Colorectal Cancer Surgery and Acute Kidney Injury

A Review with Special Reference to
the Risk and Prognosis of Renin-Angiotensin System Blocker Use

PhD dissertation

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Thesis papers

I. Slagelse C, Gammelager H, Iversen LH, Sørensen HT and Christiansen CF. Acute kidney injury and one-year mortality after colorectal cancer surgery: A population-based cohort study. *Submitted.*

II. Slagelse C, Gammelager H, Iversen LH, Liu KD, Sørensen HT and Christiansen CF. ACE-I/ARB and the risk of acute kidney injury after colorectal cancer surgery: A population-based cohort study. *Submitted.*

III. Slagelse C, Gammelager H, Iversen LH, Liu KD, Sørensen HT and Christiansen CF. Renin-angiotensin system blockers and one-year mortality in patients with postoperative acute kidney injury. *Draft*

Abbreviations

ACE-I	Angiotensin-converting enzyme inhibitors
AKI	Acute Kidney Injury
AKIN	Acute Kidney Injury Network
aHR	Adjusted Hazard Ratio
aRR	Adjusted Relative Risk
ARB	Angiotensin-receptor Blocker
ASA	American Society of Anesthesiologists Score
BMI	Body Mass Index
BP	Blood Pressure
CCI	Charlson Comorbidity Index
CI	Confidence Interval
CKD	Chronic Kidney Disease
CKD-EPI	The CKD Epidemiology Collaboration (CKD-EPI) estimating equation
CRC	Colorectal Cancer
CRS	Danish Civil Registration System
DCCG.dk	Danish Colorectal Cancer Group
DNPR	Danish National Patient Registry
eGFR	Estimated Glomerular Filtration Rate
GFR	Glomerular Filtration Rate
HR	Hazard ratio

Abbreviations (continued)

ICU	Intensive Care Unit
KDIGO	Kidney Disease: Improving Global Outcomes
LABKA	The Clinical Laboratory Information System at Aarhus University
MDRD	The Modification of Diet in Renal Disease study equation
NHSPD	The National Health Service Prescription Database
NSAID	Non-steroidal Anti-inflammatory Drugs
RRT	Renal replacement therapy
PCr	Plasma creatinine
RR	Relative Risk
SCr	Serum creatinine

CONTENT

1. Introduction

Acute kidney injury (AKI), a sudden decline in the excretory function of the kidneys, is a frequent complication of major surgery and thus, constitutes a major and growing health issue.[1]

The occurrence of postoperative AKI has been reported in up to 35% of patients after major abdominal surgery and is associated with increased 30-day and one-year mortality.[2,3] Despite an annual increase in colorectal cancer (CRC) surgeries, high mortality, and risk of complications, little is known about the clinical course of AKI in patients undergoing CRC surgery.[4]

The aging population and the increasing number of patients with significant comorbidities (hypertension, heart disease, diabetes mellitus, and chronic kidney disease (CKD)) undergoing surgery have led to more CRC surgeries in patients with chronic conditions.[5,6] The result is a higher prevalence of CRC patients treated with angiotensin-converting enzyme inhibitors (ACE-Is) or angiotensin receptor blockers (ARBs), also known as *renin-angiotensin system blockers*, than in the overall Danish population.[7] Despite the potential nephrotoxicity of ACE-I/ARBs, it is unknown whether their use is associated with increased AKI risk or affects the prognosis for CRC surgery patients with postoperative AKI.

In this dissertation, we continue the ongoing Danish national effort to reduce and identify factors contributing to the worse survival of CRC patients in Denmark, compared with neighbouring countries, as observed in studies at the end of last century.[8–10] For this purpose, in the introductory study I, we assessed the impact of postoperative AKI on the prognosis of patients undergoing CRC surgery. Subsequently, in studies II and III, we examined whether, preoperative use of ACE-Is and/or ARBs affects the risk for and prognosis of AKI.

The thesis contains nine chapters, and the studies included in this dissertation are designated throughout the text as studies I–III.

In the introduction and background, we describe the epidemiology, definition, and pathophysiology of AKI and its association with ACE-I/ARBs in CRC surgery patients. The next three chapters describe the methods and results of studies I–III, followed by a discussion of our findings, methodological considerations, and perspectives. The last chapters of the dissertation contain summaries in Danish and English, as well as references and appendices, including the full versions of the three papers.

2. Background

2.1. The CRC surgery population

CRC is the third most common cancer in the world with an estimated global incidence of 1,360,000 cases annually as of 2012.[11] Two-thirds are diagnosed at an early disease stage without distant metastases (Union of International Cancer Classification stage II or III) in most high-income countries, whereas, Danish CRC patients are more often diagnosed with distant metastases.[12] At the end of the 20th century, survival during the first year after CRC surgery was inferior in Denmark when compared with neighboring countries, and leading to speculation that diagnosis at a later stage was the main contributing factor.[8–10] Patients with advanced CRC are likely to be older, undergoing emergency surgery and are more prone to developing postoperative complications such as anastomotic leakage and sepsis, which are all associated with an increased risk for postoperative AKI.[13–16]

With the aim of improving survival after CRC surgery, several initiatives were instituted including regularly updated national evidence-based CRC guidelines,[17] the establishment of the Danish Colorectal Cancer Group (DCCG).dk, and a national clinical quality database (DCCG database).[18] The Danish National Board of Health (DNBH) initiated "cancer packages" in 2000, and DCCG.dk became multidisciplinary in 2006. In 2010 DNBH introduced the 2-week waiting time guarantee. This suite of initiatives resulted in changes in stage- and disease-specific treatments, as well as national treatment guidelines, which may have played an important role in the increased one-year survival after diagnosis from 73% to 78% in colon cancer and from 78% to 83% in rectal cancer, observed during 2001–2012.[19] These one-year survival estimates approximate those of patients in other high-income countries (e.g., Australia, Canada, Norway, Sweden) today.[12]

The introduction of CRC screening in Denmark in March 2014 has led to earlier CRC detection, but CRC remains a disease predominantly of the elderly, with a median age at diagnosis of 72 years.[4,20] The decision regarding which treatment to initiate (surgery, chemotherapy, radiation, standard CRC immunotherapy drugs) is based largely on patient's condition and the CRC stage. Surgical removal of the primary tumor is still the cornerstone of CRC treatment and plays an important role even in palliative treatment where removal of the tumor is considered to avoid obstruction or tumor perforation.[17] Thus, CRC surgery is common and often performed in elderly patients. Elderly patients have a high prevalence of comorbidities such as hypertension, chronic obstructive pulmonary disease, heart disease, or diabetes mellitus, which can negatively affect outcome after CRC surgery.[19,21,22] CRC surgery incurs significant morbidity from postoperative medical (e.g., sepsis, heart disease, pneumonia) and surgical complications (e.g., anastomotic leakage, ileus, wound dehiscence) with up to 65% of patients developing complications within 30 days after surgery.[23–26] Thirty-day mortality in elective CRC surgery has declined from 7.3% in 2001 to 1.8% in 2011.[19] Mortality after CRC surgery seems to be associated with postoperative surgical (e.g., anastomotic leakage)

and medical complications (e.g., renal, cardiopulmonary, thromboembolic and infectious) and the introduction of laparoscopic surgery for colon cancer and total mesorectal excision for rectal cancer[16,19,27,28]

However, because of the aging population, the number of elderly patients with CRC will increase along with medical costs, and resources for treatment and postoperative surveillance of CRC. Therefore, identifying potentially modifiable risk factors for mortality in the CRC population can have major potential clinical implications.

2.2. Definition and staging of acute kidney injury

The kidneys are essential for maintaining overall health.[29,30] Through a highly complex feedback system, driven by the nervous and endocrine systems, the kidneys play a central role in maintaining fluid and electrolytes homeostasis. The feedback system allows the kidneys to do so despite significant and constant changes in requirements imposed by intake, extra-renal losses and other factors.[30]

The initial descriptions of what is known as AKI today were made in 1802, by William Heberden, who termed it *Ischuria renalis*.[31] Later, in the 1950s, it was renamed 'acute renal failure, and until about 10 years ago, there was no specific biochemical definition of ARF and no consensus on the diagnostic criteria or clinical definition of the syndrome. The result was that at least 35 definitions existed in the literature.[32] The initial guidelines for diagnosing and staging AKI were developed by the Acute Dialysis Quality Initiative group in 2004 (RIFLE criteria)[33] and followed by the Acute Kidney Injury Network (AKIN criteria)[34] in 2007. A combined set of criteria for AKI was suggested in 2012 by the Kidney Disease Improving Global Outcome (KDIGO) group criteria.

Table 2.1 Acute kidney injury staging according to the Kidney Disease Improving Global Outcomes (KDIGO) group criteria.

Stage	Serum creatinine	Urine Output
1	1.5–1.9 times baseline OR ≥ 0.3 mg/dl (≥26.5 μmol/L) increase	< 0.5 ml/kg/h for 6–12 hours
2	2.0–2.9 times baseline	< 0.5 ml/kg/h for ≥ 12 hours
3	3.0 times baseline OR Renal replacement therapy OR Increase in serum creatinine to ≥ 4.0mg/dl (≥353.6 μmol/L)[1]	< 0.3 ml/kg/h for ≥ 24 hours OR Anuria for ≥ 12 hours

[1]Given that the stage 1 criterion of ≥ 0.3 mg/dl (≥26.5 μmol/L) increase is met.

Identifying AKI from serum creatinine (SCr) measurements has its pitfalls. Muscle wasting from, for example, immobilization or malnourishment, reduces the concentration of SCr. Combined with AKI, SCr may thus seem to be within normal range, despite the presence of AKI. In the case of fluid overload, SCr may be artificially diluted. Finally, acute illness may reduce SCr production, further complicating SCr-based AKI analyses.

Baseline creatinine

Defining and classifying AKI poses the methodological issue of how to define baseline SCr. To diminish misclassification of AKI, several approaches have been proposed to identify the most accurate baseline SCr for the staging of AKI.[35–43] The consensus has been that if a measured preoperative SCr is available, then using that as baseline SCr is recommended.[13,33,35–41] If no preoperative SCr is available, then the KDIGO criteria suggest using the lowest in-hospital SCr as a reference; in the absence of that, then the baseline SCr, should be estimated from the Modification of Diet in Renal Disease (MDRD) study equation for estimating glomerular filtration rate is recommended, provided the patient does not have CKD.[13,33] When the MDRD is used, the baseline glomerular filtration rate (GFR) is set at 75ml/min/1.73 m^2 and commonly referred to as the MDRD-75. Bernier-Jean et al. compared MDRD, the CKD Epidemiology Collaboration (CKD-EPI) estimating equation, and the lowest SCr within 2 weeks after intensive care unit (ICU) admission and found that they all overestimated AKI compared to known preoperative SCr (Table 2.2), even in a population with a CKD prevalence of 16%.[37]

Table 2.2 Sensitivity and specificity of acute kidney injury defined by the use of different approaches to estimate baseline creatinine.[35–40,42,44]

	AKI	
Approaches to estimate baseline serum creatinine	**Sensitivity (%)**	**Specificity (%)**
First SCr at hospital admission	93[a]	
Mean SCr of the non-AKI population	63.5[c];78.7[b]	7.4
Multiple imputation	55-71[d]	91-97[d]
MDRD (fixed eGFR of 75ml/min/1.73 m^2)	57.7[c];75.1[b]	6.8
MDRD (age-adjusted; fixed eGFR of 75 ml/min/1.73 m^2)	85.5 [e];90.1[e]	97.8 [e]; 95.7[e]
CKD-EPI	94[a]	
CKD-EPI (age-adjusted; fixed eGFR of 75 ml/min/1.73 m^2)	81.8 [e]; 88.7[e]	98.2 [e];96.9[e]
MQ (age-adjusted; fixed eGFR of 75 ml/min/1.73 m^2)	74.3 [e]; 79.6[e]	98.4 [e]; 99.1[e]
Minimum SCr at more than 2 weeks after ICU admission	87%[a]	

[a] Reference is measured preoperative SCr in intensive care patients.
[b] Using 0.3mg/dL within 48hours from the KDIGO AKI criteria
[c] Using 1.5× baseline criteria from KDIGO AKI criteria.
[d] Compared to an assumed eGFR above 75ml/min/1.73 m^2
[e] Reference is a measured baseline SCr in surgical patients.
Abbreviations: Serum Creatinine, SCr; Estimated Glomerular Filtration Rate, eGFR; The CKD Epidemiology Collaboration estimating equation, CKD-EPI; Mayo Quadratic equation, MQ; Modification of Diet in Renal Disease study equation for eGFR, MDRD

In a retrospective cohort study of the Japanese population ages 18–80 years, Hatakeyama et al. compared mean SCr of the non-AKI population and MDRD-75 using measured baseline SCr as reference. They demonstrated more accuracy in AKI diagnosis when using the mean SCr of the non-AKI population

(sensitivity = 63.5–78.7%) as compared with MDRD-75 back-calculation with a fixed estimated GFR (eGFR) of 75ml/min/1.73 m^2 (sensitivity = 57.7–75.1%).[44] Kork and colleagues compared an age-adjusted and a 75ml/min/1.73 m^2 fixed creatinine version of MDRD, CKD-EPI, and the Mayo Quadratic equation in surgical patients.[35] They found that estimated baseline SCr overestimated the AKI prevalence but with sensitivities still ranging from 74.3% to 90.1%. In a cohort of hospitalized patients, Liu et al. found that inpatient SCr values were above 110% of outpatient SCr values in 22 % of the patients and, as expected, a higher percentage of the patients developed AKI.[43] Additionally, they found that patients with diabetes mellitus, hypertension, sepsis, and greater severity of illness were more likely to have a low first inpatient SCr, which poses a risk of underestimating AKI.[43]

In line with this finding, Siew et al. studied methods to estimate baseline SCr from outpatient SCr measurements and showed that the mean outpatient SCr (7–365 days before surgery) was the most appropriate method to identify baseline SCr.[40] In another study, Siew et al. validated the use of multiple imputation against a fixed eGFR of 75ml/min/1.73 m^2 showed a specificity of 91-97%.[42]

Urine output

Urine output measurements in patients outside ICU are often not reliable and/or not available. Therefore, urine output is often left out when staging AKI outside the ICU. Leaving out urine output may result in underestimation of AKI, but SCr is alone has a stronger association with mortality compared to urine output.[45,46]

2.3. Pathophysiology of AKI in CRC surgery

The etiology of AKI is complex, and the clinical courses are many. Loss of glomerular filtration is the unifying phenotype of the numerous syndromes that may cause AKI. Often AKI is multifactorial, and a number of pathophysiologic processes take place simultaneously and in sequence (e.g., endothelial dysfunction, dysfunctional microcirculation, tubular injury, venous congestion, and intrarenal inflammation).[47–51] Thus AKI may be a combination of prerenal, intrarenal, or postrenal causes and pathophysiologic processes, as well as a combination of these.[52]

During a drop in the systemic arterial pressure, the extent of kidney oxygenation will depend on the balance between the reduction in renal blood flow, the changes in GFR and sodium delivery to the renal tubule.[47] Paradoxically, evidence shows that the kidney is more sensitive than other organs to acute hypoxia and anemia, despite the excess renal blood flow and consequent high oxygen supply compared with the oxygen consumption.[53,54] This distinction may be explained by the low oxygen tension of the renal medulla.[47]

In CRC surgery, several patient- and procedure-related factors may contribute to the development of global hypoperfusion or dysfunctional intrarenal microcirculation, which may lead to AKI.[47,52] In fact, undergoing

major surgery, such as colon or rectal resections, introduces the risk of hypotension and reduced renal vascular resistance and renal blood flow at several stages of the admission, such as preoperative nil-by-mouth regimen, bowel preparation, intraoperative blood and intravascular fluid loss, extravasation of fluid from the vascular compartment (third-space effect), insensible losses, local/general anesthetics, vasopressor or diuretic administration, prolonged duration of surgery, and postoperative complications.[2,13,47,55,56] Hypotension, reduced renal vascular resistance, and renal blood flow may then decrease kidney perfusion and increase oxidative stress, endothelial dysfunction, inflammatory response, and tubular cell necrosis due to ischemia.[57]

Moreover, patient-related factors such as older age, female gender, African American race, hypertension, diabetes mellitus, chronic obstructive pulmonary disease, CKD, and medications may add to the development of AKI.[2,13,55] During a reduction in the systemic arterial pressure, the kidneys will respond with afferent arteriolar dilatation and efferent arteriolar constriction. Interestingly, ACE-I/ARBs inhibit efferent arteriolar constriction. In this situation, restoring blood pressure (BP) may thus be prevented by ACE-I/ARBs and BP may fall outside the autoregulatory range of the kidneys.[47]

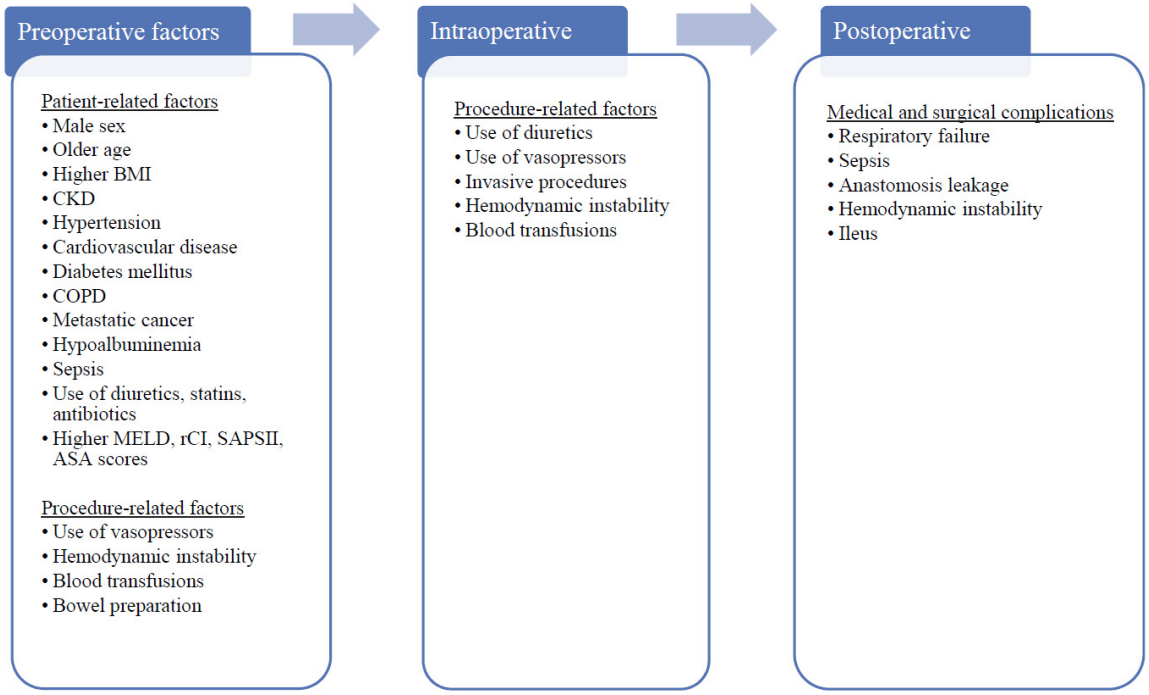
2.4. Risk factors for AKI after major abdominal surgery

The aging population, use of iodinated contrast for imaging and cardiovascular intervention, and the increasing prevalence of CKD and other comorbidities in hospitalized patients have all been identified as important contributors to the increasing global incidence of AKI.[58,59] Because no pharmacological treatment is available for AKI, identifying modifiable risk factors and factors affecting prognosis.

Studying risk in medicine relates to the probability that a disease will arise, whereas a risk factor is any attribute, characteristic, or exposure that increases the likelihood of an event (i.e., disease or injury).[60] Identifying risk factors for AKI is central for understanding and predicting it. Moreover, identifying modifiable and non-modifiable risk factors for AKI is paramount for reducing the occurrence of AKI by prevention and by improving early recognition of AKI through identification of at-risk patients. Hemodynamic instability before surgery is an example of a factor that increases AKI risk.

Knowledge of risk factors for AKI is important to develop preventive strategies to reduce postoperative AKI (Figure 2.3).

