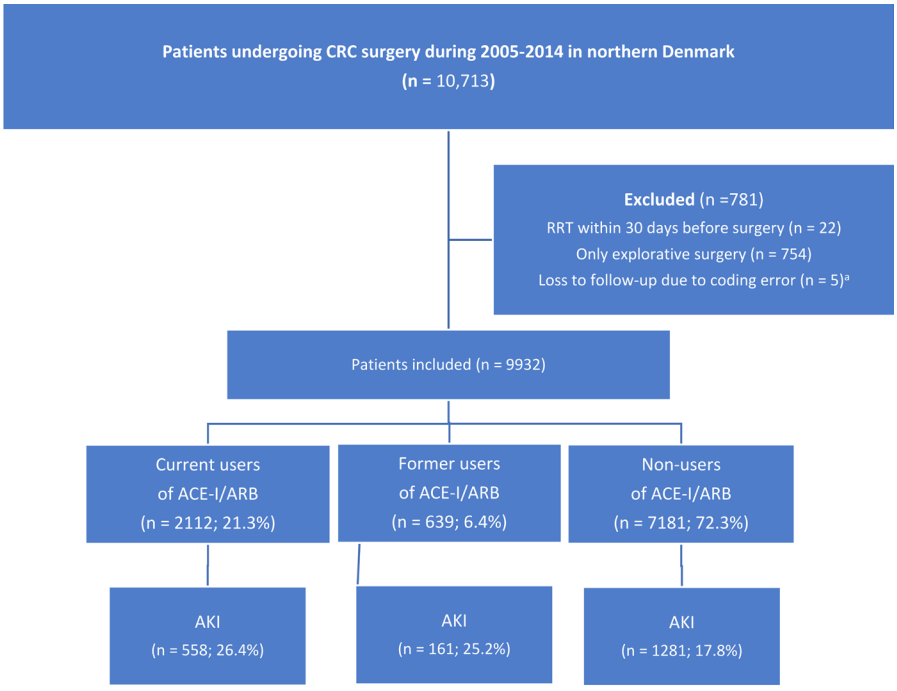
Study population

We identified 10 713 patients with CRC living in northern Denmark who underwent CRC surgery during 2005–2014. Of these, we excluded 781 patients for the following reasons: on RRT prior to CRC surgery (n=22); only undergoing explorative surgery (n=754); no follow-up data due to a coding error (n=5). In total, 9932 patients were included in the analyses (figure 2). Twenty-one per cent of the included patients were current ACE-I/ARB users, 6.4% former users and 72.3% were non-users. Of the current users (n=2112), we had information regarding in-hospital medication for 1113 of these patients. Of the 1113 patients with information regarding in-hospital medication, 619 patients were registered with an administration of ACE-I/ARB on the day of surgery.

Median age was 70.1 years, 53.3% were male and 66.2% had colon cancer (table 1). Information on lifestyle variables (BMI, smoking and alcohol use) and preoperative CKD were missing for approximately 20% (table 1).

Current users of ACE-I/ARBs were older, had a higher BMI, American Society of Anesthesiology classification score and Charlson Comorbidity Index than non-users of ACE-I/ARB.[39 40] Moreover, current users more frequently were female, had diabetes mellitus, CKD or hypertension compared with non-users (table 1). Diuretic, statin, calcium-channel blocker or beta-blocker use was more common in current and former users of ACE-I/ARBs than in non-users (online supplementary table S2).

Postoperative complications (sepsis, pneumonia, anastomosis leakage, wound abscess, intra-abdominal abscess) were comparable among current, former and non-users of ACE-I/ARBs (online supplementary table S3).



[a] Death registered before surgery.
Abbreviations: Acute Kidney Injury, AKI; Angiotensin-converting Enzyme Inhibitor, ACE-I; Angiotensin-receptor Blocker, ARB; Renal Replacement Therapy, RRT.

Figure 2 Flow chart. [a]Death registered before surgery. ACE-I, ACE inhibitor; AKI, acute kidney injury; ARB, angiotensin receptor blocker; CRC, colorectal cancer; RRT, renal replacement therapy.