Figure 2.3 Shows known risk factors for postoperative acute kidney injury in major abdominal surgery.[3,13,66–68,51,55,58,61–65]



Abbreviations: American Society of Anesthesiologists Score, ASA; Body Mass Index, BMI; Chronic Kidney Disease, CKD; Chronic Obstructive Pulmonary disease, COPD;
Model For End-Stage Liver Disease, MELD, Non-steroidal Anti-inflammatory Drugs, NSAID; revised Cardiac Index, rCI; Simplified Acute Physiology Score II, SAPSII.

Patient-related risk factors such as preexisting CKD, male sex, older age, higher body mass index (BMI), hypertension, cardiovascular disease, diabetes mellitus, chronic obstructive pulmonary disease, metastatic cancer, diuretics, antibiotics, and statin use have been studied as potential risk factors for AKI.[3,13,69–75] Whether use of ACE-I/ARB is a risk factor for postoperative AKI, potentially through an increased risk of hypotension, has been discussed widely,[76–82] and the results are conflicting.[56,64,66,83–87] One large cohort study of patients after major surgery reported an increased risk of AKI with ACE-I/ARB use,[56] whereas two other cohort studies of patients undergoing major surgery[83,84] showed a reduced risk in ACE-I/ARB users. The ambiguous results may in part be explained by inconsistency in AKI staging and the definition of ACE-I/ARB exposure, as well as the varying surgical procedures included, but data are still not sufficient for conclusion on the question.[56,64,66,83–87]

Additionally, several procedure-related risk factors have been described and are shown in Figure 2.3.[71,72,88,89] Postoperative complications, such as anastomotic leakage, respiratory failure, and sepsis, have been reported to be associated with an increased rate of AKI.[90–93] They may affect the clinical course of AKI greatly, and at the same time, the development of AKI is associated with poor prognosis after postoperative complications.

Anastomotic leakage may lead to AKI by the development of peritonitis and then sepsis that causes loss of intravascular volume and consequently reduced kidney perfusion.

Reoperation for anastomotic leakage (as well as for ileus or fascial dehiscence) may also contribute to the postoperative stress response and increase AKI risk. In patients with respiratory failure, positive pressure ventilation may alter cardiac afterload, venous return, cardiac output, GFR, renal blood flow, and osmolar and water clearance.[94] Moreover, the hypoxia can result in decreased renal perfusion because of increased central venous pressure and induce kidney damage.[95] Respiratory failure also can decrease the activity of the renin–angiotensin–aldosterone system.[96] On the other hand, AKI arising from causes other than respiratory failure may also worsen the prognosis of respiratory failure because of an activation of apoptotic and pro-inflammatory pathways from renal ischemia and/or reperfusion.[97] Moreover, the decreased ability (during AKI) to excrete acid load and generate bicarbonate may add to the worsening prognosis of the patient with respiratory failure.

During anesthesia, arterial pressure is highly dependent on the renin–angiotensin or the vasopressin axis. Therefore, if a drug affecting either of these axes is administered (such as an ACE-I/ARB), there may be an increased risk of hypotension, which can lead to AKI.[98,99] In light of this, the zero fluid balance aimed for in fast-track (Enhanced Recovery After Surgery) patients may be too restrictive in users of ACE-I/ARBs by adding a factor that further hampers maintaining arterial pressure within the autoregulatory range of the kidneys.[23,24] Thus, restrictive fluid administration may act as an intermediate step, strengthening the association between ACE-I/ARB use and the supervening of postoperative AKI.[47,100]

Potentially nephrotoxic drugs are important and modifiable factors contributing to the supervening of AKI. Non-steroidal anti-inflammatory drugs (NSAIDs) have been shown to be safe in the perioperative period with careful patient selection, although attention should be paid to the potential nephrotoxicity during initiation of treatment.[101,102] Also, ACE-I/ARB, diuretics and NSAIDs in combination (“triple whammy”) have been suggested to increased risk of AKI.[103] Research on the role of ACE-I/ARB use in postoperative AKI is inconclusive.[2,79,87] ACE-I/ARB use may increase AKI risk through their inhibition of the angiotensin–renin–system, which in hypovolemic patients may hinder the vasoconstrictive counterbalancing effect of angiotensin II.

2.5. AKI and prognosis after CRC surgery

A risk factor can also be a prognostic factor. A prognostic factor is a factor that affects the course of a disease. Whether a factor is a risk factor, a prognostic factor, or both depends on which part of the exposure-disease-outcome association it represents. CKD is an example of a risk factor for AKI but is also a prognostic factor for death after AKI.

Studying the course of a disease over a specific time is called prognosis.[60] Prognosis is frequently related to specific outcomes (in this thesis, AKI or death) and reported as the probability that an outcome will develop over a particular period. It is common to divide studies of prognosis into 1) clinical prediction studies, aiming to predict the likelihood of an outcome based on a number of patient characteristics or 2) causal prognostic studies, also known as etiological prognostic studies, in which the impact of a specific exposure on the outcome is examined, as in studies I and III.

In this thesis, we examine the prognosis of patients with AKI after CRC surgery, as well as the prognosis of patients with AKI and use of ACE-I/ARBs.

Many factors, intermediate steps, may be involved in the causal pathway from AKI to mortality. In study I, AKI can progress to CKD as a result of persistent inflammation and increased pericyte-to-myofibroblasts (tubular injury) transformation leading to permanent scarring of renal structures and alterations in renal function.[104–107]Developing CKD is associated with increased long-term mortality, whereby CKD secondary to AKI acts as an intermediate step in the association between AKI and long-term mortality. Likewise, as intermediate steps, sepsis or respiratory failure secondary to AKI may worsen the clinical course of AKI and thus the prognosis. Consequently, depending on the study, a factor may be a risk factor, a prognostic factor, and/or an intermediate step.

The detrimental impact of AKI on outcomes during the first 30 days after surgery including increased mortality,[1,3,27,72,108,109] increased healthcare costs,[110] and longer length of hospital stay[56,72] has been shown in several studies.

The prognostic implications of AKI may vary within subgroups of CRC surgery patients. Variation across subgroups of an association between an exposure and an outcome is defined as “effect modification”.[111]Addressing effect modification may advance our knowledge of the clinical course of AKI in subgroups of CRC surgery patients. Identifying differences allows for more individualized estimation of prognosis in postoperative CRC surgery patients.

For these reasons, we examined if a potential association between 1) postoperative AKI and mortality after CRC surgery, or 2) ACE-I/ARB use and mortality in CRC surgery patients with postoperative AKI, varied across subgroups including CKD, age, sex, or urgency of surgery, by stratifying our analyses by these variables. CKD was chosen based on the increased risk of AKI and mortality in patients with preexisting CKD.[13] We stratified on age and gender because increasing age and male sex increase the risk of AKI. Emergency surgery increases the risk for AKI in some surgical populations.[3,27]

2.6. ACE-I /ARB and the risk and prognosis of AKI after CRC surgery

ACE-Is and ARBs are commonly prescribed in the treatment of heart disease, arterial hypertension, and prevention of diabetes mellitus and CKD complications. They have been on the market as an oral treatment since 1987 (ACE-I)[112] and 1991 (ARB).[113] Around 30% of the Danish population above 40 years were prescribed an ACE-I/ARB during 2016, and because the median age at initial CRC diagnosis is 72 years, the prevalence of ACE-I/ARB use is high in CRC patients.[7]

In hypertensive patients, without hypertensive complications, thiazides, calcium-channel blockers, ACE-Is or ARBs are equally indicated as first-line treatment.[114,115] Choosing an ACE-I/ARB requires electrolyte and creatinine monitoring. In addition, if BP rises to 160–79/100–109 mmHg, two of these should be combined, although an ACE-I in combination with an ARB should be avoided.

In chronic heart failure patients, ACE-I is indicated if ejection fraction is below 45%, regardless of New York Heart Association class.[114] If the use of ACE-I leads to side effects such as non-tolerated cough, an ARB is suggested as a replacement with the same effect. Moreover, ACE-I/ARBs are often recommended in the treatment of ischemic heart disease or atrial fibrillation.

In patients with diabetes mellitus, ACE-I or ARB is recommended to lower the BP below 135–140/80–85 mmHg. If the patient also has heart disease or micro-/macroalbuminuria, ACE-I or ARB treatment should be initiated even if the BP is normal.[114,116]

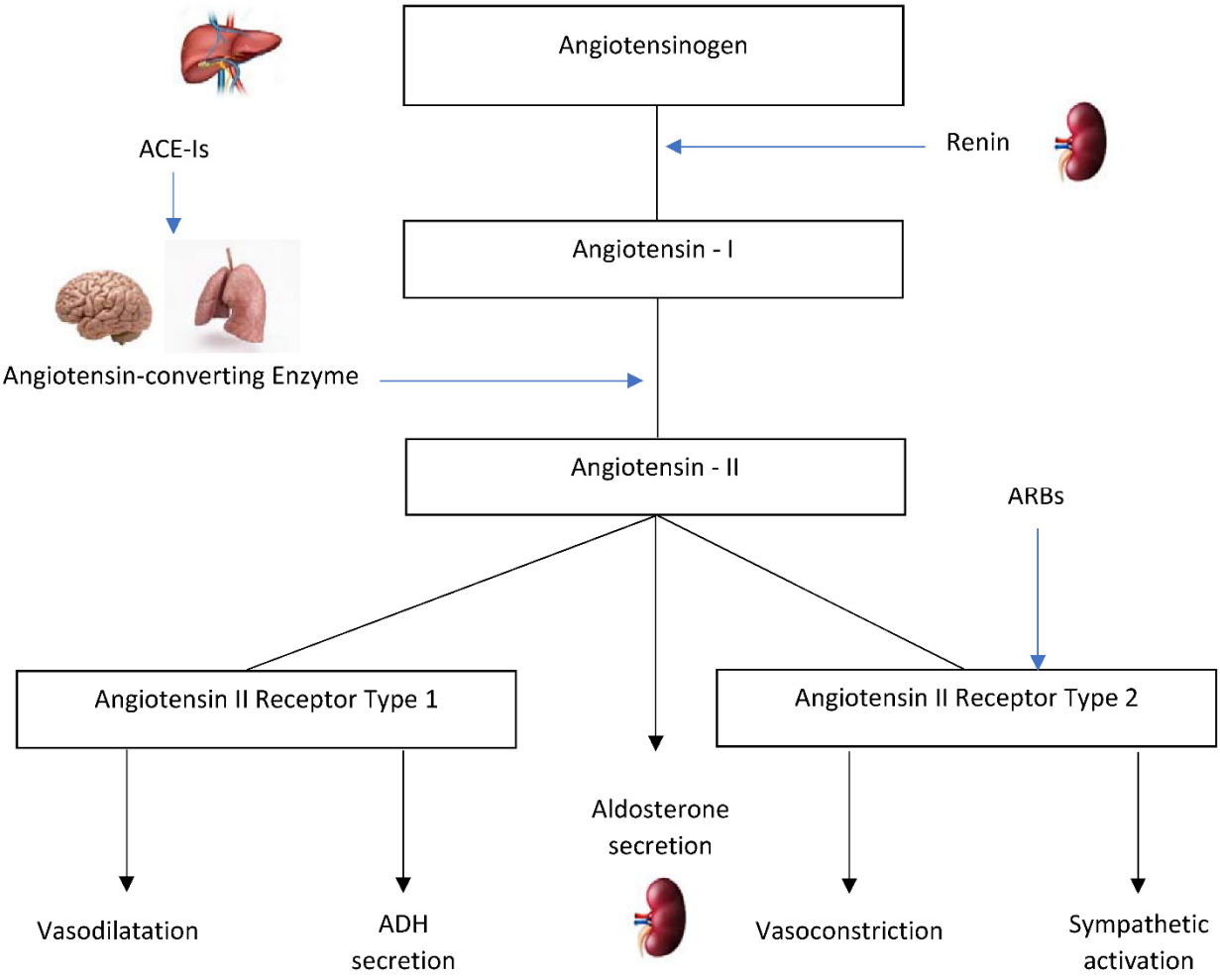
In CKD patients not on renal replacement therapy (RRT), an ACE-I/ARB is recommended if BP is >140/90 mmHg and urine albumin excretion is <30 mg/24h, or if BP >130/80 and urine albumin excretion is 30–300 mg/24 h, regardless of whether the patient has diabetes. In elderly CKD patients, the recommendation is to tailor the treatment regimen to the age, comorbidities, and other treatments of the patient and increase the dose gradually under careful consideration for electrolyte disorders, acute deterioration in kidney function, orthostatic hypotension, and drug side effects.[117]

The benefits of BP control with ACE-I/ARB (decreased risk of cardiovascular disease, as well as limit progression of heart failure, CKD and nephrotic complications of diabetes) commonly outweighs the potential side effects (cough, decrease cerebral perfusion, i.e., risk of dizziness, confusion, and falls).

In pharmacoepidemiology, such as studies II and III, where intended and unintended drug effects are studied, confounding by indication is an important phenomenon to consider as a potential source of bias. Confounding by indication refers to the fact that the underlying disease, disease severity and other risk factors for the outcome in question often differ between patients taking the drug and patients not taking the drug, as is reflected by the varying indications for ACE-I/ARB described above. [118]

ACE-Is block the effects of angiotensin II by inhibiting the conversion of angiotensin I to angiotensin II,[119] whereas ARBs exert their effects by blocking only the angiotensin II type 2 receptor (Figure 2.4).

Figure 2.4 The effect of angiotensin-converting enzyme inhibitors (ACE-I) and angiotensin receptor blockers (ARB) on the renin–angiotensin system.



Abbreviations: angiotensin-converting enzyme inhibitor, ACE-I and angiotensin receptor blocker, ARB; Antidiuretic hormone, ADH

The overall effect is vasodilatation without sympathetic activation, enhanced natriuresis, lowered BP, and prevention of smooth muscle and cardiac myocytes remodeling.[119] The overall renal effect of ACE-Is and ARBs is an increased renal blood flow and a decreased filtration pressure caused by a greater dilation of the efferent arteriole than of the afferent arteriole (Figure 2.4).[30]

The relationship between preoperative use of ACE-I/ARB and intra- or postoperative hypotension and the association with several postoperative complications has been studied in the non-cardiac surgery setting (e.g. cardiac complications, stroke, AKI and mortality). [86,120,121]

In a recent meta-analysis of thirteen cardiac or non-cardiac surgery studies, including three RCTs and ten observational studies,[87] preoperative use of ACE-I/ARBs was associated with hypotension during anesthesia (relative risk (RR) = 1.41; 95% confidence interval (CI): 1.21–1.64), but postoperative complications were not more common in hypotensive patients with preoperative ACE-I/ARB treatment compared with patients with ACE-I/ARB treatment (RR 1.25; 95% CI: 0.76–2.04).[87]

The use of ACE-Is/ARBs may in some cases lead to refractory hypotension during the administration of anesthesia.[122] Because of the inhibitory effect of anesthesia on sympathetic tone, maintenance of arterial pressure during surgery relies predominantly on the renin–angiotensin axis or the vasopressin axis. Thus, refractory hypotension may be a result of these systems being inhibited in the presence of an additional drug affecting either of them,[123] and medication withdrawal would be expected to result in reduced hypotensive episodes.[2,124–126]

The venodilatation produced by the decreased sympathetic tone of anesthesia, may, in combination with the increased renal perfusion and decreased GFR from ACE-I/ARB cause the intravascular volume to pool in the blood vessels. This pooling can result in decreased cardiac filling resulting in a decreased cardiac output, which in turn can induce insufficient renal hypoperfusion and AKI.[127]

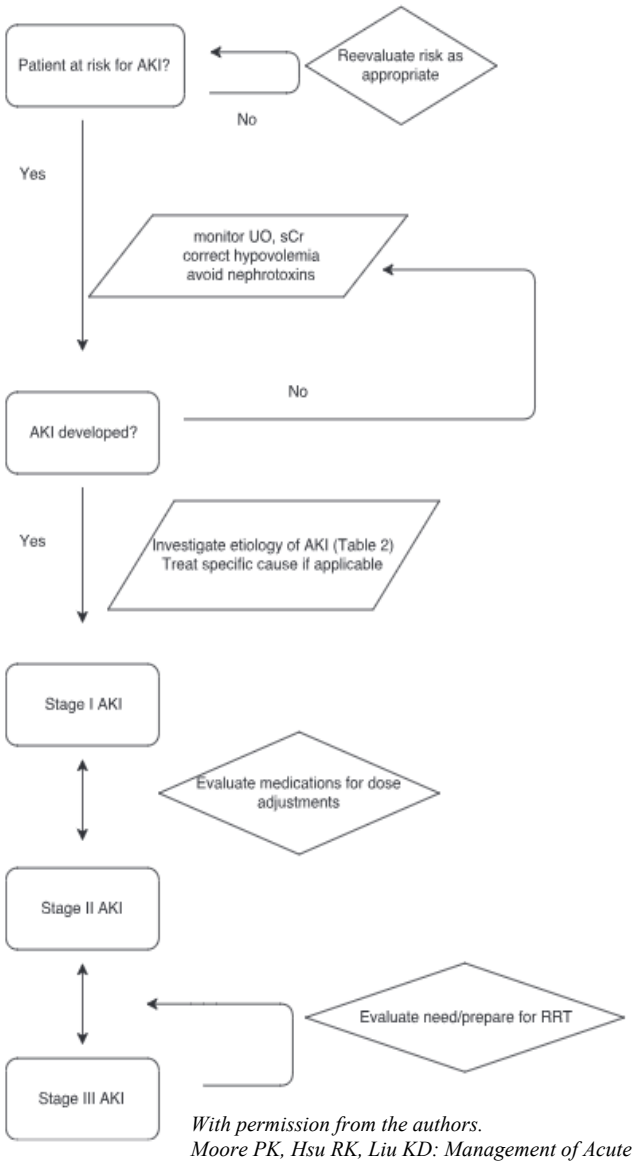
Therefore, in the operative setting, ACE-I/ARB use could result in an increased risk of functional AKI (e.g., GFR decrease) through inhibition of the constrictive effect of angiotensin II on the efferent arteriole. At the same time, the inhibition of angiotensin II could reduce the risk for "true" postoperative AKI (e.g., true tubular injury) by inhibiting 1) the reduction in renal blood flow and 2) the increase in oxidative stress, endothelial dysfunction, inflammatory response, and renal vascular resistance. Thus improving renal tubule perfusion and oxygenation, might potentially prevent tubular cell death during ischemic insults.[78,126,128–131]

2.7. Treatment and monitoring of AKI

No pharmacological agent is available for the treatment of AKI, and because of its multifactorial origin, finding a single therapy is highly challenging. Several trials are ongoing, including trials focusing on sepsis-associated AKI (alkaline phosphatase, L-carnitine), postoperative AKI (remote ischemic preconditioning), and on post-cardiac surgery AKI (p53-targeted siRNA).[52] In the absence of an existing treatment, prevention is crucial, and management of AKI requires prompt work-up to identify the underlying cause, specifically focusing on reversible factors (Figure 2.5). Preventing AKI requires attention to volume status and electrolyte homeostasis, and potential nephrotoxic medication or harmful procedures should be avoided. Because of the reduced GFR, AKI patients are at risk of developing hyperkalemia, metabolic acidosis, volume overload or symptoms of uremia.

Even when these consequences of a reduced GFR are medically managed, there may ultimately be a need for RRT.

Figure 2.5 Treatment and monitoring of acute kidney injury.[52]



With permission from the authors.
Moore PK, Hsu RK, Liu KD: Management of Acute Kidney Injury: Core Curriculum 2018. Am. J. Kidney Dis. [Internet] 2018 Available from: http://dx.doi.org/10.1053/j.ajkd.2017.11.021

Abbreviations: Acute Kidney Injury, AKI; Urine Output,UO; Renal Replacement Therapy, RRT

2.8. Literature review

The following two sections comprises a thorough literature review of the studies included in this thesis. The first section describes the literature search for study I, the limitations, and the results of the existing literature. In the second section, a combined search for studies II and III is described, followed by a review of the limitations and results of the existing literature.

2.8.1. AKI and mortality after CRC surgery (study I)

In the literature search, we focused on studies examining the occurrence and prognostic impact of AKI after major colorectal surgery. The risk of AKI has been shown to vary widely across procedure type for gastrointestinal surgery.[3] Therefore, we decided to include only studies with a population and procedures included that resemble that of CRC surgery patients (e.g., colorectal surgery, CRC surgery or studies reporting results for colorectal surgery separately).

We used the following query to search MEDLINE (last search August 29th, 2018):

((surgery, colorectal[MeSH Terms]) OR abdominal surgery[Title/Abstract] OR major surgery[Title/Abstract]) AND ("acute kidney injury"[MeSH Major Topic] OR "renal insufficiency"[MeSH Major Topic])).

We limited the search to English or Danish language articles and studies conducted in humans, which resulted in 227 hits. After title review, 40 were found to be of relevance. Among these, 19 were excluded after title and abstract review because of irrelevant aims such as diagnostic tests or irrelevant population (i.e., children, intensive care patients, or procedures other than abdominal). Twenty-one were selected for full article review. One study examined the risk of AKI and mortality associated with AKI in patients undergoing CRC surgery,[132] and two studies focused on patients undergoing colorectal resections.[1,133] One additional study of patients undergoing CRC surgery[108] and three studies of patients undergoing colorectal surgery were identified by cross-references of these articles and review articles.[3,72,109] Furthermore, one study of CRC patients was known before the search, because it was a publication by one of the co-authors of studies I–III.[27] The eight studies of colorectal or CRC surgery patients are summarized in Table 2.6.[1,3,27,72,108,109,132–134] The occurrence of AKI varied widely among the included studies, and six of the studies reported on mortality[1,3,27,72,108,133] in patients with AKI.

Limitations

AKI was not the primary outcome in two of the CRC-specific studies,[27,132] and one of the colorectal surgery studies[109] and none of these studies followed any of the suggested classification systems (AKIN, RIFLE, KDIGO) for staging AKI.[13,33,34] Iversen et al. reported crude mortality and did not provide a specific relative measure of mortality in patients requiring RRT compared to patients without the need for RRT.[27] Therefore, their results on the association between RRT and 30-day mortality may suffer from confounding. Six studies

did not follow any of the known guidelines for diagnosis and staging of AKI and their results, and thus may not be generalizable to all AKI CRC surgery or colorectal resection patients.[3,27,109,132,133,135] Three studies included only the most severe stage of AKI,[3,27,135], and another two applied an overall definition for AKI but no staging, and the last one did not provide a definition.[133]

Thus, when comparing the results of the association between AKI and mortality across the existing literature, the risk of under- or overestimating the overall occurrence of AKI must be taken into consideration. Overestimating AKI will cause a weakening of the association between AKI and mortality if the patients who are misclassified with AKI are less likely to die than those who are correctly classified as AKI patients. Likewise, underestimating AKI would weaken the association between AKI and mortality if the patients misclassified into the category of patients without AKI were more likely to die.

The majority of the studies included a population with a lower mean or median age than the median age at CRC diagnosis. Moreover, in two out of eight studies, it was not possible to identify the AKI-associated postoperative mortality of colorectal or colorectal cancer patients[132,133], but estimates pooled into "major surgical procedures",[3] "gastrointestinal surgery",[71] "GI abdominal",[56] and "general surgery"[64,66]. Most of the studies were single center studies, and there were no randomized clinical trials.

Background and summary

Cohort studies of AKI after CRC surgery or colorectal resections report that AKI occurs in up to 11.8 % of patients during the first 30 days after surgery (Table 2.6). [1,3,27,72,108,109,132–135] In-hospital and 30-day mortality in patients with AKI after undergoing CRC surgery or colorectal resections was higher than in patients without AKI (up 68.2%, depending on the urgency of surgery and the severity of AKI).[1,3,27,56,64,108,109] Developing postoperative AKI is associated with elevated 30-day mortality and in-hospital mortality, except in a study by Alves et. al[109] where mortality was slightly lower in the AKI group (Table 2.6). Even after taking into account potential confounders, 30-day mortality was associated with an adjusted RR of 2.01 (95 % CI: 1.79–2.25, $AKI_{mortality}$ = 28.9%, non-$AKI_{mortality}$ = 2.9%) and seemed to increase with increasing stage of AKI.[1,3] In conclusion, the findings of the seven studies examining the association between AKI and mortality show that in-hospital and 30-day mortality is higher in patients with AKI. The results are ambiguous with regard to association between AKI (and stage of AKI) and one-year mortality. No studies on CRC surgery that include all stages of AKI and examine mortality up to a year after surgery have been performed.

Table 2.6. Studies of postoperative acute kidney injury and mortality in patients undergoing colorectal cancer surgery or colorectal resections (Study I).

First Author\ Year	Design/ Country	Study Population	AKI Definition	Occurrence of Postoperative AKI (%)	AKI-associated Mortality (95% CI)
Alves A. 2002[109]	Single center, cohort study, France	707 colonic or rectal resections during 1990–1997.	SCr 110 mol/L; uremia serum level 7 mmol/L	9.3	Without AKI: 2.3%[a] AKI: 1.5%
Causey M. 2011[72]	Single center cohort study, USA	339 medical records from colorectal surgeries during 2001-2009, patients ≥18 years	>50% rise in SCr	11.8	Without AKI: 0.9%[a] AKI: 6.3% P=0.065
Lim S. 2016[67]	Single center, cohort study, Korea	288 medical records from elective rectal cancer open/robot/laparoscopic surgeries during 2011–2013, patients ≥18 years	AKIN	3.8	Without AKI: 0%[a] AKI: 18.2% P = 0.001
Li L. 2017[132]	Single center, cohort study, USA	619 patients (primarily male) undergoing CRC surgery at a tertiary referral institution during 2005–2011.Veterans Affairs electronic medical records	Readmission because of any increase in SCr	4.0[b]	-
Iversen LH. 2008[27]	Multi center cohort study, Denmark	2,157 patients who underwent emergency major surgery for CRC during 2001–2005 were identified in the national Danish Colorectal Cancer Group database	RRT	2.0	Without AKI:8.5 %[d] AKI: 68.2%
Kim M. 2014[3e]	Multi center, cohort study, USA	457,656 records (102,503 colorectal resections) during 2005–2010, American College of Surgeons National Surgical Quality Improvement Program (ACS-NSQIP) database	RRT or ≥2mg/dL increase from preoperative value	1.8	Without AKI: 2.9% [de] AKI: 28.9% aRR 2.01 (1.79–2.25)
Masoomi H. 2012[133]	Cohort study, USA	975,825 patients undergoing colorectal resection during 2006–2008.	-	10.8	-
O'Connor M. 2017[1e]	Single center, cohort study, UK	1,869 patients undergoing elective major non-cardiac surgery in the Royal London Hospital main operating theatre suite between 14 January 2013 –30 June 2014	KDIGO	5.7	In-hospital mortality[f]: Without AKI: 0.9% AKI: 13.3% 1-year mortality: aRR 1.25 (0.58–2.71) Without AKI: 6.1% AKI: 26.6%

Abbreviations: Acute Kidney Injury Network, AKIN; adjusted Relative Risk, aRR; Kidney Disease Improving Global Outcomes, KDIGO; Renal Replacement Therapy, RRT; Serum Creatinine, SCr.
[a] In-hospital mortality
[b] Frequency corresponds to patients with ileostomy who were readmitted due to AKI
[c] No absolute estimates
[d] 30-day mortality
[e] Results are given for colorectal surgeries.
[f] P <0.001 no 95% CI given. AKI stage not associated with mortality.

2.8.2. ACE-I/ARB and the risk for and prognosis of AKI after CRC surgery (studies II/III)

In the literature search for studies II and III, we focused on:

1) Studies examining the impact of preoperative use of ACE-I/ARBs on the risk of postoperative AKI in patients undergoing CRC surgery (study II).
2) Studies examining the impact of preoperative use of ACE-I/ARBs on prognosis after AKI in postoperative CRC patients (study III).

We used the following two queries to search MEDLINE (last search August 29, 2018):

#1 (((((((ACE[Title]) OR ARB[Title]) OR angiotensin converting enzyme inhibitor[Title]) OR angiotensin receptor blocker[Title]) OR RAAS[Title]) OR RAA[Title]) OR renin angiotensin aldosterone system antagonists[Title]) AND acute kidney injury[MeSH Terms])

#2 (surgery[Title]) AND Surgery and angiotensin converting enzyme inhibitors[Title]

We limited the search to English or Danish language articles and studies conducted in humans, which resulted in 101 hits (search #1;72 hits, #2:31 hits). After title review, we found no studies of patients undergoing CRC. Therefore, we decided to expand the inclusion to major surgery because CRC surgeries are extensive procedures involving a high mortality rate.[3] We did not include cardiac surgery because the hemodynamic alterations that occur during cardiac surgery and the population may vary widely from CRC surgery with regard to AKI risk.[136] Seven articles from search #1 and six articles from search #2 were found to be of relevance. Among these, four studies were excluded after title and abstract review because the study population was intensive care patients only. Ten studies were selected for full article review. Three studies examined the risk and postoperative mortality associated with use of ACE-I/ARBs in patients with AKI after non-cardiac surgery.[84,85,137] A further six studies were identified by cross references of these articles and review articles.[56,64,83,86,88,138] The eight studies of the risk of postoperative AKI in ACE-I/ARB users undergoing non-cardiac or major abdominal surgery (study II) are summarized in Table 2.7.[56,64,66,83–86,137] The six studies reporting on mortality within the first year after non-cardiac surgery in users of ACE-I/ARB (study III) are summarized in Table 2.8.[56,83–85,137,138]

Study II

Background

Use of ACE-I/ARBs and the risk for AKI and postoperative mortality after non-cardiac surgery have been widely debated and the ongoing discussion is a result of the mixed evidence base.[80,81,87,139–141] US guidelines

suggest continuation of ACE-I/ARB for non-cardiac surgery,[142] whereas Canadian guidelines recommend withholding ACE-I/ARB for 24hours before the surgery.[143] In line with the Canadian guideline, European guidelines advise withholding ACE-I/ARB 24hours before surgery in patients treated with ACE-I/ARB mainly for hypertension and to continue if treated for heart failure.[144]

Limitations

A clear definition of the exposure "use of ACE-I/ARB" lacked in five studies, which may explain the variations in ACE-I/ARB prevalence and in the risk of AKI associated with ACE-I/ARB use.[56,64,66,83,85,138] Moreover, some studies did not define AKI according to any of the known guidelines, potentially causing information bias.[84,86,122] Two studies included only hypertensive patients undergoing non-cardiac surgery. This inclusion may improve internal validity but can limit the generalizability of their results to hypertensive CRC patients.[83,86]

Summary

Several large cohort studies have examined the prevalence of ACE-I/ARB use and the risk of AKI in patients undergoing non-cardiac surgery. [56,64,66,83,85,122] ACE-I/ARB prevalence is reported to be from 12.5% to 34% [56,64,66,83,85,122] and the occurrence of AKI in patients with use of ACE-I/ARB before major or non-cardiac surgery varies from 1.2% to 7.4%.[64,83,85,122] ACE-I/ARB use was associated with a decreased risk of AKI showing an adjusted RR of 0.83 (95% CI: 0.71–0.98) in one study,[84] an increased risk of AKI in another study (aRR 1.20; 95 % CI: 0.71–0.98]), and no association in a third study with an adjusted odds ratio (aOR) of 1.21 (95 % CI: 0.84-1.72). In conclusion, the results are conflicting, and studies including CRC surgery patients are lacking.

Table 2.7. Risk of postoperative acute kidney injury in users of ACE-I/ARB after non-cardiac surgery (study II)

First Author\ Year	Design/ Country	Study Population	AKI and ACE-I/ARB Definition	ACE-I/ARB Clinical Practice	ACE-I/ARB Prevalence (%)	Association of ACE-I/ARB use with Postoperative AKI (95% CI)
STARSurg[137] 2018	Multicenter, cohort study, UK, Ireland	949 patients undergoing elective gastrointestinal or liver surgery during September 23 and November 18 2015	KDIGO ACE-I/ARB from drug chart, 1 dose within 7 days before surgery	Withheld likely due to clinically evaluated at AKI risk	NA	Non-users 18.1% Users 18.7% aOR 0.89 (0.58–1.34)
Xu N.[83] 2018	Cohort study, China	12,545 hypertensive patients undergoing non-cardiac surgery during 2007–2015.	KDIGO ACE-I/ARB from electronic prescription system. Within 7 days before surgery,	No info of meds on day of surgery	18.8	Non-users 12.3% Users 7.4% aOR 0.68 (0.57–0.82)
Grams ME.[56] 2016	Single center, cohort study, USA	161,185 major surgery hospitalizations during 2004–2011. Including 44597 major abdominal surgeries.	KDIGO ACE-I/ARB pharmacy dispensation records in the 3 months prior to surgery	-	34.0	aRR 1.20 (1.16–1.23)[a]
Sun LY.[88] 2015	Single center, cohort study, Canada	5,127 patients undergoing elective non-cardiac surgery during 2009-2012.	AKIN ACE-I/ARB from hospital electronic databases	Continue/withhold info in database	16.4	Non-user 5.7% User 9.2% aOR 1.21 (0.84–1.72)
Shah M.[84] 2014	Cohort study, Canada	237,208 patients undergoing major elective surgery in 118 hospitals during 1995–2010.	RRT <14 days after surgery. ICD-codes. Filled at least one prescription for an ACE-I/ARB in the 120 days prior to surgery	-	43.0	Non-users 0.3% Users 0. 4% aRR 0.83 (0.71–0.98)
Biteker M.[64] 2014	Single center, cohort study, Turkey	1,200 consecutive patients undergoing non-cardiothoracic, non-vascular surgery during 2010–2012.	RIFLE Recorded ACE-I/ARB use on admission.	No standard practice.	32.0	Non-user 6.1% User 8.1% p-value 0.22
Turan A.[85] 2012	Cohort study, USA	79,228 patients undergoing non-cardiac surgery during 2005-2009.	ICD-9 codes ACE-I/ARB from perioperative health documentation system	Routinely instruct no ACE-I on the day of surgery	12.5	Non-users 1.5% Users 1.6%[b]
Comfere T. [86] 2005	Single center, Cohort study, USA	267 outpatient/ elective hypertensive Patients undergoing surgery between July 2003 and September 2003.	Postoperative creatinine increase of 0.5 mg/dl ACE-I/ARB therapy for at least 3 months with admission preoperative	No standard of care, anesthesiologists blinded to enrollment	ACE-I 70.0 ARB 50.0	Non-user 2.4% User 0%[d]

[a] Mortality period unspecified
[b] 30-day mortality
Abbreviations: Acute Kidney Injury Network, AKIN; Adjusted Odds Ratio, aOR; Adjusted Relative Risk, aRR; Angiotensin-converting enzyme inhibitors, ACE-I; Angiotensin receptor blockers, ARB; International Classification of Diseases, ICD-10; Kidney Disease Improving Global Outcomes, KDIGO; Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease, RIFLE, Renal Replacement Therapy, RRT.

Study III

Limitations

We were unable to identify any studies examining ACE-I/ARB use and mortality in patients with AKI after CRC surgery, non-cardiac surgery, major surgery patients or major abdominal surgery patients.

We did though identify two studies of ICU patients, reporting on the association between ACE-I/ARB and mortality in patients with AKI, but the populations were not comparable to ours.[145,146] Neither of the studies gave results for surgical patients separately. Gayat et al. reported a reduced one-year mortality (aHR 0.47; 95% CI: 0.27–0.82) in ICU patients treated with mechanical ventilation or vasopressors and an ACE-I/ARB prescription at discharge.[145] In contrast, Wang and colleagues did not find an association between ACE-I/ARB use versus non-use and 90-day mortality (aHR 0.78; 95% CI: 0.51–1.21) in patients undergoing RRT at the ICU.[146]

Therefore, the comparison with the existing literature is limited to studies examining ACE-I/ARB use and mortality after surgery as background for study III.

The results of the study by Roshanov et al. are limited by the lack of control for age and comorbidities.[138] Moreover, a definition for ACE-I/ARB was not provided by Grams et al.[56] In the STARSurg collaborative study, only a P-value, and no CI was given for the association between ACE-I/ARB use and mortality.

Summary

Two studies found a protective effect (aHR 0.91; 95% CI: 0.87–0.95 and aRR 0.82; 95 % CI: 0.70–0.96) of ACE-I/ARB use on mortality.[84,138] One study found that use of ACE-I/ARB was associated with increased postoperative mortality (aRR 1.20 95% CI: 1.16-1.23), and another three found no association.[83,85,137] In conclusion, results are conflicting, and no overall conclusion on the direction of the estimates can be made. Patients with postoperative AKI have increased postoperative mortality compared to patients without AKI. Therefore, it is important to recognize if patients with AKI and ACE-I/ARB use are at higher risk of mortality compared to patients without AKI because ACE-I/ARB use may be a risk factor for AKI that is modifiable.

Table 2.8. Mortality associated with use of ACE-I/ARB in patients with AKI after surgery (study III)

First Author\ Year	Design/ Country	Study Population	ACE-I/ARB Definition	ACE-I/ARB associated Mortality (95% CI)	ACE-I/ARB Prevalence (%)
STARSurg[137] 2018	Multicenter, cohort study, UK, Ireland	949 patients undergoing elective gastrointestinal or liver surgery during September 23 and November 18 2015	ACE-I/ARB from drug chart, 1 dose within 7 days before surgery	P = 0.87	NA
Xu N.[83] 2018	Cohort study, China	12,545 hypertensive patients undergoing non-cardiac surgery during 2007–2015.	ACE-I/ARB from electronic prescription system. Within 7days before surgery	aOR 0.88 (0.32–2.45)[a]	18.8
Grams ME.[56] 2016	Cohort study, USA	161,185 major surgery hospitalizations during 2004–2011. Including 44597 major abdominal surgeries.	-	aRR, 1.20 (1.16–1.23][b]	34.0
Shah M.[84] 2014	Cohort study, Canada	237,208 patients undergoing major elective surgery in 118 hospitals during 1995–2010.	Filled at least one prescription for an ACE-I/ARB in the 120 days prior to surgery.	aHR 0.91 (0.87–0.95)[c]	43.0
Turan A.[85] 2012	Cohort study, USA	79,228 patients undergoing non-cardiac surgery during 2005–2009.	ICD-9 codes	OR 0.93 (0.73–1.19)[d]	12.5
Roshanov PS.[138] 2017	Cohort study, 8 countries	14,687 patients at least 45 years old who had in-patient non-cardiac surgery 2007–2011.	Interview of medical history	aRR 0.82 (0.70–0.96)[e]	32.7

[a] all-cause mortality, period unspecified
[b] mortality period unspecified
[c] all-cause mortality within 90 days of surgery
[d] 30-day mortality
[e] 30-day all-cause death
Abbreviations: Acute Kidney Injury Network, AKIN; Adjusted Odds Ratio, aOR; Adjusted Relative Risk, aRR; Angiotensin-converting enzyme inhibitors, ACE-I; Angiotensin receptor blockers, ARB; International Classification of Diseases, ICD-10; Kidney Disease Improving Global Outcomes, KDIGO; Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease, RIFLE, Renal Replacement Therapy, RRT.

2.9. Hypothesis and Aims

Study I:

Hypothesis: Postoperative AKI in patients undergoing CRC surgery is common and associated with increased mortality within the first year after surgery

Aim: To examine the occurrence and prognostic impact of postoperative AKI after CRC surgery

Study II:

Hypothesis: ACE-I/ARB use is associated with increased risk of postoperative AKI.

Aim: To examine the impact of preoperative use of ACE-I/ARB use on the postoperative risk of AKI in patients undergoing CRC surgery

Study III:

Hypothesis: ACE-I/ARB use is associated with increased mortality within the first year after CRC surgery in patients with postoperative AKI.

Aim: To examine the impact of preoperative use of ACE-I/ARBs on prognosis after AKI in postoperative CRC patients.

3. Methods

The following sections offer a description of the methods used in studies I, II, and III.

3.1. Setting

The studies included in this thesis were conducted in the Central Denmark Region and the North Denmark Region. These regions include approximately 2 million residents. As part of the Danish population, these residents are provided with tax-supported medical care and partial or full reimbursement of most prescription medicine by the Danish National Health Service.[147,148]

3.2. Data sources

Studies I, II, and III are based on individual-level linkage of medical and administrative databases using the unique Civil Registration number assigned to all Danish citizens at birth or immigration. The studies are registered as DCCG database projects.

The Danish CRC Group (DCCG.dk) Database

The database includes information on all Danish CRC surgery patients registered since May 2001. The purpose of the database is to monitor and improve clinical quality. It describes, among other, patient demographics, lifestyle factors, treatments, complications within 30 days after surgery, and mortality. Information regarding RRT-requiring AKI has been registered since 2005.[18] The patient completeness of the database is 98-99 %.