Table 1 Demographics and surgical information tabulated by ACE inhibitor (ACE-I) and/or angiotensin receptor blocker (ARB) user status

	ACE-I/ARB use			
	Non-user	Former user	Current user	All patients
	(n=7181) N (%)	(n=639) N (%)	(n=2112) N (%)	(n=9932) N (%)
Sex				
Female	3464 (48)	286 (45)	891 (42)	4641 (47)
Male	3717 (52)	353 (55)	1221 (58)	5291 (53)
Age, years				
Mean (SD)	69.0 (±11.7)	73.4 (±9.4)	72.8 (±9.0)	69.5 (±11.2)
0–59	1520 (21)	50 (8)	177 (8)	1747 (18)
60–69	2136 (30)	175 (27)	586 (28)	2897 (29)
70–79	2186 (30)	240 (38)	865 (41)	3291 (33)
>79	1339 (19)	174 (27)	484 (30)	1997 (20)
Smoking				
Current smoker	1197 (16)	90 (14)	271 (13)	1558 (16)
Former smoker	2373 (33)	257 (40)	872 (41)	3502 (35)
Never smoker	2092 (29)	179 (28)	553 (26)	2824 (28)
Alcohol consumption (units/week)				
0	1583 (22)	167 (26)	509 (24)	2259 (23)
1–14	3436 (48)	299 (47)	980 (46)	4715 (48)
>14	616 (9)	54 (9)	197 (9)	867 (9)
Body mass index (BMI)				
Underweight (BMI <18.5 kg/m^2)	224 (3)	19 (3)	30 (1)	273 (3)
Normal weight (BMI 18.5–25 kg/m^2)	2781 (39)	198 (31)	644 (31)	3623 (37)
Overweight (BMI >25 kg/m^2)	2704 (38)	316 (50)	1062 (50)	4082 (41)
ASA score				
1	2033 (28)	38 (6)	95 (5)	2166 (22)
2	3520 (49)	361 (57)	1217 (58)	5098 (51)
3	1300 (18)	197 (31)	679 (32)	2176 (22)
4	102 (1)	25 (4)	57 (3)	184 (2)
5	5 (0.1)	0 (0.0)	3 (0.1)	8 (0.1)
CCI score				
0	5032 (70)	301 (47)	1076 (51)	6409 (65)
1–2	1609 (22)	235 (37)	735 (35)	2579 (26)
>2	540 (8)	103 (16)	301 (14)	944 (10)
Heart disease	120 (2)	27 (4)	107 (5)	254 (3)
Diabetes	450 (6)	138 (22)	497 (24)	1085 (11)
Liver disease	88 (1)	2 (0.3)	26 (1)	116 (1)
Hypertension	1223 (17)	383 (60)	1230 (58)	2836 (29)
Obstructive pulmonary disease	726 (10)	82 (13)	270 (13)	1078 (11)
Chronic kidney disease (CKD)*				
No CKD	5193 (72)	439 (69)	1457 (69)	7089 (71)
CKD	508 (7)	120 (19)	366 (17)	994 (10)
Baseline eGFR, median (25th percentile, 75th percentile)	89.6 (75.3, 104.7)	81.4 (63.4, 98.9)	80.5 (64.7, 96.9)	76.9 (67.0, 89.0)
Cancer type				
Colon	4699 (65)	461 (72)	1413 (68)	6573 (66)
Rectum	2482 (35)	178 (28)	699 (33)	3359 (34)

Continued

Table 1 Continued

	ACE-I/ARB use			
	Non-user	Former user	Current user	All patients
	(n=7181) N (%)	(n=639) N (%)	(n=2112) N (%)	(n=9932) N (%)
Palliative or curative treatment				
Curative	6562 (91)	572 (90)	1937 (92)	9071 (91)
Palliative	619 (9)	67 (10)	175 (8)	861 (9)
Urgency of surgery				
Elective	6443 (90)	583 (91)	1914 (91)	8939 (90)
Acute	738 (10)	56 (9)	198 (9)	991 (10)
Surgical categories				
Colon resection+A	3768 (53)	333 (52)	1073 (51)	5174 (52)
Colon resection÷A	2155 (30)	199 (31)	700 (33)	3054 (31)
Rectum resection+A	1258 (18)	107 (16)	339 (16)	1704 (17)

Missing data: alcohol, BMI, CKD and smoking (~20%); ASA (3.1%).
*CKD was defined as an estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2 lasting at least 3 months within 2 years before CRC surgery.
A, anastomosis;AKI, acute kidney injury;ASA, American Society of Anesthesiology; BMI, body mass index; CCI, Charlson Comorbidity Index.