The Civil Registration System (CRS)

The CRS assigns a unique 10-digit civil registration number to all Danish residents at birth or immigration. The CRS holds information on all changes in vital status and migration for the Danish population since 1968. The database is electronically updated daily.[149]

The Danish National Patient Registry (DNPR)

The registry is nationwide and was established in 1977, including information on all Danish hospital contacts, outpatient visits since 1994, and emergency room visits since 1995. Data include: hospital, department, discharge diagnosis, surgical and diagnostic procedures and treatments such as RRT.[150]

The Clinical Laboratory Information System at Aarhus University (LABKA)

The database includes data on all laboratory results since 1997 from blood samples collected from general practice and hospitals analyzed at the hospital laboratories in Aarhus County and North Jutland County (North and Central Denmark Regions).[151] Two of the hospitals included in the database did not have

acceptable completeness registration until January 2006 and 2009. Therefore, patients undergoing surgery at these hospitals were included only after data availability of 90% or higher was reached because data availability was 90% or higher for most hospitals.

National Health Service Prescription Database (NHSPD)

The NHSPD, formerly called "The Danish National Database of Reimbursed Prescriptions", contains records for all reimbursable drugs dispensed in community pharmacies in Denmark since 2004. It does not include information on drugs dispensed during a hospital stay or directly at outpatient clinics. It includes patient details, dispensing details (e.g., product ATC code, no. packets, and trade name, strength, amount dispersed), prescriber details, and pharmacy details. The database records data from approximately 3.5 million users annually. In Denmark ACE-I/ARB, beta-blockers, antibiotics, diuretics, nitrates and statins are available only by prescription.[148]

3.3. Study designs

The three studies included in this thesis (studies I, II, and III) were conducted as historical cohort studies based on prospectively registered data. In study I, the exposure, AKI, was identified within the first 7 days after CRC surgery and patients were followed for up to a year after surgery to determine the outcome, mortality. In study II CRC patients were identified as exposed (ACE-I/ARB current or former use) or non-exposed (non-users of ACE-I/ARB) and followed to determine the outcome, which was AKI within 7 days after CRC surgery. In study III patients with AKI within 7 days after CRC surgery were identified as exposed (ACE-I/ARB current or former use) or non-exposed (non-users of ACE-I/ARB) and followed from the day of AKI to determine the outcome, mortality within a year after AKI.

Studies I-III are prognostic etiological studies.[60,152] In etiological studies, the aim is to explain if an outcome can be attributed to a specific risk factor while adjusting for potential confounders (causal factors) using a multivariable approach. Prognostic studies can be prognostic course studies, prognostic factor (explanatory) studies, or an outcome prediction (risk group) study. The purpose of prognostic studies is to provide patients and their doctors with information about the future course/risk of a disease, to guide in decision-making. [153]

The study periods for all studies were chosen based on availability of plasma creatinine in LABKA at the time of intiation.

3.4. Study populations

All studies

We included all patients who underwent first time CRC surgery January 1, 2005 to December 31, 2011 in study I and January 1, 2005 to December 31, 2014 in studies II and III. Patients were identified in the DCCG

database. To ensure availability of baseline laboratory data, we required residency in the study area a year before surgery. In some hospitals, reporting to LABKA was initiated at a later. Thus, to achieve data completeness of 90% or higher, patients undergoing surgery were included only after 2005 for one hospital and after 2009 at the another hospital. [151] Moreover, patients with RRT within 30 days before surgery were excluded in all studies.

Study I

Patients who died within 7 days after surgery were excluded from study I.

Study III

In study III, we restricted the analyses to patients with AKI within 7 days after CRC surgery.

3.5. Exposures

AKI

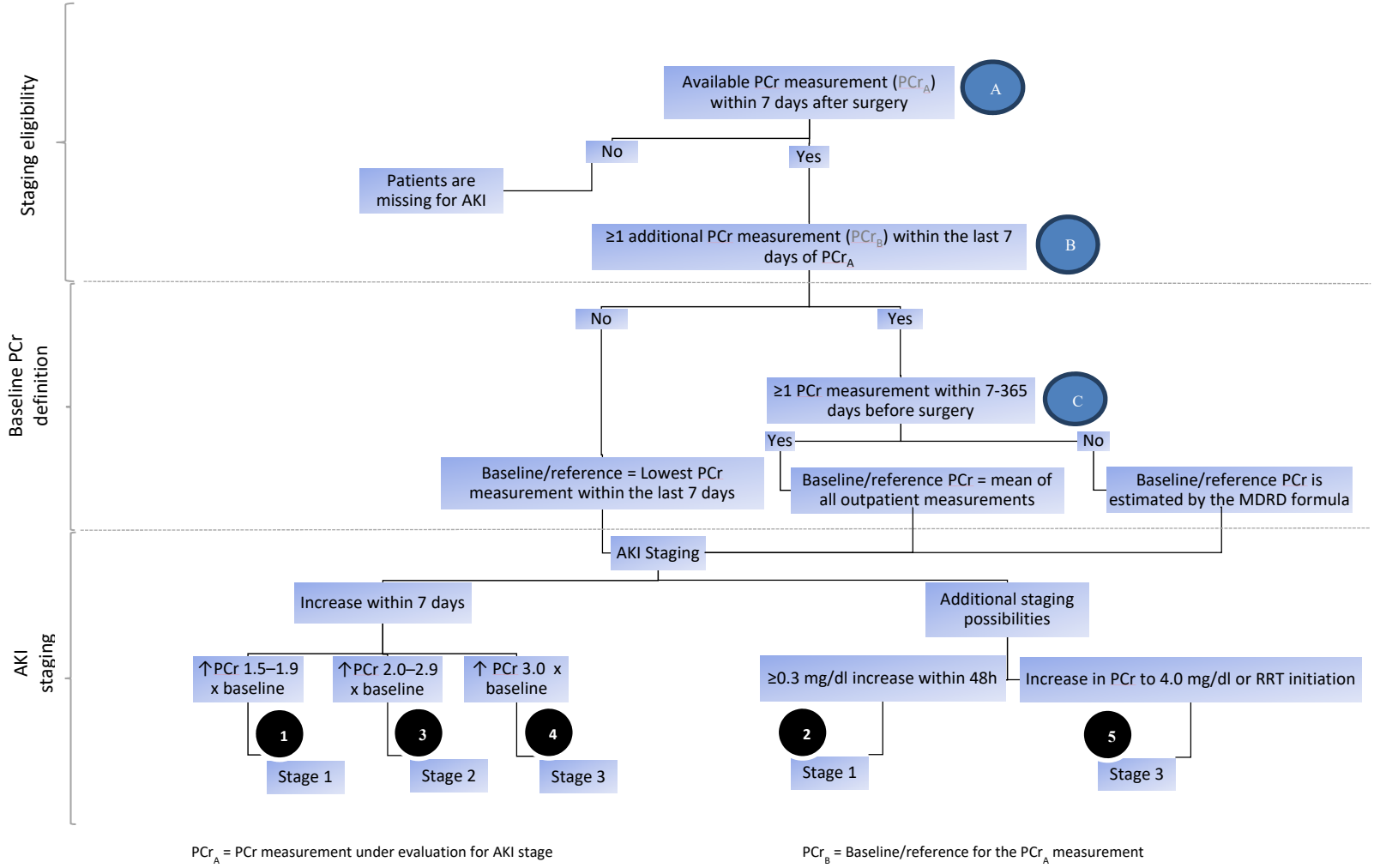
AKI was the exposure in study I, outcome in study II, and the study population in study III.

The staging of AKI according to KDIGO includes changes in PCr within the last 7 days, and the occurrence of postoperative AKI has been shown to be highest during the first 2–4 days and slowly decreasing towards days 7–8.[3]

Data on plasma creatinine (PCr) (equivalent to SCr) were retrieved from the LABKA research database.[151,154] As described earlier in the section "data sources", this database contains PCr test results collected by general practices and hospitals in the study area since 1990. We defined AKI as a 50% increase in PCr, initiation of RRT within 7 days after surgery, or an absolute increase in creatinine of 26μmol/L within 48 hours. The 7-day window for staging AKI was chosen based on the fact that postoperative AKI most commonly occurs within the 7 days after surgery, as was the case in our studies (Appendix I, Supplementary files, Figure S1).

We also identified the highest AKI stage occurring within 7 days after CRC surgery according to the KDIGO SCr criteria, as follows: no AKI, Stage 1 AKI, Stage 2 AKI, and Stage 3 AKI (Figure 3.1).[13]

*Figure 3.1. Flow chart of AKI definition. Including staging eligibility criteria, and baseline definition required for AKI staging. C**ircles** correspond to examples of AKI staging in Figure S2 (Appendix I, Supplementary files).*



In studies I and II, we included patients without a PCr measurement within 7 days following surgery (i.e., missing exposure information) in the group of patients without AKI, for the following two reasons. First, the blood draw is minimally invasive and low cost, so therefore the indication threshold is low. Second, the hospitals that provided the most patients without exposure information adhered to a fast-track protocol.[23,24] The fast-track protocol recommends a restrictive fluid and blood analysis regime where blood analyses are performed only if a patient is not healthy and well in recovery. Consequently, we expected patients with no exposure information to be similar to healthy patients without AKI.

Additionally, after tabulating patient characteristics and procedure-related factors by AKI status (e.g., categories: AKI patients, patients without AKI and patients without exposure information), patients without one or more PCr measurements within 7 days following surgery (~ 10%) did appear healthier than patients with AKI and, in general, were similar to patients without AKI.

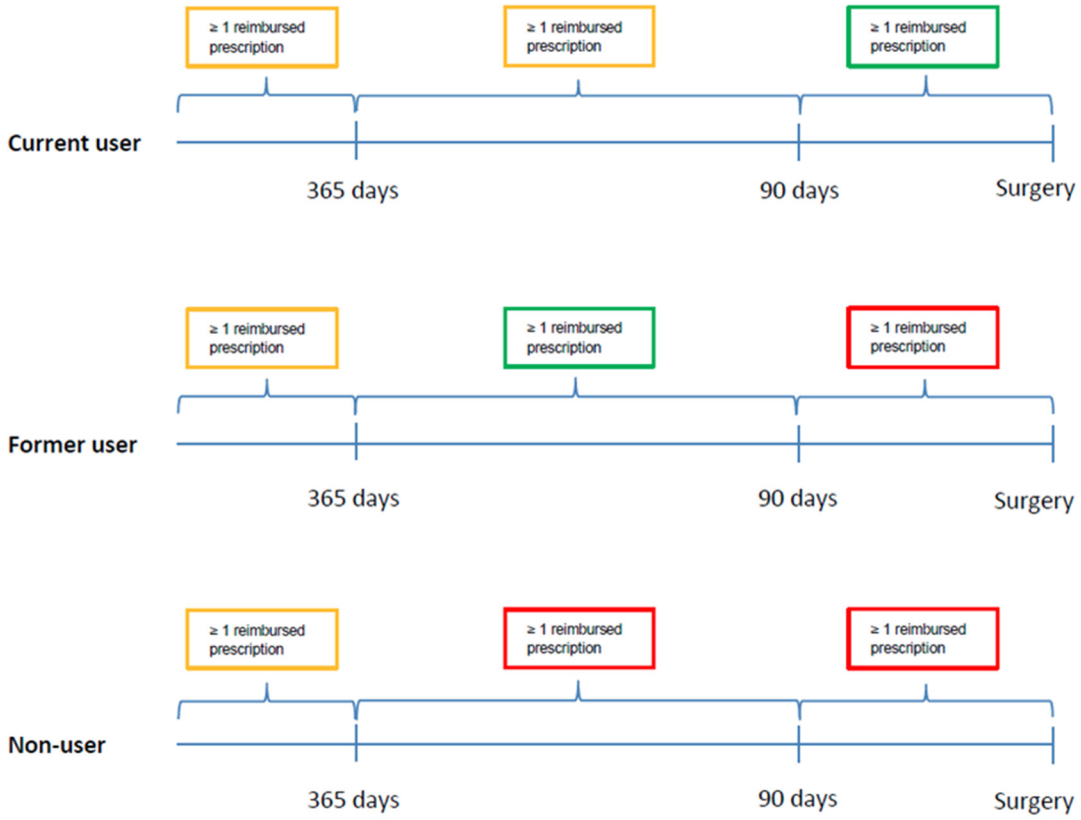
ACE-I/ARB

ACE-I/ARB use was the exposure in studies II and III. Preoperative use of ACE-I/ARB was identified through the NHSPD.[148] We defined current, former and non-users according to Figure 2.

Patients were classified as current users of ACE-Is/ARBs (≥1 prescription within 90 days before surgery), former users (≥1 prescription in the period 90–365 days before surgery), or non-users (no prescriptions during 365 days before surgery).

In studies II and III, we had information on in-hospital ACE-I/ARB use from the electronic patient chart of patients undergoing surgery at hospitals in the Central Denmark region. If patients were registered with an administration of an ACE-I/ARB on the day of surgery, they were considered as patients with confirmed current use of ACE-I/ARB.

Figure 2. Definition of preoperative use of angiotensin-converting enzyme inhibitors (ACE-I) and angiotensin receptor blockers (ARB). Color codes: Red = not allowed, Yellow = allowed, but not required, and Green = required.



Outcomes

Mortality was the outcome in studies I and III. In study II the outcome was AKI risk.

Mortality (Studies I and III)

From the CRS, we obtained data on mortality, starting on the day of CRC surgery and continuing until one year after the surgery.[149] In study I, we chose to start follow-up on day 8 instead of the day of surgery to avoid immortal time bias because patients with AKI otherwise would have to survive until their AKI, thereby representing a healthier group of patients.[60] In study III, we chose to start follow-up on the day of AKI, because the population was patients with AKI.

AKI risk (study II)

AKI risk was the outcome in study II (see definition in the section "acute kidney injury" under exposures in the methods section).

3.6. Covariates

Preoperative covariates (confounders or effect modifiers) were chosen based on their association with AKI, postoperative mortality, and ACE-I/ARB.[2,3,13,33,55,64,155] CKD, a strong predictor for AKI, was identified using PCr measurements from the LABKA database.[151] We defined CKD as an eGFR <60 ml/min/1.73 m^2 lasting at least 3 months within the 2 years before CRC surgery.[117]

The following covariates were identified from the DNPR, based on an inpatient or outpatient hospital contacts for a given condition within 10 years before CRC surgery: obstructive pulmonary disease, arterial hypertension, diabetes mellitus, heart disease, and liver disease.

To limit residual confounding, we sought to increase the completeness of diabetes mellitus and obstructive pulmonary disease diagnoses we searched the NHSPD for previous (within one 1 year before surgery) prescriptions of medications used to treat these conditions (Appendix I-III, Supplementary files, Tables A).[148] The NHSPD contains records for all reimbursable drugs dispensed in community pharmacies in Denmark since 2004. BMI was computed from weight and height data retrieved from the DCCG database[18] divided into three categories: underweight (<18.5m^2/kg), normal weight (18.5–24.9m^2/kg), and overweight (≥25m^2/kg).[156]

Users of statins, beta blockers, calcium-channel blockers, acetylsalicylic acid, antibiotics, and nitrates were identified according to the following definition: current users (≥1 prescription within 90 days before surgery), former users (≥1 prescription in the period 90–365 days before surgery), or non-users (no prescriptions during 365 days before surgery). The rational for this definition was that these medications are typically prescribed in packages of 90–100 tablets in Denmark and is often administered once a day.[115] NSAIDs are typically redeemed every 60 days, so current NSAID users were defined within 60 days before surgery.[157] Furthermore, NSAIDs by prescription were included in the variable.[157] In addition to the association of these drugs with AKI, postoperative mortality, or ACE-I/ARB, these drugs were included in the subgroup analyses of studies II and III because they are relatively commonly prescribed to the CRC population. Therefore, identifying differences in risk within subgroups of these drugs may have important clinical implications on the burden of AKI in CRC patients, especially because these drugs are modifiable risk factors.

3.7. Statistical analyses

All analyses were conducted using the Stata software package, version 13.1 (StataCorp, College Station, TX, USA).

3.7.1. Study I

Main analyses

We tabulated patient characteristics (including demographics, comorbidities, and information from the hospitalization that included CRC surgery) by AKI stage (Appendix I, Paper I, Table 1).

Patients were followed from day 8 after surgery until death, emigration, or up to one year after surgery, whichever came first. We computed cumulative mortality curves (1 - survival function) for patients with and without AKI, using the Kaplan–Meier method[158] and further we separated AKI into AKI Stages 1–3[13] We computed hazard ratios (HRs) of death within 8 to 30, 31 to 90, and 91 to 365 days after surgery, comparing patients with AKI (and individual stages of AKI) to patients without AKI, using a Cox proportional hazards regression model adjusted for potential confounding. Confounders included age group, sex, BMI category, CKD, diabetes mellitus, obstructive pulmonary disease, arterial hypertension, liver disease, heart disease, tumor site (colon or rectum), and urgency of surgery (acute or elective). The assumption of proportional hazards was checked graphically and found appropriate within all follow-up periods.

Stratifications

Paying attention to potential effect modification may provide us with information that supports the formulation of etiological hypotheses that can advance knowledge of the pathologic processes involved in the association of interest and help to identify high-risk population subgroups.

Accordingly, we examined potentially different effects across subgroups (effect modification), by repeating the analyses stratified by sex, age, CKD, acute vs. elective surgery, surgical approach (open or minimally invasive), type of surgical procedure, diabetes mellitus, and year of surgery. Interactions between covariates and the exposure were tested.

Around 30% of the patients were missing information on lifestyle variables (BMI, smoking, and alcohol use) (Appendix I, paper I, Table 1). In approximately 3% of patients, postoperative anastomotic leakage, sepsis, stroke, venous thromboembolism, pneumonia, pulmonary insufficiency, or myocardial infarct was missing. Further, around 70% of patients were missing information on the postoperative complications: fascial dehiscence, bleeding, ileus or heart failure.

Sensitivity analyses

Sensitivity analyses are repetitions of the analyses, in which alternative methodological decisions to those made in the main analysis, are introduced.[60] The goal is to ensure that the findings are robust to the methodological decision and determine whether the findings change if assumptions other than those made in the main analyses are used.[159] Furthermore, if a study is susceptible to a limited number of systematic errors, it may be suitable to extend the analyses with a bias analysis.[160] Bias analyses offer quantitative estimates of the magnitude, direction, and uncertainty originating from systematic error.

Missing data

Missing data was around 30% in the CKD, BMI, alcohol, and smoking variables. We used two methods to address potential misclassification stemming from missing data: a complete case analysis and a sensitivity analysis. In this sensitivity analysis, we performed multiple imputations of missing data. The purpose of multiple imputation is to avoid the effect of missing data undermining the validity of our results. In multiple imputation, multiple different plausible imputed datasets are formed, and results from each of these datasets are then appropriately combined to give the overall estimate, considering the uncertainty of missing data.[161] We calculated average HRs for 30 imputed datasets. In the sensitivity analysis, we estimated values for missing data for six categorical variables (AKI stage, CKD stage, acute/elective surgery, BMI, smoking, and alcohol intake) using all covariates, the outcome, and the Nelson–Aalen estimator of the cumulative baseline hazard to observed survival time.[161] Younger and healthier patients were less likely to have a PCr measurement. Therefore, we expected that data were missing at random, but not completely at random in our study. Multiple imputation is recommended over complete case if data are missing at random. [161]

Furthermore, we performed sensitivity analyses changing the exposure period for the definition of AKI to assess the robustness of our decision of defining AKI within 7 days after surgery. The following intervals for developing AKI was tested: AKI within 3 days, 10 days, and 30 days after surgery to evaluate changes in association between AKI and postoperative mortality.

Timing of AKI and complications

Postoperative complications occurring sometime within 30 days after surgery were registered by the surgeons in the DCCG database. Therefore, we could not identify whether AKI or other complications came first. We addressed timing of AKI and other complications as follows. For all patients who developed AKI within 7 days after CRC surgery, we cross-tabulated the first day of AKI with typical late complications (occurring 6–8 days post-surgery), e.g., anastomotic leakage and fascial dehiscence and calculated prevalence rate ratios with 95% confidence intervals for the postoperative complications, comparing complications in patients with AKI to those without AKI (Appendix I, Supplementary files, Figure S3).

3.7.2. Study II

Main Analyses

Patient characteristics, including demographic characteristics, preexisting comorbidities, and information from the hospitalization associated with the CRC surgery, were tabulated by current use/former use/non-use of ACE-I/ARB.

We computed 7-day post-operative cumulative incidence proportions (risk) of AKI with 95% CIs for patients with current, former, and no use of ACE-I/ARB, including death as a competing risk.[162,163] Risk ratios (RRs) for current users compared with non-users, and for former users compared with non-users, were computed using log-binomial regression on a multiple imputed dataset.

Multiple imputation

Because information on some variables was missing, we performed multiple imputations (average RR of five imputed datasets) of the covariates with missing data and included them in the log-binomial regression. We imputed missing data (~20%) for four categorical covariates (CKD stage, smoking, BMI, and weekly alcohol intake) with multiple imputation using the mi impute chained procedure in Stata 13.1 to create 5 imputed data sets.[161] These imputations were based on the relation among all the variables included in this study.

The decision to perform the main analyses on a multiple imputed dataset was based on the fact that we had around 20% missing data in some of the variables in the model and that we expected missing data to be missing at random. Moreover, losing 20% of patients would have affected the power of the study greatly and potentially lead to selection bias of our estimates of the association between ACE-I/ARB and risk of AKI.

We controlled for potential confounders including: age (0–59, 60–69, 70–79, ≥80 years), sex, CKD, diabetes, obstructive pulmonary disease, hypertension, liver disease, heart disease, cancer type, urgency of surgery, smoking, BMI, and alcohol. To address any potential effect modification of the association between ACE-I/ARB and risk of AKI, we repeated the analyses stratified by sex, age group, BMI, alcohol, smoking, CKD, diabetes, hypertension, heart disease, urgency of surgery, beta-blockers, nitrates, acetylsalicylic acid, statins, antibiotics, NSAIDs, and diuretic use.

Sensitivity analyses

To test the robustness of our analysis method, we repeated the analyses as a complete case analysis using a log-binomial regression.

To test the robustness of our definition of the exposure, we repeated analyses with the following definition: current users of ACE-Is/ARBs (≥1 prescription within 90 days before surgery), former users (≥1 prescription in the period 90–365 days before surgery), and non-users (no prescriptions during 365 days before surgery). Furthermore, we changed the exposure window for being a user from 90 days to 30, 60, and 100 days to evaluate our assumption that ACE-I/ARB users would have redeemed a prescription within 90 days before surgery. Additionally, we repeated the analyses according to the description in the exposure paragraph of the methods section, and we also tested an alternative definition of ACE-I/ARB use. We identified all patients with one or more prescriptions of ACE-I/ARB within 365 days before surgery. Patients with no reimbursed prescription of ACE-I/ARB were defined as non-users and patients with a reimbursement were further divided into current and former user. A current user was defined as a patient redeeming a prescription with enough medication to be able to take medication on the day of surgery. If two identical prescriptions (concentration and number of pills) were reimbursed on the same day, then the number of pills was summed. We assumed that patients were taking one pill a day.[115] If the patients with a reimbursed prescription did not meet the requirements for being a current user, they were defined as former users (Appendix II, Supplementary files, Table S1). Additionally, with information from the electronic patient chart of patients

undergoing surgery in the Central Denmark Region, we assessed whether patients withheld or continued their medication during surgery.

3.7.3. Study III

Main analyses

Patient characteristics, including demographics, preexisting comorbidities, and information from the hospitalization associated with the CRC surgery, were tabulated by use of ACE-I/ARB. We followed patients from the day they developed AKI after surgery and until death, emigration, or up to 1 year after surgery, whichever came first. The Kaplan–Meier method was used to compute cumulative mortality curves (1 - survival function) for current, former, and non-users of ACE-I/ARB.[158] We compared mortality at 30, 31 to 90, and 91 to 365 days in current and former users with the mortality in non-users, using a Cox proportional hazards regression model adjusted for potential confounders. We adjusted for age (0–59, 60–69, 70–79, ≥80), sex, BMI, CKD, diabetes, obstructive pulmonary disease, hypertension, heart disease, cancer type, urgency of surgery, smoking, and alcohol. The assumption of proportional hazards was checked graphically and found appropriate within all follow-up periods. We estimated missing data by multiple imputation (average HR of twenty imputed datasets) for four categorical variables (CKD, BMI, smoking, alcohol intake) using all covariates, the exposure and outcome, and the Nelson–Aalen estimator of the cumulative baseline hazard to the observed survival time.[161] The multiple imputation of the missing data was performed by the *mi impute chained* procedure in Stata 13.1 and multiple imputation was included in the Cox proportional regression. We expected that data were missing at random in our study.

Sensitivity analyses

To address the potential selection bias that would arise if patients with missing data were excluded, we conducted a complete case analysis in addition to the main analysis (where missing data were imputed). Misclassification of the exposure was addressed in sensitivity analyses where the window for being a current user (main analysis 90 days) was changed to 30, 60 and 100 days. Moreover, we addressed the potential direction and size of selection bias stemming from whether exposed patients developed AKI earlier than non-exposed. As in study II, we assessed information from the electronic patient chart of patients undergoing surgery in the Central Denmark Region, to obtain information of whether these patients withheld or continued their medication during surgery.

Stratifications

To test further for potential effect modification, we repeated the analyses stratified by sex, age, urgency of surgery, diabetes mellitus, preoperative use of nitrates, beta-blockers, antibiotics, statins, and NSAIDs. Acetylsalicylic acid was not included in the subgroup analyses because of the low number of patients.

3.8. Ethical considerations

All data were obtained from Danish registries and, in accordance with Danish law, their use did not require ethical approval or informed consent. The studies were approved by the Danish Data Protection Agency (record no. 2015-57-0002, Aarhus University record no. 2016-051-000001/423).

4. Results

4.1. Population

Flow charts for each study are provided in appendices I, II, and III. In both studies I, II, and III, median age was, as expected, above 70. Women and men were rather evenly distributed and more patients had colon cancer (~65%) than rectal cancer (~35%).

In study I, when comparing patients with AKI and without AKI, patients with AKI were more commonly were above 70 years, had a history of smoking, BMI categorized as "overweight", a higher American Society of Anesthesiologists' (ASA) Classification of Physical Health score.[23] (Appendix I, Study I, Table 1.) They also more frequently developed postoperative complications such as ileus, bleeding, fascial dehiscence, and infectious complications.

In study II, the exposed patients (current users of ACE-I/ARB) more often were older, had higher BMI, and had higher ASA score compared to non-users (Appendix II, Study II, Table 1.). They also more frequently had comorbidities and were women. 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. Postoperative surgical complications were comparable.

In Study III, all patients had AKI, and again current users of ACE-I/ARB were older, more often had a BMI above normal, and had more comorbidities (Appendix III, Study III, Table 1). Use of diuretics, acetylsalicylic acid, beta-blockers, calcium-channel blockers, and nitrates appeared more common in current users (Appendix III, Study III, Table S3). Postoperative bleeding seemed to be more common in current users (Appendix III, Study III, Table S1).

In studies II and III, confirmed current users did not seem to differ in preoperative risk factors from current users without confirmed use of ACE-I/ARB, although patients without a continued registration of ACE-I/ARB use had fewer comorbidities (CCI = 0) compared with confirmed current users.

4.2. AKI and mortality in patients undergoing CRC surgery (Study I)

Twenty percent (1,337) of the 6,580 CRC surgery patients included in the analyses developed AKI within 7 days after surgery. The most severe stage, AKI stage 3, was seen in 3 % of patients, and 66% of these patients were treated with RRT. The occurrence increased with decreasing stage of AKI to 4.3% for AKI stage 2 and 13.0% for AKI stage 1. AKI occurrence peaked in the early postoperative phase (1–4 days after surgery), and there seemed to be more postoperative complications in patients with AKI (Appendix I, Supplementary, Figure S3). For example, the prevalence rate ratio of anastomotic leakage in patients with AKI compared with patients without AKI was 3.71 (95%: CI 3.03–4.53) (Appendix I, Supplementary files, Table S3).

Table 4.1. Mortality outcomes (8–30, 31–90, and 91–365–day mortality) by acute kidney injury stage.

Exposure group	Person-time (days)	Number of outcomes	Cumulative mortality % (95% CI)	Crude HR (95% CI)	Adjusted HR[a] (95% CI)
8-30-day mortality					
Without AKI	124,430	115	2.2 (1.8–2.6)	Ref.	Ref.
With AKI	30,004	135	10.1 (8.6–11.9)	4.83 (3.76–6.19)	4.01 (3.11–5.17)
Stage 1	19,712	62	7.2 (5.7–9.2)	3.38 (2.49–4.61)	2.62 (1.91–3.59)
Stage 2	6,243	30	10.6 (7.5–14.8)	5.16 (3.45–7.70)	4.83 (3.21–7.25)
Stage 3	4,049	43	22.1 (16.9–28.6)	11.20 (7.92–16.0)	10.40 (7.17–15.0)
31-90-day mortality					
Without AKI	307,089	168	3.3 (2.8–3.8)	Ref.	Ref.
With AKI	70,051	92	7.8 (6.4–9.5)	2.45 (1.90–3.15)	2.08 (1.60–2.69)
Stage 1	46,696	57	7.2 (5.6–9.2)	2.23 (1.65–3.00)	1.87 (1.38–2.54)
Stage 2	14,980	16	6.3 (3.9–10.1)	1.95 (1.17–3.25)	1.80 (1.08–3.02)
Stage 3	8,375	21	13.8 (9.2–20.4)	4.55 (2.89–7.17)	3.78 (2.36–6.06)
91—365-day mortality					
Without AKI	1,296,433	487	9.8 (9.0–10.7)	Ref.	Ref.
With AKI	285,258	131	12.0 (10.3–14.2)	1.25 (1.03–1.51)	1.11 (0.92–1.35)
Stage 1	189,637	92	12.5 (10.3–15.1)	1.29 (1.03–1.61)	1.12 (0.89–1.41)
Stage 2	61,774	25	10.5 (7.2–15.2)	1.08 (0.72–1.61)	1.06 (0.71–1.58)
Stage 3	33,847	17	13.0 (8.3–20.0)	1.33 (0.82–2.16)	1.16 (0.71–1.91)

[a] Adjusted for age (categories: 0–49, 50–59, 60–69, 70–79, and ≥80 years), sex, BMI, CKD stage (3-5), diabetes mellitus (yes/no), obstructive pulmonary disease, hypertension, liver disease, heart disease, tumor site, and urgency of surgery.
Abbreviations: AKI, Acute Kidney Injury; BMI, Body Mass Index; CKD, Chronic Kidney Disease; CI, Confidence Interval; HR, Hazard Ratio

Cumulative mortality within 30 days after surgery was substantially higher in patients with AKI, and mortality seemed to increase with increasing stage of AKI. The hazard of dying was 2-4 times higher in patients with AKI compared with patients without AKI ($aHR_{8\text{-}30day}$ 4.01; 95% CI: 3.11–5.17 and $aHR_{31\text{-}90day}$ 2.08; 95% CI: 1.60–2.69) and seemed to increase with increasing stage of AKI within the 8–30 days after the surgery (Table 4.1). After 90 days and up to a year, we found no association between AKI and mortality after adjusting for potential confounders. Sensitivity analyses (multiple imputation, complete case, and changed

exposure period) yielded no discernible changes in mortality. We also did not observe any major differences in estimates between subgroups, but wide confidence intervals preclude definite conclusions about the presence of effect modification.

4.3. ACE-I/ARBs and AKI risk after surgery for CRC (Study II)

Twenty-eight percent of the 9,932 patients included in the analyses were current (21.3%) or former (6.4%) users of ACE-I/ARB. Taking death into account as a competing risk, the risk of AKI within 7 days after surgery for current and former users was around 25% (Table 4.2). The crude RR of current and former users vs. non-users were 1.41 (95 % CI: 1.37–1.45) and 1.42 (95 % CI: 1.35–1.49), respectively (Table 4.2). After adjusting for potential confounders, RRs were closer to one but still showed a clinically relevant association between use of ACE-I/ARB and risk of AKI for current users ($aRR_{current}$ 1.20; 95% CI: 1.09–1.32; aRR_{former} 1.16; 95% CI: 1.01–1.34). The risk of AKI in current and former users did not seem to differ substantially and CIs were overlapping. Further supporting the robustness of our results, sensitivity analyses of the altered exposure window and the alternative definition of ACE-I/ARB current use did not change the results notably and there did not seem to be a difference in the effect of ACE-I/ARB on the risk of AKI in strata of sex, age group, BMI, alcohol, smoking, CKD, diabetes, heart disease, urgency of surgery, or preoperative medication (Appendix II, Study II, Figure 3). In current users, we found a higher relative risk of AKI (aRR 1.39; 95 % CI: 1.23–1.59) in non-hypertensive patients than in current users with hypertension (aRR 1.03; 95% CI: 0.90–1.17). In study II, 53% (1,113/2,112) the current users of ACE-I/ARB had information on in-hospital medication. Of those 53% patients, 56 % (619/1,113) were confirmed current users.

Table 4.2 Seven-day AKI risk outcomes according to use of angiotensin-converting enzyme inhibitor (ACE-I) and angiotensin-receptor blocker (ARB).

Exposure group	No. of outcomes	Seven-day Incidence Proportion % (95% CI)	Crude RR (95% CI)	Adjusted RR[a] (95% CI)
Non-user	1281	17.8% (17.0–18.7)	Ref.	Ref.
Former user	161	25.2% (21.9–28.6)	1.42 (1.35–1.49)	1.16 (1.01–1.34)
Current user	558	26.4% (24.6–28.3)	1.41 (1.37–1.45)	1.20 (1.09–1.32)

Abbreviations: Relative Risk, RR; Acute Kidney Disease, AKI, Confidence Interval, CI

[a] Log-binomial regression adjusted for age (0–59, 60–69, 70–79, ≥80) sex, CKD, diabetes, obstructive pulmonary disease, hypertension, liver disease, heart disease, cancer type, urgency of surgery, smoking, BMI, and alcohol

4.4. ACE-I/ARBs and prognosis of AKI after CRC surgery (Study III)

We included 2,000 patients with AKI after CRC surgery in the study and found 27.9% were current users, 8.1% were former users and 64.0% non-users. The cumulative mortality within 0–30, 31–90, 91–365, and 0–365 days after the day of AKI were comparable among current, former, and non-users (Table 4.3). Adjusting for potential confounders had only minor effects on the estimates, and no association was found for either of the follow-up periods. In the sensitivity analyses of the exposure period and missing data, the results remained largely unchanged and, in the subgroup, analyses we did not find any discernable differences (Appendix III, Supplementary material, Figure S3, Table S4-8). In study III, 65% (363/558) current users of ACE-I/ARB had information on in-hospital medication. Of those 65% patients, 33% (119/363) were confirmed current users.

Table 4.3. Mortality outcomes (8–30, 31–90, 91–365, and 0–365–day mortality) according to use of angiotensin-converting enzyme inhibitor (ACE-I) and angiotensin-receptor blocker (ARB).

Mortality outcomes	**Person-time (days)**	**Number of outcomes**	**Cumulative Mortality % (95% CI)**	**Crude HR (95% CI)**	**Adjusted HR[1] (95% CI)**
0-30 day mortality					
Non-user	35836	172	13.4 (11.7–15.4)	Ref.	Ref.
Former user	4380	26	16.2 (11.3–22.8)	1.22 (0.80–1.85)	1.19 (0.78–1.82)
Current user	15283	92	16.5 (13.7–19.8)	1.25 (0.97–1.61)	1.26 (0.96–1.65)
31-90-day mortality					
Non-user	65281	60	5.4 (4.2–6.9)	Ref.	Ref.
Former user	7858	13	9.6 (5.7–16.0)	1.80 (0.99–3.27)	1.87 (1.00–3.51)
Current user	27393	231	6.7 (4.7–9.3)	1.23 (0.80–1.90)	1.22 (0.76–1.96)
91-365-day mortality					
Non-user	271232	118	11.3 (9.5–13.3)	Ref.	
Former user	31870	15	12.3 (7.6–19.6)	1.08 (0.63–1.85)	1.11 (0.64–1.95)
Current user	113357	39	9.0 (6.6–12.1)	0.79 (0.55–1.13)	0.81 (0.55–1.20)
1- year mortality					
Non-user	370315	350	24.7 (22.4–27.2)	Ref.	Ref.
Former user	43865	54	29.8 (23.2–37.8)	1.27 (0.96–1.69)	1.29 (0.96–1.73)
Current user	155183	362	26.4 (22.9–30.4)	1.09 (0.90–1.31)	1.11 (0.91–1.35)

[1] Adjusted for age (0–59, 60–69, 70–79, ≥80), sex, urgency of surgery, cancer type, CKD, diabetes mellitus, hypertension, heart disease, BMI, smoking, and alcohol.
Abbreviations: AKI, Acute Kidney Injury; BMI, Body Mass Index; CKD, Chronic Kidney Disease; CI confidence Interval; HR, Hazard Ratio.

5. Discussion

5.1. Comparison with the existing literature

In the subsequent sections is an updated discussion of our findings for each study in the context of the relevant literature published at the time of writing.

5.1.1.AKI and mortality in patients undergoing CRC surgery (Study I)

Occurrence of AKI

In our study, among patients undergoing CRC surgery, AKI frequently occurred within 7 days after surgery. As seen in Table 2.6, occurrence of AKI varied (2.0–11.8%) in the included studies, reflecting their heterogeneity.[1,3,27,72,108,109,132,133,135] In the three studies of exclusively colon and/or rectal cancer surgeries, AKI occurrence ranged from 0.6% to 4%.[27,108,132] Hu et al. assessed the occurrence of RRT after CRC in 42,403 CRC patients and found RRT to be initiated in 0.6% of patients after CRC surgery. Likewise, Iversen et al. conducted a Danish population-based study of 2,157 patients undergoing major emergency surgery for CRC,[27] reporting the need for RRT, the most severe stage of AKI, within 30 days and found that 2% required RRT. In our study, patients with stage 3 included 66% patients on RRT, so the results of the two earlier studies should be compared to our stage 3 patients.[27,135] We found a similar occurrence of stage 3 AKI.[27] In the study by Lim et al. 288 medical records of patients undergoing elective rectal cancer surgery were reviewed, and 3.8% (n = 11) of patients developed AKI according to the AKIN criteria.[67] Six of these patients developed AKI stage 1, one patient AKI stage 2, and four patients AKI stage 3.[108] The explanation for the lower occurrence may be found in the exclusion of patients with a GFR of less than 60mL/min/1.73m^2 and the use of the most recent serum creatinine (SCr) within 30 days before surgery and the baseline/reference when staging/identifying AKI. Excluding patients with GFR below 60ml/min/1.73 m^2 may have led to a healthier study population with a lower risk of AKI, than what is representative for the CRC population. Moreover, they may have underestimated AKI by applying the "most recent outpatient" criteria for identifying baseline SCr because this has been shown to be appropriate in patients with GFR below 60ml/min/1.73 m^2 (e.g., CKD patients) and less feasible in patients with a GFR above 60ml/min/1.73 m^2.[40] In the last of the three CRC surgery studies AKI-related readmission in 619 patients was investigated and 4% of the patients developed AKI. Assuming this is only the more severe stages of AKI that leads to readmission, the results are in line with AKI stage 3 in our study. [132] Five studies examined the occurrence of AKI in patients undergoing colorectal surgery.[1,3,72,109,135] AKI occurrence varied from 1.8% to 11.8%. Kim al. studied the variations in risk of AKI across intra-abdominal procedures and found the risk of AKI to be 1.8%.[3] They defined AKI as RRT or as a ≥2mg/dl increase from the preoperative SCr value. Therefore, their results were limited to AKI stage 3 and in agreement with our results for the most severe stage of AKI. In the other four studies, less severe stages of AKI were examined, and correspondingly they found higher occurrence of AKI (5.7–11.8%).[1,72,109,133] One study applied the KDIGO criteria for AKI staging and

definition,[1] two studies defined all patients with an SCr increase of more than 50% as patients with AKI,[72,133] and the last study defined all patients with a SCr of >110µmol/L and a uremia serum level of 7 mmol/L as patients with AKI[109]. The lower occurrence of AKI may be explained by a combination of factors such as the younger age of the populations, fewer emergency surgeries and inclusion of more simple procedures in these studies compared to ours.