Seven-day risk of AKI

The 7-day risk of AKI for current users was 26.4% (95% CI 24.6% to 28.3%), compared with 25.2% (95% CI 21.9% to 28.6%) for former users and 17.8% (95% CI 17.0% to 18.7%) for non-users (table 2). Compared with non-users, the crude RR of AKI for current users was 1.41 (95% CI 1.37 to 1.45) and for former users it was 1.42 (95% CI 1.35 to 1.49) (table 2). After adjusting for potential confounding, the RR for current users compared with non-users was 1.20 (95% CI 1.09 to 1.32). The aRR for former users compared with non-users was 1.16 (95% CI 1.01 to 1.34).

Sensitivity analyses

The complete case analysis yielded aRR estimates similar to those obtained in the primary analyses, although the CIs, as expected, were wider. Changing the exposure period from 90 to 30, 60 or 100 days resulted only in minor changes (online supplementary table S4). Estimated propensity score matched analyses were close to unity (online supplementary tables S5 and S6). Neither did we find any major differences in results after restricting the analyses to patients without stoma formation (online supplementary table S7). Moreover, after restricting the study population to patients with one or more creatinine measurements, results in line with those from the main analysis were found (online supplementary table S8).

Subgroup analyses

Current use of ACE-I/ARB was more strongly associated with AKI in patients without a diagnosis for hypertension (aRR 1.39, 95% CI 1.23 to 1.59; absolute risk: 25.7% for current users, 16.2% for non-users) than in patients with hypertension (aRR 1.03, 95% CI 0.90 to 1.17; absolute risk: 26.9% for current users, 25.7% for non-users) (figure 3). Although users of calcium-channel blockers, diuretics and antibiotics seemed to have a lower relative risk of AKI, there were no major differences in the association between current use of ACE-I/ARBs and the risk of AKI across subgroups of gender, age group, smoking, alcohol, CKD, diabetes mellitus, heart disease, urgency of surgery, and use of beta-blockers, calcium-channel blockers, acetylsalicylic acid, statins, antibiotics, NSAIDs or diuretics (figure 3).

Table 2 Seven-day acute kidney injury risk by ACE inhibitor and/or angiotensin receptor blocker use

Exposure group	Number of outcomes	Seven-day incidence proportion % (95% CI)	Crude RR (95% CI)	Adjusted RR* (95% CI)
Non-user	1281	17.8% (17.0 to 18.7)	Ref	Ref
Former user	161	25.2% (21.9 to 28.6)	1.42 (1.35 to 1.49)	1.16 (1.01 to 1.34)
Current user	558	26.4% (24.6 to 28.3)	1.41 (1.37 to 1.45)	1.20 (1.09 to 1.32)

*Log-binomial regression adjusted for age (0–59, 60–69, 70–79, ≥80 years), alcohol, body mass index, cancer type, chronic kidney disease, diabetes mellitus, heart disease, hypertension, liver disease, obstructive pulmonary disease, sex, smoking and urgency of surgery.
RR, relative risk.