A limitation of using the DCCG database is that data on BMI, alcohol, and smoking were missing for around 30% of patients in this study. Moreover, surgeons were asked to report postoperative complications within 30 days after surgery and not with a specific date. Therefore, we did not know if postoperative complications occurred preceding AKI or following AKI. Moreover, although not very likely, some patients may have been discharged or transferred to another department within the 30 days after surgery and subsequently developed complications that would have been unlikely to be registered by the surgeons. For these reasons, we cannot distinguish whether postoperative complications precede AKI or if AKI leads to postoperative complications. However, it is clear from the existing literature as well as our study that AKI is a frequent complication of CRC surgery and colorectal resections.

AKI and mortality

No previous study has examined the impact of AKI and AKI stages on mortality within a year after CRC surgery. Two cohort studies of CRC surgery[27,108] and four cohort studies of colorectal surgery[1,3,72,109] reported on short-term mortality associated with AKI. As discussed in the previous paragraph, the study population and procedure-related factors adjusted for in the studies were heterogeneous, which may account for the variation in mortality across the studies as well as from our results. In-hospital mortality in patients with AKI ranged from 1.5% to 18.2 %.[1,72,108,109,133,135] Only one of these studies did not find an association between AKI and in-hospital mortality[72]. Mortality was seen in 6.3% of the patients with AKI and only in 0.9% of patients without AKI. They reported only P values (P = 0.065) and no CIs and had a small sample size. Therefore, we cannot rule out type-2 errors to be responsible for the lack of association.[111] Thirty-day mortality was reported in two studies as 68% in emergency CRC surgery[27] and 28.9% in colorectal resections[3] of patients with the most severe stage of AKI, similar to that of our AKI stage 3 patients. In a large cohort study by Kim and colleagues, after adjustment for potential confounders, those with AKI had an increased RR of 2.01 (95% CI: 1.79–2.25) for mortality after colorectal surgery compared with patients without AKI.[3] O'Connor et al. studied one-year mortality after colorectal surgery and found an unadjusted RR of 4.36 (95% CI: 3.10–6.14) for patients with AKI compared with patients without AKI. This is in contrast to our findings of one-year mortality, which did not show an association between AKI and 91–365day mortality. This divergence may be explained by their estimates including 0–365-day mortality, whereas our study divided the postoperative mortality into three periods. Furthermore, they did not find an association with increasing stage of AKI and early postoperative mortality, as was implied in our study.[1]

5.1.2. Use of ACE-I/ARB and AKI risk after surgery for CRC (Study II)

No studies of ACE-I/ARB use and the risk of AKI have focused specifically on patients undergoing surgery for CRC. In the current literature on use of ACE-I/ARB and the risk of AKI after major non-cardiac or major abdominal surgery, results are conflicting despite the fact that several major cohort studies from different countries have been conducted. Eight studies have explored the association between ACE-I/ARB use and AKI after major surgery or non-cardiac surgery.[56,64,83–86,88,137]

Prevalence of ACE-I/ARB use

We included 9,932 patients in our cohort study and found use of ACE-I/ARB to be common. In the seven studies included in the background literature of study II, ACE-I/ARB use varied from 12.5% (in a non-cardiac surgery population) up to 70% (in a non-cardiac surgery population with exclusively hypertensive patients).[56,64,83–86,88] The identification and definition of ACE-ARB use was heterogeneous across studies, with heterogeneous data sources for receipt of ACE-I/ARB including redeemed prescriptions, electronic medical records and anesthesia records. Because ACE-I/ARBs are frequently prescribed for, hypertension, as anticipated, the highest prevalence of ACE-I/ARB use was found in a small prospective cohort study by Comfere et al. of 267 hypertensive (BP ≤150/90 mmHg) patients undergoing outpatient or elective surgery.[86] As seen in Table 2.7, the prevalences in studies with patients undergoing major surgery (may include cardiac or vascular surgery)[56,84] were higher than for studies including minor or major non-cardiac surgery[66,83,85] without restricting to major surgery. In one study of non-cardiac surgery, the prevalence was similar to that of major surgery.[64] An explanation may be that the study included patients from 2010-2012, and ACE-I/ARB use is known to have become more prevalent with time since their introduction.[7,164]

ACE-I/ARB and the risk of AKI

We found an increased risk of AKI in current and former users of ACE-I/ARB, but no difference between their risk as would have been expected if the medication itself could explain the increased risk of AKI. Grams et al. conducted a cohort study including 161,185 hospitalized patients undergoing major abdominal surgery, and in line with our results, found an increased risk of AKI in ACE-I/ARB current users (aRR 1.20; 95% CI: 1.16–1.23). In contrast, in a Chinese cohort study of 12,545 hypertensive patients undergoing non-cardiac surgery, ACE-I/ARB use was found to decrease the risk of AKI (aOR 0.68; 95% CI: 0.57 – 0.82), even after adjustment for potential confounding in a multivariate regression model and by propensity score matching.[83] Likewise, in a Canadian study of 237,208 patients undergoing major surgery, ACE-I/ARB use was associated with a lower risk of AKI (aOR 0.83; 95% CI: 0.71–0.98). Another large cohort study did not find an association between ACE-I/ARB use and risk of AKI.[85] The patients included in this study were instructed to take their ACE-I until the day before surgery.[85] Four cohort studies addressed withholding or continuing ACE-I/ARB on the day of surgery and the risk of AKI.[64,66,86,137] Three of them found no association with continuing ACE-I/ARB and the risk of AKI after non-cardiac surgery.[64,66,137] Two of these studies included only around 1,000 patients, and in the study by the STARSurg Collaborative, the results

may have been confounded by indication despite propensity matching, because the physicians may have withheld ACE-I/ARB in patients considered to be at higher risk of developing AKI.[64,137] The last study, with only hypertensive patients, found no patients with AKI in the group of patients withholding their medication until 10 hours before the surgery, whereas 2.4% of the patients continuing their use developed renal impairment.[86] In our study, for four reasons, we expect the majority of our population of current users of ACE-I/ARB to have full or some effect on the day of surgery. First, withholding the drug on the day of surgery may not be sufficient to ensure the effect of the drug is eliminated, because several of the drugs affect BP for more than 24 hours, and almost of the drugs are detectable in the blood for at least 24 hours.[141] Second, at the hospitals included in our study there was no overall standard of practice as to withholding or continuing the drug before surgery. Third, 65% of the current users that had in-hospital information were confirmed as current users continuing the drug on the day of surgery (in the electronic patient chart). Fourth, some patients may have been instructed to take their ACE-I/ARB at home in the morning on the day of surgery, which would go undetected because typically only medication taken after admission is registered in the electronic patient chart.

As discussed above, results are conflicting because of the heterogeneity across the existing literature in terms of surgical population and procedures, as well as the definition of ACE-I/ARB use and AKI. There is a need for further studies within the non-cardiac surgery population, including information on whether the medication is truly taken and still active in the patients at the time of surgery, preferably conducted as large randomized clinical trial including the current guidelines for defining and staging AKI.

5.1.3.ACE-I/ARB and mortality in patients with AKI (Study III)

We could not identify any studies on ACE-I/ARB use and mortality in patients with AKI after cardiac or non-cardiac surgery. Therefore, we compare our results to those of six studies on ACE-I/ARB use and mortality after non-cardiac or major surgery as displayed in Table 2.8.[56,83–85,137,138] Two large studies (>12,000 patients) and one smaller (949 patients) cohort study found no association between ACE-I/ARB use and mortality in patients undergoing non-cardiac surgery.[83,85,137] For the two large studies, this may be explained by the uncertainty about whether the patients took the medication on the day of surgery.[83,85] In the smaller study, it is possible that the smaller sample size in combination with the fact that withholding ACE-I/ARB may be decided in patients considered at higher risk of AKI.[137] Turan et al. that routine clinical practice was to withhold ACE-I/ARB on the day of surgery, so, depending on the specific drug taken, the effect of the ACE-I/ARB might already have ceased, leading to non-differential information bias and a non-association. This may also be the case for our results because one-third of the current users with in-hospital data were not registered with ACE-I/ARB use on the day of surgery. In two studies, ACE-I/ARB use was found to decrease mortality after non-cardiac or major surgery.[84,138] These were studies with a high prevalence of ACE-I/ARB use (33-43%). One of them[84] included a large proportion of cardiac surgeries and vascular surgeries in their analyses which inevitably will add to the varying composition of preoperative and

perioperative factors and thereby a potential higher risk of AKI in some types of surgeries driving the estimates in a direction overall that may not be true for subgroups of surgery, such as CRC surgery. There is considerable heterogeneity among the existing studies which may explain the conflicting results. Thus, the true effect of ACE-I/ARB on mortality in patients undergoing major surgery or non-cardiac surgery may be very different from what has been suggested. Larger studies with sound data on whether ACE-I/ARB was taken on the day of surgery are required to reveal the true association between ACE-I/ARB use and mortality after surgery.

5.2. Methodological considerations

The ambition of every scientific study should be to strive for valid estimates of occurrence and the impact of the exposure on the outcome. Regardless of the aim and study design, it is crucial for a proper interpretation to explore the degree to which random or systematic error may have affected the accuracy of the estimates.[60] Selection bias, information bias, and confounding are all systematic errors that may affect the accuracy of an estimate. A critical evaluation of these potential threats to the internal validity of the study is of paramount importance in any careful appraisal of a study.

In the succeeding sections, we will discuss issues related to systematic errors and generalizability of our studies.

5.2.1. Statistical precision

Statistical precision relates to random error. We quantified the precision of our studies by the width of the CIs.[165] CIs allow for inference based on precision and the strength of the association and they reflect the minimum statistical uncertainty. To avoid reducing inference to dichotomy, based on statistical instead of clinical significance, we did not include P values.[165,166]

Statistical precision in our studies was high for the main analyses of studies I and II, although when conducting the stratified analyses of our studies, the CIs widened. Likewise, in study III, the smaller number of patients compared with those in studies I and II may have led to the non-conclusive association between ACE-I/ARB and mortality after CRC surgery. If PCr had been available for the entire country, we would have been able to include a larger sample of patients, so that any true difference between user and non-users would have been more likely to be found. Based on the relatively large number of patients included in studies I and II, and the frequent outcomes we believe chance contributed little to the total error of these studies.

5.2.2. Selection bias

The validity of the study population for each of the three studies included in this thesis is addressed below.

We employed nationwide population-based registries from the Danish tax-supported healthcare system with virtually complete follow-up. [18,148–151] We limited the studies to Central Denmark Region and the North Denmark Region, a reasonable restriction because the Danish healthcare system is homogeneous across regions, hospitals, coding practice, socioeconomic characteristics and health care usage, so the patient- and procedure-related factors of the exposed and non-exposed groups, respectively, is likely to be comparable.[167]

The DCCG database includes 99% (since 2010, previously 95%) of all incident CRC surgery patients in Denmark.[18] The high patient completeness is accomplished by the surgeons reporting patients undergoing surgery and lists (from DNPR[168]) of patients not yet registered in the DCCG database being provided by the database.[18] Only CRC patients who were diagnosed on death certificate without a surgical admission are not included in the database.

In study I, we excluded patients dying during the 7-day window for being exposed to AKI. This factor may introduce the risk of differential loss to follow-up. Of the 175 patients dying within 7 days after surgery, 113 (64.6%) had AKI and 62 (35.4%) did not have AKI. This could have caused a minor selection bias if we wanted to draw conclusions about mortality of all CRC surgery patients from the day of surgery because more exposed (with AKI) with the outcome (death) than unexposed with the outcome were excluded. If starting follow-up on day 8 affected the results, excluding these patients would have weakened the association towards no difference in the association between AKI and mortality. On the other hand, including them in the analysis by starting follow-up at the day of surgery would introduce the risk of immortal time bias.

In study III, we started follow-up on the day of AKI because the target population was patients with AKI. If current users of ACE-I/ARB developed AKI more slowly than former and non-users, then we assume they would also be less likely to die early because postoperative mortality decreases substantially over the first week after surgery. This factor could have strengthened the association between ACE-I/ARB and mortality, through the combined effect of high early postoperative mortality and the potential increased mortality attributed to ACE-I/ARB use. Therefore, we tabulated day of AKI by ACE-I/ARB use but found no difference across current, former, and non-users (Appendix II, Supplementary material. Table S6). Thus, we believe this potential source of bias is not responsible for the non-association.

5.2.3. Information bias

Information bias is a distortion of the association by the presence of systematic errors in the information about study participants, that is in exposure and outcome as well as covariables.[60] The types of information bias and the potential effect on the association under study depend on the study design.

Information bias in our study concerns the validity of the exposure and outcome and arises from differential or non-differential misclassification. The direction and size of a potential information bias also depends on whether the exposure and outcome are dichotomous or categorical. In studies I–III the exposure was

categorical, and not dichotomous, so the direction of bias from a non-differential misclassification cannot be expected to be towards the null hypothesis as it is in dichotomous exposures.

In study I, AKI was the exposure; in study II, it was the outcome; and in study III, it was the study population. For some patients, AKI may have been misclassified, despite the use of consensus criteria.[13] Misclassification could have occurred because of the lack of urine output[169], the estimation of baseline PCr [35] in patients without a PCr before surgery or only one PCr measurement after surgery, or due to potential systematic errors in the laboratory measurements

Additionally, in studies I and II, we conclude that misclassification due to inclusion of patients lacking exposure information in the group without AKI (11%) posed only a minor risk of information bias, as their risk factors of AKI and associations with mortality resembled that of patients without AKI (sensitivity analyses). Moreover, AKI is an inevitable state arising in the time immediately before death, and we checked for how many patients with missing AKI information that died before they were able to be defined as having AKI and found no patients.

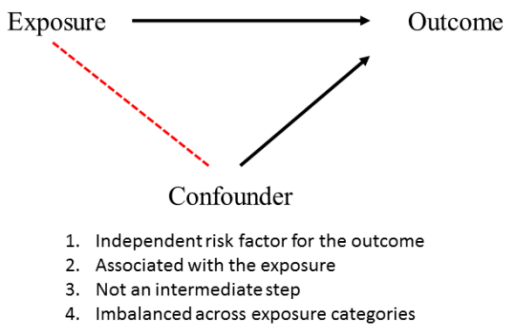
A central etiological issue of study II and III is defining the exposure window of current ACE-I/ARB use to result in the highest possible sensitivity (ability of the definition to identify current user) under consideration to specificity (the ability of the definition to avoid misclassifying former users into the user category). The effect on the outcome of adjusting the exposure window from 90 days to 30, 60 and 100 only weakened the association mildly, supporting the robustness of our definition.

ACE-I/ARB users may be misclassified in part by redeeming their prescriptions or treated differently from the common practice of these drugs. Moreover, we had only data on whether medication was continued or withheld on the day of surgery in patients undergoing surgery in one of the Danish regions (Central Denmark Region); even in these patients, some may have been advised to take their medication before admission on the day of surgery, whereby a registration of the drug was not necessarily completed. In the remaining patients we cannot know if they took their medication, because we had only information regarding whether they collected it from the pharmacy. Last, the pharmacology of ACE-I/ARB suggests that most of the drugs will still be active or present in the blood during 24 hours after the drug is taken. Therefore, some of the current users who discontinued their medication the day before surgery could still have an effect of their treatment.[131] We anticipate that the misclassification of the exposure (ACE-I/ARB current users) was likely to have been non-differential (independent of AKI in study II and of mortality in study III) and could have weakened the association between ACE-I/ARB current use and risk of AKI, as well as ACE-I/ARB current use and mortality.

Misclassification of death (outcome in study I and III, competing risk in study II) is unlikely since the Civil Registration System is updated daily and holds data on the exact date of death on all Danish citizens since 1968.

5.2.4. Confounding

A confounder is a factor that is unbalanced between the exposure groups, is associated with the exposure, is an independent risk factor for the outcome and is not a part of the causal pathway (intermediate factor) between the exposure and the outcome.[60] We can address confounding as a restriction or matching in the design phase or in the analyses phase by adjustment, stratification, or by standardization.



With the goal of minimizing any mixing effect (confounding) on the estimates of the associations from factors other than the exposure and outcome of interest, we adjusted for potential and known confounders. Furthermore, we stratified our analyses by subgroup with the purpose of revealing any difference in effect across subgroups (effect modification).

In study I, we dealt with confounding by adjusting and stratifying for potential confounders (i.e., demographics, comorbidities, and procedure-related factors) as previously described. We dealt with confounding likewise in studies II and III, although with the addition of drug use and addressing confounding by indication.

A central issue of studies II and III, as in every pharmacoepidemiological study, is the risk of confounding by indication. Confounding by indication is the issue of contrast between outcomes of individuals under treatment and those not treated because differences in disease, disease severity and other risk factors between the two groups.[118] Therefore, patients with ACE-I/ARB use undergoing CRC may be more likely to develop AKI or die, due to the indication (hypertension and heart disease) for ACE-I/ARB, and therefore anticipated inferior preoperative physical status compared with non-users. In addition to the adjustment for differences in risk factors between the exposed and non-exposed groups, we evaluated some of the confounding by indication by including a former user group in which we expected many of the same risk factors for AKI to be present. A stronger association in the current user group would then be expected to stem from the drug effect, although potentially still include the effect of a smaller difference in risk profile of patients no longer needing the medication (i.e., being healthier). Confounding by indication cannot be excluded despite these attempts to reveal and adjust for it.

We had information on lifestyle factors such as smoking, BMI, and, alcohol. Unfortunately, around 30% were missing in study I and 20% in studies II and III. Furthermore, in all studies, 20% of patients were missing in the CKD variable. We addressed this missing information by multiple imputation with the intention of reducing the potential residual confounding from misclassification of these covariates. We also investigated whether these 20% were most likely CKD or non-CKD patients, by assuming patients without

RRT and a GFR>60ml/min/1.72 m^2 after CRC surgery were non-CKD patients. According to this assumption, only 3% remained missing. However, we did not include this assumption in the CKD variable used as a covariate in the analyses, because it would be conditioning on future events/status. Moreover, preoperative comorbidities treated in the primary care setting are subject to low sensitivity in the DNPR.[168] Therefore, we included medication for the diseases from the NHSPD [148] when identifying diabetes mellitus or obstructive pulmonary disease.

In study II, we found non-hypertensive patients with current use of ACE-I/ARB to be at higher risk of AKI. This may in part be explained by the fact that patients with ACE-I/ARB prescribed for heart failure and that European guidelines are recommending to continue ACE-I/ARB in non-cardiac surgery patients with heart failure.[170] Therefore the higher risk of AKI in non-hypertensive patients with current ACE-I/ARB use compared with hypertensive patients with current use could be explained by the combination of 1) a higher proportion of current users continuing their ACE-I/ARB during surgery and 2) a higher baseline risk of AKI in patients with heart failure.

Despite the actions taken, there may still be residual confounding from available confounders (disease severity) and unmeasured confounding from unknown factors associated with the exposure and outcome (e.g. muscle waste, BP measurements, fluid balance, etc.) of information regarding certain potential confounders.

For example, we did not have data on perioperative fluid regime. When undergoing anesthesia, arterial pressure depends highly on the renin–angiotensin or the vasopressin axis. Thus, if a drug affecting either one of these axes is administered (e.g., ACE-I/ARB), it may result in an increased risk of hypotension, which can lead to AKI.[98,99] The zero fluid balance aimed for in the fast-track patients may, therefore, be too restrictive in ACE-I/ARB users by adding a factor that further complicates maintaining arterial pressure within the autoregulatory range of the kidneys.[23,24]. Consequently, administration of fluid by a restrictive regime may act as an intermediate step by strengthening the association between ACE-I/ARB use and the supervening of AKI after CRC surgery.[47,100]

5.3. Main Conclusions

The studies in this dissertation adds scientific knowledge regarding the occurrence of AKI and prognostic impact of AKI (study I), the impact of preoperative use of ACE-I/ARB on the risk of AKI (study II) and the prognostic impact of preoperative ACE-I/ARB use in patients with AKI after CRC (study III).

Study I: AKI and mortality after CRC surgery

In this population-based cohort study, AKI within 7 days after CRC surgery was frequent and associated with a 2–3-fold increased risk of death within 90 days after the surgery. Mortality seemed to increase with stage of AKI during 8-30 days after surgery and even increases in creatinine as small 50% increased mortality considerably. Although we cannot determine whether AKI itself or other postoperative complications contributed to the increased postoperative mortality in AKI patients, AKI should be considered an important prognostic factor for 90-day mortality.
Awareness of postoperative AKI, including recognition that even a small increase in creatinine is a significant marker for increased postoperative mortality in CRC patients, has been relatively limited, possibly because of the lack of studies reporting on AKI risk and prognosis in this population. Typically, a small increase in creatinine has led to a "wait and see" approach rather than initializing new steps to optimize the current status of the patient. We recommend that special attention must be paid to patients with postoperative increases in creatinine of 50% or more to optimize postoperative care with the aim of restoring normal kidney function.

Study II: ACE-I/ARB and the risk of AKI after CRC surgery

In this population-based cohort study, we found that current and former use of ACE-I/ARB was associated with an increased risk of AKI within 7 days after surgery, in particular in current users without hypertension. Although we cannot rule out that these associations were causal, it is possible that confounding by indication could have contributed to the difference in risk of AKI among non- and current users of ACE-I/ARB as well as an increase in attention paid to patients using ACE-I/ARB because their effect on postoperative AKI is still unclear. Thus ACE-I/ARB users may represent a vulnarable group of CRC surgery patients at higher risk of AKI, and we advise clinicians to keep this in mind during postoperative care to prevent or identify AKI as early as possible with the aim of reversing AKI and potentially decreasing postoperative mortality.

Study III: ACE-I/ARB use and mortality in patients with AKI after CRC surgery

In this population-based cohort study of patients with AKI after CRC surgery, we found that preoperative use of ACE-I/ARB was not substantially associated with increased mortality within the first year after AKI. As

most point estimates points towards an increased mortality, we suggest paying special attention to patients with ACE-I/ARB use and postoperative AKI during postoperative care.

6. Perspectives

The fundamental goal of medical science is to prevent disease and improve prognosis in patients, by identification of risk factors for disease and developing treatments. Through the unique identifier, the CPR number, given to all Danish citizens at birth studies linking medical and administrative databases can accomplish this by conducting large national population-based studies of risk and prognostic factors of AKI.

The available databases hold complete data on residency and vital status, information from hospital and clinical data from in- and outpatient visits, reimbursed prescriptions and laboratory data.

In light of the mortality associated with postoperative AKI and the lack of treatment for AKI, identification of risk factors for AKI and of factors affecting the prognosis of AKI is essential to prevent and improve the clinical course of patients with AKI.

This thesis leaves a number of unanswered questions:

1) Does AKI precede these complications or develop as a consequence of them?
2) Is the restrictive fluid regime of the Enhanced Recovery after Surgery protocol (the fast-track regime) contributing to the occurrence of AKI after CRC surgery?
3) If preoperative use of ACE-I/ARB is truly associated with AKI after CRC surgery, should these drugs be withheld during CRC surgery or continued?
4) Would a larger study change the results of study III? If mortality is related to the use of ACE-I/ARB in CRC surgery patients with postoperative AKI, can it then be explained by differences in factors such as vasopressor/inotrope therapy, fluid administration or the development of certain complications related to the pharmacological effect of ACE-I/ARB?

To limit potential misclassification when studying postoperative complications on data from the DCCG database, the Clavien–Dindo grading was introduced in 2014 to define categories of the severity of postoperative complications. The DCCG database also included other more precise definitions of postoperative surgical complications. Furthermore, since 2015, anastomotic leakage has been registered with a date, so that from 2015 an onwards, it is now possible to study the timing of AKI and postoperative complications after CRC surgery using data from the DCCG database.

As the electronic patient chart has been introduced in Denmark, detailed perioperative information on medications, complications, fluid administration, urine output, and complications can be linked with administrative and clinical databases. In this way, the validity of future non-experimental studies can be strengthened, and the association between the restrictive fluid regime and the development of AKI after CRC surgery can be studied. The Danish registries and access to the electronic patient chart provide us with a unique chance to conduct large-scale pharmacoepidemiological studies, in which we could test whether ACE-I/ARBs should be withheld or continued before non-cardiac surgery to reduce the risk of AKI and

postoperative mortality, such as in a head-to-head comparison with other antihypertensive drugs as an alternative to a randomized clinical trial. Randomized clinical trials are not suitable for a population of many patients with multimorbidity because they are likely to be ineligible.

At the time of study, we had only access to laboratory data from northern Denmark and in-hospital medication for Central Denmark Region. But the Danish data protection agency has established a nationwide database for routine biomarkers (initial enrollment of data in 2013 from some regions), which together with data from electronic patient charts from hospital contacts, could enable a larger study in the future, that could answer the question of whether being a current user of ACE-I/ARB is associated with increased mortality in patients with AKI after CRC surgery. Moreover, the availability of data on perioperative vasopressor/inotrope therapy as well as fluid administration enables us to address whether the underlying mechanism of a potential increased mortality is related to the development of other postoperative complications.

7. Summary

Acute kidney injury (AKI), a sudden decline in the kidneys excretory function, is a common complication of major surgery. and susceptibility to AKI increases with age and comorbidities. With colorectal cancer (CRC) being a disease primarily of the elderly and life expectancy currently increasing, the number of patients with comorbidities undergoing CRC surgery is rising. To prevent and manage AKI, it is of great importance to understand the clinical course of AKI in CRC surgery patients.

This thesis includes three registry-based cohort studies on risk for and prognosis of AKI in patients undergoing CRC surgery in the Northern Denmark in 2005–2011 (study I) and 2005–2014 (study II and III). We examined the occurrence and prognostic impact of AKI after CRC surgery. In study II, we examine the impact of ACE-I/ARB use on the risk of AKI in CRC surgery patients, and in study III, we examined the association of ACE-I/ARB use on prognosis after AKI in CRC surgery patients.

We included 6,580 patients study I and 20.3% developed AKI. Among patients with AKI, 8–30, 31–90 and 91–365–day mortality rates were 10.1% (95% confidence interval [CI]: I 8.6–11.9%), 7.8% (95% CI: 6.4–9.5%), and 12.0% (95% CI: 10.3–14.2%), respectively. AKI was associated with increased 8–30 day–mortality (adjusted hazard ratio (aHR) 4.01 95% CI: 3.11–5.17) and 31–90 day mortality (aHR 2.08 95% CI: 1.60–2.69), while 91–365 day mortality was not increased. Also, the strength of the association seemed to increase with increasing stage of AKI during 8–30 days after surgery.

In study II, we identified 9,932 patients, 21.3% ACE–I/ARB current users, 6.4% former users, and 72.3% non–users. The seven–day AKI risk, including death as a competing risk, was 26.4% (95% CI: 24.6%–28.3%) for current users, compared with 25.2% (95% CI: 21.9%–28.6%) for former users, and 17.8% (95% CI: 17.0%–18.7%) for non–users. The adjusted relative risks of AKI within 7 days after surgery were 1.20 (95% CI: 1.09–1.1.32) for current users and 1.16 (95% CI: 1.01–1.19) for former users, compared with non–users.

In study III, we included 2,000 patients with AKI after CRC surgery. A total of 28% were current users, 8.1% were former users, and 64.0% were non–users. Among current users, 0–30, 31–90, and 91–365–day mortality rates were 16.3% (95% CI: 15.6–19.6), 6.7% (95% CI: 4.7–9.3) and 9.0% (95% CI: 6.6–12.1%).

We did not find a substantial association between current (aHR 1.11; 95% CI: 0.91–1.35) or former (aHR 1.29; 95% CI: 0.96–1.73) use of ACE-I/ARB and one–year mortality.

In conclusion, our studies showed that AKI after CRC surgery is common and associated with increased mortality, if creatinine increases 50% or more, within the first 90 days after the surgery. ACE-I/ARB users is a subgroup of CRC surgery patients with increased increased risk of AKI, and we did not find substantial evidence of increased one-year mortality in ACE-I/ARB users with AKI after CRC surgery.

8. Dansk resume

Akut nyrepåvirkning (AKI), er beskrevet ved et pludseligt fald i nyrens udskillelsesevne. Det er en hyppigt forekommende komplikation til store operationer og følsomheden for at udvikle AKI øges med alder og konkurrerende sygdomme. Tyk- og endetarms kræft (CRC) opstår primært sent i livet og da den forventede middellevetid er stigende, vil et øget antal operationer for CRC blive udført på patienter med konkurrerende sygdomme og behandlinger herfor. For at kunne forebygge og håndtere patienter med AKI efter operationer for CRC er det yderst vigtigt at forstå the kliniske forløb af AKI hos disse patienter.

Denne afhandling omhandler tre registerbaserede kohortestudier om risiko og prognose for patienter med AKI efter CRC operation foretaget i det nordlige Danmark mellem 2005-2011 (studie I) og mellem 2005-2014 (studie II & III). Formålet med afhandlingen er at undersøge: (1) hyppigheden af AKI og effekten af AKI på prognosen for patienter opereret for CRC, (2) effekten af angiotensin-converting enzyme hæmmere (ACE-I) og angiotensin receptor blokkere (ARB) brug på risikoen for at udvikle AKI efter operation for CRC, (3) sammenhængen mellem brug af ACE-I/ARB og et-års dødeligheden hos patienter med AKI efter CRC operation.

I studie I inkluderede vi 6.580 patienter og 20,3 % af disse udviklede AKI. Blandt patienter med AKI var 8-30, 31-90 og 91-365 dages dødeligheden henholdsvis 10,1 %, 7,8 % og 12,0 %. Efter justering for potentielle konfoundere fandt vi at AKI var associeret med en fire gange øget 8-30 dages dødelighed og en to gange øget 31-90 dages dødelighed. 91-365 dages dødeligheden derimod var ikke øget for patienter med AKI. Yderligere fandt vi at associationen mellem AKI og dødeligheden 8-30 dage efter operationen steg med stigende sværhedgrad af AKI.

I studie II, identificerede vi 9.937 patienter, hvoraf 21,3 % var ACE-I/ARB nuværende brugere, 6,4 % tidligere brugere og 72,3 % ikke-brugere. Syv-dages risikoen for AKI, under hensynstagen til konkurrerende risici fra død, var 26,4% for nuværende brugere, 25,2 % for tidligere brugere og 17,8 % for ikke brugere. Efter justering fandt vi at nuværende brug af ACE-I/ARB inden operationen var forbundet med en 20% højere risiko for AKI inden for syv dage efter operationen end ikke brugere og at tidligere brug var forbundet med en 16% højere risiko for AKI end ikke brugere.

In studie III, inkluderede vi 2.000 patienter med AKI efter CRC operation. Otteogtyve procent var nuværende, 2.1 % var tidligere og 64.0 % var ikke brugere af ACE-I/ARB. Blandt nuværende brugere var 0-30, 31-90 og 91-365 dages dødeligheden henholdsvis 16.3, 6.7 % og 9.0 %. Efter justering for konfounding fandt vi ikke evidens for en sammenhæng mellem brug af ACE-I/ARB og et-års dødelighed hos patienter med AKI efter operation for CRC.

Vi konkluderer at AKI efter CRC operation er hyppigt forekommende og forbundet med øget dødelighed, selv ved små stigninger (>50 %) i kreatinin i de første 90 dage efter operationen. CRC kirurgiske patienter i behandling med ACE-I/ARB udgør en gruppe med højere risiko for AKI sammenlignet CRC kirurgiske

patienter der ikke er i behandling med ACE-I/ARB. ACE-I/ARB brug er ikke substantielt forbundet med et-års dødelighed hos patienter med AKI efter CRC operation.

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10. Appendices

Appendices I–III contain the full version of papers I-III:

- Appendix I: Paper I
- Appendix II: Paper II
- Appendix III: Paper III

- **Appendix I:**

Paper I

Acute kidney injury and 1-year mortality after colorectal cancer surgery: A population-based cohort study

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ABSTRACT

Objectives Although acute kidney injury (AKI) is a frequent postoperative complication, its impact on mortality after colorectal cancer (CRC) surgery is poorly understood. We examined occurrence of postoperative AKI among CRC surgery patients and the impact of AKI on subsequent one-year mortality.

Design Observational cohort study. We defined the exposure, AKI, as a 50% increase in plasma creatinine or initiation of renal replacement therapy within seven days after surgery or an absolute increase in creatinine of 26μmol/L within 48 hours.

Setting Population-based Danish medical databases.

Participants A total of 6 580 patients undergoing CRC surgery in Northern Denmark during 2005-2011 were included from the Danish Colorectal Cancer Group database.

Outcomes measure Occurrence of AKI and 8-30, 31-90, and 91-365 day mortality in patient with or without AKI.

Results: AKI occurred in 1 337 patients (20.3%) of the 6 580 patients who underwent CRC surgery. Among patients with AKI, 8-30, 31-90, and 91-365-day mortality rates were 10.1% (95% CI 8.6%-11.9%), 7.8% (95% CI 6.4%-9.5%), and 12.0% (95% CI 10.3%-14.2%), respectively. Compared with patients without AKI, AKI was associated with increased 8-30-day mortality (adjusted hazard ratio [aHR] = 4.01 [95% CI 3.11-5.17]) and 31-90-day mortality (aHR=2.08 [95% CI 1.60-2.69]), while 91-365-day mortality was not increased. We observed no major differences in stratified analyses.

Conclusions: AKI after surgery for CRC is frequent and associated with a substantially higher risk of death within 90 days after surgery. AKI should be considered an important prognostic factor for 90-day mortality.

ARTICLE SUMMARY

Strengths and limitations of this study

- No former studies examined the impact of AKI (and stages) on 1-year mortality CRC surgery.
- 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 (KDIGO).
- Urine output was unavailable which may have led to a minor underestimation of AKI.

INTRODUCTION

Colorectal cancer (CRC) is the third most common cancer in the world with an annual incidence of 1 360 000.[1] Surgery plays a crucial role in the treatment of CRC. As the median age is above 70 years at the time of CRC diagnosis, CRC surgery is often performed in elderly patients with comorbidities. Thirty-day mortality[2–5] after CRC surgery has been reported to range from 0.4 to 23% and 7 to 65% of CRC surgery patients experience postoperative complications[2,6] within 30 days after the surgery. The wide range of complication and mortality rates could be explained by the fact that the studies are heterogeneous as regards the included procedures and the urgency of surgery.

Acute kidney injury (AKI) is a common postoperative complication[7] defined by a sudden decline in the excretory function of the kidneys, ranging from mild subclinical AKI to AKI requiring renal replacement therapy (RRT).[8,9] In a Danish population-based study of mortality after emergency surgery for colon cancer, mortality during the first 30 days after surgery was increased in patients with decreased kidney function (requiring renal replacement therapy).[10] A small cohort study included 288 medical records from elective rectal cancer surgeries and found an AKI occurrence of 3.8% and an in-hospital mortality of 18.2% in patients with AKI, whereas, patients without AKI had an in-hospital mortality of 0.7%.[11] Studies of other major abdominal surgery reported postoperative AKI in 3% -35% of patients,[7] and found AKI to be associated with increased mortality. [2] However, no previous study has examined the impact of AKI and AKI stages on mortality within a year after CRC surgery. This is of particular interest, because patients undergoing CRC surgery may be more susceptible to postoperative AKI than patients undergoing other abdominal surgery, as CRC patients frequently present with risk factors for AKI, such as advanced age, comorbidities as well as the cancer itself.[8,12] Knowledge about occurrence and prognosis of postoperative AKI in patients undergoing CRC surgery could help determine whether these are high-risk patients requiring special attention after surgery. Therefore, we examined the occurrence of AKI and its prognostic impact on mortality within one year after CRC surgery.

MATERIALS AND METHODS

Study Design and Setting

This cohort study was conducted in Northern Denmark (the North and Central Denmark Regions, with 2,074,956 cumulative inhabitants during the study period) using prospectively collected data from medical databases.[13–17] Tax-supported health care is provided by the Danish National Health Service to all Danish residents. Since 1968, all residents have been assigned a unique 10-digit civil registration number (CPR number), which allows unambiguous individual-level linkage between public databases.[15] In the current study, CRC surgeries were performed at nine hospitals in the study area.

Patient and public involvement

Patients and public were not involved in the development or the design of this study

Study Population

This study included all patients who underwent first time CRC surgery January 2005 to December 2011. Patients were identified in the Danish Colorectal Cancer Group (DCCG.dk) database.[17] This database, established in May 2001, contains information on CRC patients covering demographics, treatments, complications including occurrence of AKI requiring RRT, and mortality within 30 days after surgery. To ensure availability of baseline laboratory data, we required residency in the study area in a period with laboratory data available.[13] Moreover, patients with dialysis within 30 days before surgery and patients who died within seven days after surgery were excluded from the study.

Acute Kidney Injury

Data on plasma creatinine (PCr) (equivalent to serum creatinine [SCr]) were retrieved from the clinical laboratory information system (LABKA) research database.[13,18] This database contains PCr test results collected by general practices and hospitals in the study area since 1990. We defined AKI

as a 50% increase in PCr, initiation of RRT within seven days after surgery, or an absolute increase in creatinine of 26μmol/L within 48 hours. We also identified the highest AKI stage occurring within seven days after CRC surgery according to the SCr criteria in the recent Kidney Disease Improving Global Outcome (KDIGO) consensus criteria, as follows: no AKI, Stage 1 AKI, Stage 2 AKI, and Stage 3 AKI (Figure 1).[8] In our main analysis, we included patients without a PCr measurement within seven days following surgery (*i.e.*, lacking exposure information) in the group of patients without AKI, based on two rationales. First, a blood draw is minimally invasive and low cost; hence, the indication threshold is low. Second, the hospitals that contributed the most patients without exposure information followed a fast-track protocol.[2,3] This protocol advises physicians and nurses to refrain from postoperative blood analyses if a patient is healthy and recovering well. Hence, we expected patients without exposure information to resemble healthy patients without AKI. To examine this assumption, we created a second version of Table 1, putting patients with missing AKI data in a separate category. Patients lacking one or more PCr measurements within seven days following surgery (10.9%, n = 602) appeared healthier than patients with AKI and, in general, resembled patients without AKI.

Table 1. Patient characteristics by acute kidney injury stage, Denmark, 2005-2011.