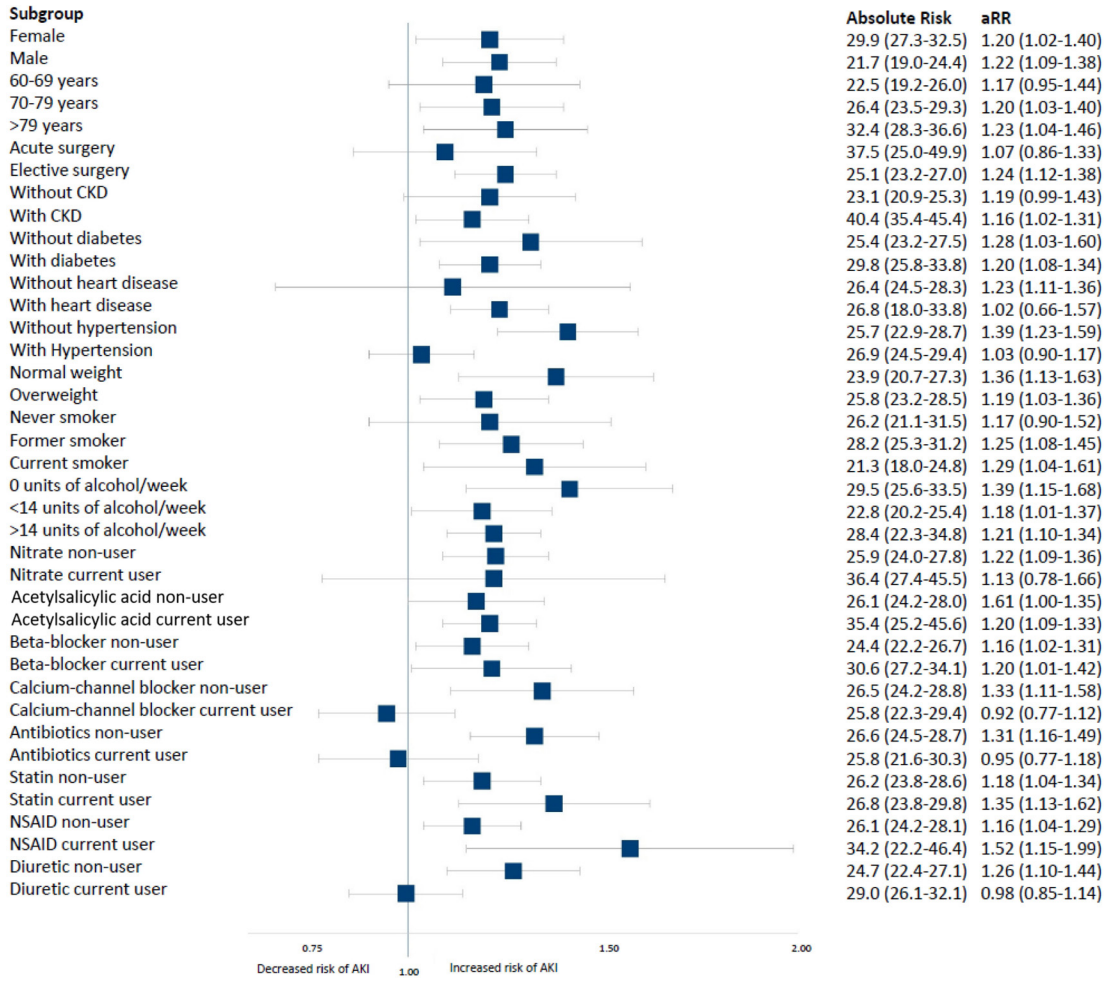


Figure 3 Forest plot (subgroup analyses). Current use of ACE inhibitors and/or angiotensin receptor blockers and the risk of acute kidney injury within 7 days after colorectal cancer surgery across subgroups of demographics and comorbidities. Underweight, <18.5 kg/m^2; normal weight, 18.5–25 kg/m^2; overweight, >25 kg/m^2. AKI, acute kidney injury; aRR, adjusted relative risk; CKD, chronic kidney disease; NSAID, non-steroidal anti-inflammatory drug.

DISCUSSION

Key results

In this population-based study, ACE-I/ARB use was frequent and associated with an increased risk of AKI, especially in current users without hypertension. Current users, who had the highest risk of AKI compared with non-users, were older and less healthy. The risk of AKI was increased in both current and former ACE-I/ARB users compared with non-users.

Our study extends previous research on ACE-I/ARB use and the risk of AKI after non-cardiac surgery by providing information on former users and including only patients with CRC as opposed to the mixed surgical populations in the current literature.[18 19 41–45]

Strengths of our study include a low risk of selection bias, for two reasons. First, data were prospectively collected for administrative purposes in Danish hospitals. Second, study participants had uniform access to healthcare with virtually complete follow-up. An additional strength of the study is the availability of information on a large number of potential confounders of the association between ACE-I/ARB use and postoperative AKI.

However, some limitations need to be considered when interpreting our findings. (1) We did not have complete information on whether patients with current use of ACE-I/ARB also were exposed to their medication on the day of surgery. However, a majority of the patients with in-hospital data continued their medication on the day of surgery. Moreover, some may have been advised to take their medication at home before admission, which would not be registered in the electronic patient chart. Still, there may have been patients withholding their medication, despite being defined as current users, and these patients may have driven the estimates towards the null if they were less likely to develop AKI due to the limited or absence of ACE-I/ARB effect on the day of surgery. (2) Potential misclassification of current users as former user due to redeemed medication for an interval greater than 90 days. However, this was addressed in a sensitivity analysis, and no clinically relevant difference in the results was found. (3) We could not consider the urine output–based definition of AKI. (4) Despite extensive adjustment for potential confounders including comorbidities and lifestyle factors, we cannot rule out that the lack of

difference in association for current and former users may be explained by residual confounding or by unmeasured confounding by indication[46] from the lack of data on blood pressure, fluid balance and administration, the timing of other postoperative complications and did only partly adjust for preoperative eGFR . For example, during anaesthesia, a lower mean arterial pressure (MAP) is accepted for healthy patients, whereas patients treated for hypertension are typically held at a MAP 5–10 mm Hg higher as well as for shorter periods due the potentially impaired autoregulation. On the other hand, ACE-I/ARB users potentially have even higher risk of AKI than found in this study, due to preventive actions taken based on the indication, which we were not able to adjust for. To address this further, we included a propensity score matched analysis and found no association.

Interpretation

The debate of whether ACE-I/ARB use is potentially harmful or beneficial on outcomes after non-cardiac surgery is ongoing, due to conflicting results.[14 47] The conflicting results may be due to the heterogeneity of the methodology across the studies. Some studies retrieved data on ACE-I/ARB use from redeemed prescriptions[18 41 42] while others used perioperative databases.[19 44] In addition, different definitions of AKI were used: dialysis within 14 days after surgery,[18] creatinine increase of 0.5 mg/dL,[45] AKIN,[44] RIFLE[43] and KDIGO.[41 42] Some studies have based the definition on creatinine measurements[41–45] and others on ICD-9[19] codes or ICD-10 codes,[18] which may have underestimated AKI risk.

Two studies of non-cardiac surgery have reported a reduced risk of AKI in patients with preoperative use of ACE-I/ARB (adjusted odds ratio (aOR) 0.68 (95% CI 0.57 to 0.82) and aRR 0.83 (95% CI 0.71 to 0.98)).[18 41] Shah *et al* conducted a large multicentre retrospective cohort study of 273 208 patients undergoing major elective surgery.[18] They defined AKI as the need for RRT within 14 days after surgery and use of ACE-I/ARB was defined as at least one prescription filled within 120 days before surgery. In a cohort study of 12 545 hypertensive patients undergoing non-cardiac surgery, Xu *et al* retrieved information on ACE-I/ARB use within the last 7 days before surgery from an electronic prescription system.[41] The short interval for identifying users may explain their lower prevalence of ACE-I/ARB use compared with our analyses. In line with their results (aOR 0.68; 95% CI 0.57 to 0.82 for hypertensive ACE-I/ARB users), we found a lower relative risk of AKI in current versus non-users in patients with hypertension than in patients without hypertension.

One study of major abdominal surgeries resembled ours regarding AKI and ACE-I/ARB definition.[42] This study also found an increased risk of AKI (aRR 1.20, 95% CI 1.16 to 1.23). The prevalence of current ACE-I/ARB users was 34%, comparable with the prevalence in our study.[41–43] In contrast, two studies found no association. These studies included non-cardiac surgery patients and examined whether the use of ACE-I/ARB on the day of surgery was associated with AKI, whereas our study investigated the risk of AKI associated with being a current or former user of ACE-I/ARB.

We believe our results are generalisable to other patients undergoing CRC surgery adhering to the enhanced recovery after surgery protocol or similar perioperative settings with an elderly population.

With the ageing population, the frequency of ACE-I/ARB use and the number of CRC surgeries are expected to rise. Around 20% of patients undergoing CRC surgery develop AKI within 7 days after the surgery,[5] and of these, approximately 30% are either under current or former treatment with ACE-I/ARB. Moreover, 25% of the patients who are current or former users develop AKI after CRC surgery. Thus, patients being users of ACE-I/ARB represent a group of patients undergoing CRC surgery at increased risk of AKI, and increased awareness of postoperative AKI among ACE-I/ARB users may be needed to modify the clinical course of AKI and potentially improving the prognosis for a considerable number of patients undergoing CRC surgery.

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