Patient characteristics	Without AKI	AKI	AKI Stage			Total
			Stage 1	Stage 2	Stage 3	
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
Total	5 243 (100.0)	1 337 (100.0)	858 (100.0)	284 (100.0)	195 (100.0)	6 580 (100.0)
Sex						
Female	2 565 (48.9)	513 (38.4)	329 (38.3)	111 (39.1)	73 (37.4)	3 078 (46.8)
Male	2 678 (51.1)	824 (61.6)	529 (61.7)	173 (60.9)	122 (62.6)	3 502 (53.2)
Age (years)						
0-49	277 (5.3)	40 (3.0)	21 (2.4)	8 (2.8)	11 (5.6)	317 (4.8)
50-59	753 (14.4)	130 (9.7)	82 (9.6)	35 (12.3)	13 (6.7)	883 (13.4)
60-69	1 555 (29.7)	323 (24.2)	196 (22.8)	74 (26.1)	53 (27.2)	1 878 (28.5)
70-79	1 643 (31.3)	497 (37.2)	313 (36.5)	103 (36.3)	81 (41.5)	2 140 (32.5)
≥ 80	1 015 (19.4)	347 (26.0)	246 (28.7)	64 (22.5)	37 (19.0)	1 362 (20.7)
BMI						
Normal	1 755 (33.5)	375 (28.0)	245 (28.6)	83 (29.2)	47 (24.1)	2 130 (32.4)
Underweight	124 (2.4)	26 (1.9)	22 (2.6)	3 (1.1)	1 (0.5)	150 (2.3)
Overweight	1 835 (35.0)	512 (38.3)	317 (36.9)	111 (39.1)	84 (43.1)	2 347 (35.7)
Missing	1 529 (29.2)	424 (31.7)	274 (31.9)	87 (30.6)	63 (32.3)	1 953 (29.7)
Heart disease	67 (1.3)	23 (1.7)	16 (1.9)	5 (1.8)	2 (1.0)	90 (1.4)
Diabetes mellitus	479 (9.1)	185 (13.8)	115 (13.4)	43 (15.1)	27 (13.8)	664 (10.1)
Liver disease	50 (1.0)	19 (1.4)	10 (1.2)	6 (2.1)	3 (1.5)	69 (1.0)
Arterial hypertension	1 260 (24)	479 (35.8)	304 (35.4)	95 (33.5)	80 (41.0)	1 739 (26.4)
OPD	512 (9.8)	166 (12.4)	110 (12.8)	32 (11.3)	24 (12.3)	678 (10.3)
CKD						

Stage 3	834 (15.9)	347 (26.0)	251 (29.3)	59 (20.8)	37 (19.0)	1 181 (17.9)
Stage 4 or higher	39 (0.7)	48 (3.6)	25 (2.9)	2 (0.7)	21 (10.8)	87 (1.3)
Cancer type						
Colon	3 481 (66.4)	862 (64.5)	540 (62.9)	186 (65.5)	136 (69.7)	4 343 (66.0)
Rectum	1 762 (33.6)	475 (35.5)	318 (37.1)	98 (34.5)	59 (30.3)	2 237 (34.0)
Urgency of surgery						
Elective	4 540 (86.6)	1 102 (82.4)	713 (83.1)	232 (81.7)	157 (80.5)	5 642 (85.7)
Acute	542 (10.3)	208 (15.6)	129 (15.0)	47 (16.5)	32 (16.4)	750 (11.4)
Missing	161 (3.1)	27 (2.0)	16 (1.9)	5 (1.8)	6 (3.1)	188 (2.9)

Abbreviations: AKI, Acute Kidney Injury; ASA, American Society of Anesthesiology; BMI, Body Mass Index; CKD, Chronic Kidney Disease; OPD, Obstructive Pulmonary Disease

Mortality

We obtained data on mortality, from day 8 after CRC surgery and until one year after this 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.[15]

Covariates

Preoperative covariates were chosen based on their potential association with AKI and with postoperative mortality.[7–9,19] The Danish National Patient Registry (DNPR) contains information on all hospitalizations since 1977, outpatient visits since 1994, and emergency room visits since 1995. The DNPR includes information on diagnoses, procedures, and admission/discharge dates. Chronic kidney disease (CKD), a strong predictor for AKI, was identified using PCr measurements from the LABKA database. We defined CKD as an estimated glomerular filtration rate (eGFR) <60 ml/min/1.73 m^2 lasting at least three months within the two years before CRC surgery.[20]

The following covariates were identified from the DNPR, based on an inpatient or outpatient hospital contact for a given condition within ten years before CRC surgery: obstructive pulmonary disease, arterial hypertension, diabetes mellitus, heart disease, and liver disease. To improve the sensitivity of diabetes mellitus and obstructive pulmonary disease diagnoses, we searched the National Health Service Prescription Database (NHSPD) for previous prescriptions of medications used to treat these conditions.[16] The NHSPD contains records for all reimbursable drugs dispensed in community pharmacies in Denmark since 2004. Body Mass Index (BMI) was computed from

weight and height data retrieved from the DCCG database,[12] divided into three categories: underweight (<18.5m^2/kg), normal weight (18.5-24.9m^2/kg), and overweight (≥25m^2/kg).[21]

Statistical Methods

Patient characteristics, including demographics, comorbidities, and information from the hospitalization that included CRC surgery, were tabulated by AKI stage (Table 1).

Because we assessed AKI within the first seven days after surgery, we followed patients from day eight after surgery until death, emigration, or up to one year after surgery, whichever came first. The Kaplan-Meier method was used to compute cumulative mortality curves (1 - survival function) for patients with and without AKI.[22] AKI was further disaggregated into AKI Stages 1-3.[8] We computed hazard ratios (HRs) of death within 8 to 30, 31 to 90, and 91 to 365 days after surgery, comparing patients with AKI (and for each stage of AKI) with patients without AKI, using a Cox proportional hazards regression model adjusted for potential confounders. Confounders included age group (0-49, 50-59, 60-69, 70-79, ≥80), gender, BMI category, CKD (without CKD, stage 3 or stage 4 and higher), diabetes, obstructive pulmonary disease, hypertension, liver disease, heart disease, tumor site (colon or rectum), and urgency of surgery (acute or elective). The assumption of proportional hazards was checked graphically and found appropriate within all follow-up periods. To address potential different effects in subgroups (effect modification), we repeated the analyses stratified by sex, age, CKD stage, acute *vs.* elective surgery, surgical approach (open or minimally invasive), type of surgical procedure, diabetes mellitus, and year of surgery.

Missing Data

Information on lifestyle variables (BMI, smoking, and alcohol use) was missing for approximately 30% of patients (Table 1) and 20% for CKD. We did not have exact date of anastomosis leakage and other surgical complications occurring within 30 days after surgery and were therefore not able to assess the temporal relationship.

We used two approaches to address potential misclassification stemming from missing data. First, we conducted a complete case analysis. Second, in a sensitivity analysis, we performed multiple imputations, calculating average HRs for 30 imputed datasets. In the sensitivity analysis, we estimated values for missing data for five categorical variables (CKD, urgency of surgery, BMI, smoking, and alcohol intake) using all covariates, the outcome, and the Nelson-Aalen estimator of the cumulative baseline hazard to observed survival time.[23] We expected that data were missing at random, but not completely at random, in our study because younger and healthier patients were more likely to have missing data.

Timing of Acute Kidney Injury

We addressed timing of AKI and other complications as follows. For all patients who developed AKI within seven days after CRC surgery, we cross-tabulated the first day of AKI with typical late complications (occurring 6-8 days post-surgery), *e.g.*, anastomosis leakage and fascial dehiscence (Figure 2).

All analyses were conducted using the Stata software package, version 13.1 (StataCorp, College Station, TX, USA). All data were obtained from Danish registries and, in accordance with Danish law, their use did not require ethical approval or informed consent.

Data Statement

The study was approved by the Danish Data Protection Agency (record no. 2015-57-0002, Aarhus University record no. 2016-051-000001/423). The data, analytic methods, and study materials will not be made available to other researchers for purposes of reproducing the results or replicating the procedure. Such disclosure would conflict with the regulations for use of Danish health care data.

RESULTS

Study Population and AKI Occurrence

We identified 6 768 CRC patients residing in Northern Denmark who underwent CRC surgery during 1 January 2005 - 31 December 2011. Of these, 188 patients were excluded due to either dialysis within 30 days before surgery (n = 13) and death before start of follow-up (eight days after surgery) (n = 175). Of the 175 patients dying within seven days after surgery, 113 (64.6%) had AKI and 62 (35.4%) did not have AKI. In total, 6 580 patients were included in the analyses. Postoperative AKI within seven days after surgery occurred in 1 337 patients (20.3%). AKI stage was distributed as follows among study patients: 858 had Stage 1 AKI (13.0%), 284 had Stage 2 AKI (4.3%), and 195 had Stage 3 AKI (3.0%) (Figure 1). Among patients with Stage 3 AKI, 128 (65.6%) received RRT.

Descriptive Data

Total follow-up time was 5 741 person-years and there was no loss to follow-up. Median age was 71.3 years, 2 678 (53.3%) patients were male, and 3 481 (66.0%) had colon cancer (Table 1).

Compared to patients without AKI, those with AKI were more commonly men, aged 70 years or more, with a history of smoking, and a BMI categorized as overweight (Table 1). Patients with AKI also had a higher American Society of Anesthesiologists' (ASA) Classification of Physical Health score.[23] Thus, patients with AKI more often had preoperative CKD, diabetes mellitus, and arterial hypertension than patients without AKI. Moreover, patients with AKI more often developed postoperative bleeding, ileus, fascial dehiscence, and infectious complications than patients without AKI. The prevalence rate ratio of anastomosis leakage in patients with AKI compared to patients without AKI was 3.71 (95% CI 3.03-4.53).

Mortality

Cumulative 8-30-day mortality was higher in patients with AKI (10.1%) than in patients without AKI (Table 2). Compared to patients without AKI, the adjusted HR for patients with AKI was 4.01 (95%

confidence interval [CI] 3.11-5.17). Mortality increased by AKI stage and was higher for patients with stage 1 AKI than for patients without AKI (Table 2 and Figure 3).

Table 2. Mortality outcomes (8-30, 31-90, and 91-365-day mortality) by acute kidney injury stage.

Mortality Outcomes	Person-time (days)	Number of outcomes	Cumulative mortality % (95% CI)	Crude HR (95% CI)	Adjusted HR[a] (95% CI)
8-30-day mortality					
Without AKI	124 430	115	2.2 (1.8,2.6)	Ref.	Ref.
With AKI	30 004	135	10.1 (8.6,11.9)	4.83 (3.76,6.19)	4.01 (3.11,5.17)
Stage 1	19 712	62	7.2 (5.7,9.2)	3.38 (2.49,4.61)	2.62 (1.91,3.59)
Stage 2	6 243	30	10.6 (7.5,14.8)	5.16 (3.45,7.70)	4.83 (3.21,7.25)
Stage 3	4 049	43	22.1 (16.9,28.6)	11.20 (7.92,16.0)	10.40 (7.17,15.0)
31-90-day mortality					
Without AKI	307 089	168	3.3 (2.8,3.8)	Ref.	Ref.
With AKI	70 051	92	7.8 (6.4,9.5)	2.45 (1.90,3.15)	2.08 (1.60,2.69)
Stage 1	46 696	57	7.2 (5.6,9.2)	2.23 (1.65,3.00)	1.87 (1.38,2.54)
Stage 2	14 980	16	6.3 (3.9,10.1)	1.95 (1.17,3.25)	1.80 (1.08,3.02)
Stage 3	8 375	21	13.8 (9.2,20.4)	4.55 (2.89,7.17)	3.78 (2.36,6.06)
91-day to 1-year mortality					
Without AKI	1 296 433	487	9.8 (9.0,10.7)	Ref.	Ref.
With AKI	285 258	131	12.0 (10.3,14.2)	1.25 (1.03,1.51)	1.11 (0.92,1.35)
Stage 1	189 637	92	12.5 (10.3,15.1)	1.29 (1.03,1.61)	1.12 (0.89,1.41)
Stage 2	61 774	25	10.5 (7.2,15.2)	1.08 (0.72,1.61)	1.06 (0.71,1.58)
Stage 3	33 847	17	13.0 (8.3,20.0)	1.33 (0.82,2.16)	1.16 (0.71,1.91)

[a] Adjusted for age (categories: 0-49, 50-59, 60-69, 70-79, and ≥80 years), gender, BMI category, CKD stage (3-5), diabetes mellitus (yes/no), obstructive pulmonary disease, hypertension, liver disease, heart disease, tumor site, and acute vs. elective surgery.
Abbreviations: AKI, Acute Kidney Injury; BMI, Body Mass Index; CKD, Chronic Kidney Disease; CI, Confidence Interval; HR, Hazard Ratio

For patients who survived the first 30 days after CRC surgery, cumulative mortality during the following 31-90 days was higher in patients with AKI (7.8%) than in patients without AKI (3.3%) (Table 2). The adjusted HR (aHR) for mortality was 2.08 (95% CI 1.60-2.69) in patients with AKI compared to patients without AKI. Mortality also appeared to increase by AKI stage (Table 2 and Figure 3).

Cumulative 91-365-day mortality following surgery initially appeared higher in patients with AKI compared to patients without AKI: 12.0% *vs.* 9.8% (Table 2 and Figure 3). However, the association attenuated after adjustment (aHR = 1.11 [95% CI 0.92-1.35]).

Sensitivity Analyses

Sensitivity analyses performed to address missing data, including both multiple imputation and a complete case analysis, yielded no discernible change in mortality.

Subgroup Analyses

While we observed no major differences between subgroups, our analyses yielded aHRs with very wide CIs, making the point estimates less reliable and precluding conclusions about the presence of effect modification.

Timing of AKI and Late Complications after Surgery

Overall, as well as in patients with late complications such as anastomosis leakage or fascial dehiscence, AKI occurred most frequently within one to four days after surgery.

DISCUSSION

Key Results

In this population-based cohort study, we found that 20% of patients developed AKI within seven days following CRC surgery. AKI was associated with a twofold to threefold higher risk of mortality within the first 90 days after CRC surgery even in patients with stage 1 AKI. In the period 91-365 days after surgery, mortality was similar in patients with and without AKI, after adjustment. During the first 8-30 days after surgery, the association between postoperative AKI and mortality appeared to increase with higher AKI stage. In general, patients with AKI had more postoperative complications.

Previous Studies

Two studies reported on kidney dysfunction and mortality in postoperative CRC patients.[10,11] Iversen *et al*. examined postoperative complications and mortality in 2,157 Danish CRC patients who underwent emergency surgery.[10] However, their study included only AKI requiring RRT. While AKI was reported by surgeons to the DCCG database within 30 days, the severity of AKI requiring RRT reduced the risk of underreporting. Iversen *et al.* found that 2.0% of postoperative CRC patients had

AKI requiring RRT and 30-day mortality among these patients was 68%. This is comparable with our results for patients with Stage 3 AKI who received RRT.[10] The other study did investigate occurrence of all AKI stages after rectal cancer resections, although mortality (in-hospital) was only reported for overall AKI (18.2%).[11]

Our results also are consistent with reported prevalences of 3%-35% for postoperative AKI and 0.5%-25% rates of all-cause postoperative mortality within the first year in patients who underwent major abdominal surgery.[7]

Strengths and Limitations

The risk of selection bias in our study was limited for three reasons. First, patients were included in relevant databases as part of the prospective registration of data for administrative purposes (DNPR, CRS, LABKA, and NHSPD) or to evaluate clinical quality (DCCG) in Danish hospitals**.** Second, study participants had uniform access to healthcare with complete follow-up. Third, the completeness of the databases (85% to 99%) and of most variables were high. [13–17]

Supported by the results of our sensitivity analyses, we conclude that misclassification due to inclusion of patients lacking exposure information in the group without AKI (11%) posed a minor risk of information bias.

The KDIGO criteria include urine output. As in many other studies in non-ICU settings, AKI staging for our study was performed without information on urine output, which was unavailable. Consequently, the lack of data on urine output may have led to misclassification that could have biased our results towards the null. We expect that the bias is limited since SCr alone has a stronger association with mortality than urine output. [24,25]

In our study, AKI may have been related to other surgical complications and accompanying reoperations. Unfortunately, the date of postoperative complications is unavailable in the DCCG

database. Therefore we could not assess the timing of AKI and development of other postoperative complications that could potentially lead to AKI.

As well, information on BMI (self-reported at hospital admission) was missing for 30% of patients. A multiple imputation analysis addressing this missing information yielded only minor changes in our results. Despite this analysis and extensive adjustment for potential confounders including lifestyle variables, we cannot entirely rule out unmeasured confounding from such factors as fluid management, for which we had no information, and residual confounding. Still, our study clearly showed that AKI is a marker for increased risk of death after CRC surgery.

Interpretation

AKI is a multifactorial condition, and in the operative setting, relevant factors include response to anesthesia (*e.g.,* peripheral vasodilatation and myocardial depression) and surgery (increase in the antidiuretic hormone and aldosterone), as well as the effect of fluid depletion. Major surgery introduces the risk of fluid depletion at several stages, *e.g.,* preoperative nil-by-mouth regimen, perioperative blood and intravascular fluid loss, extravasation of fluid from the vascular compartment (third-space effect), insensible fluid losses, and the pathology of the disease itself.

AKI also could develop from complications such as sepsis or electrolyte derangement associated with ileus. This could be due to global hypoperfusion of the kidney if the afferent arteriole dilation and efferent arteriole vasoconstriction response initiated by the kidney does not result in adequate glomerular filtration. Further, hypotension can lead to dysfunctional intrarenal microcirculation due to patchy areas of hypoperfusion in the kidney and potentially add to the risk of developing AKI.[26–29]

AKI most frequently occurred during the initial days following surgery. In patients with late complications (ileus, fascial dehiscence, or anastomotic leakage) there was an additional peak after 5-6 days, corresponding to reoperations for these complications. AKI might also contribute to the

development of such postoperative complications. This hypothesis needs to be investigated further in studies in which the timing of AKI and postoperative complications can be ascertained.

The results of the study are generalizable to other CRC surgery settings with a population resembling the Danish population despite our restriction to Region Nord and Region Mid, because the Danish Healthcare system is homogenous across regions, hospitals, coding practice, socioeconomic characteristics and health care usage.[30]

In conclusion, AKI occurred in approximately 20% of patients undergoing CRC surgery and was associated with increased mortality throughout the first 90 days following surgery, even in patients with stage 1 AKI (*i.e*, with more than a 50% increase in creatinine). Thus, early detection of AKI and correction of fluid and electrolyte derangement is clearly important. An interventional study is required to examine whether such interventions will reduce the rate or at least the severity of postoperative complications.

Author Contributions

CS: Protocol, data retrieval and management, analyses, manuscript.

HG: Protocol, assistance with data management and analyses, major revision of the manuscript.

LHI: Discussion and choice of inclusion/exclusion criteria for patients, based on extensive knowledge of the Danish Colorectal Cancer Group database and clinical skills, major revision of the manuscript.

HTS: Protocol, discussion and choice of analyses, major revision of the manuscript.

CFC: Protocol, discussion and choice of analyses, major revision of the manuscript.

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Competing interests

None to declare.

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TABLE AND FIGURE LEGENDS

Table 1. Patient characteristics by acute kidney injury stage, Denmark, 2005-2011.

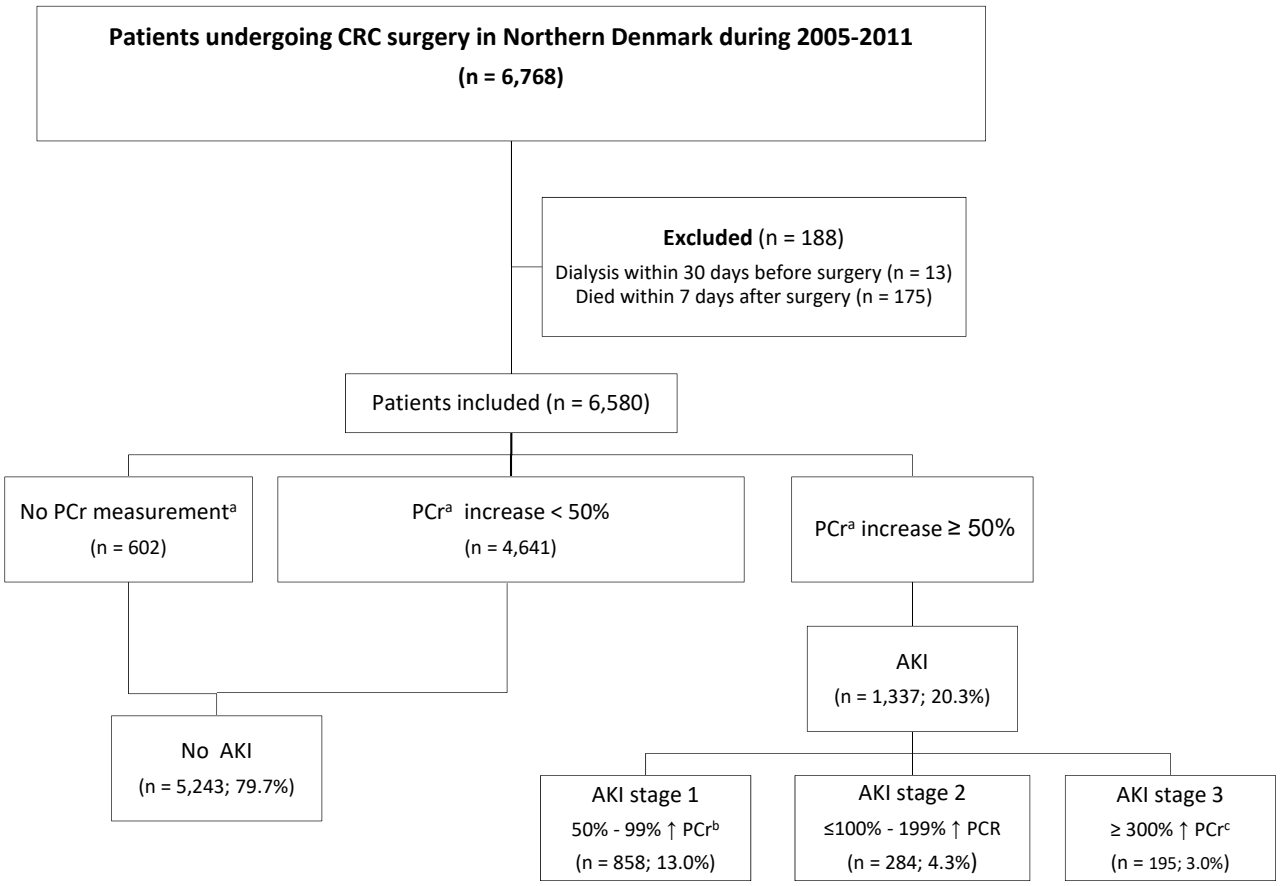
Table 2. Mortality outcomes (8-30, 31-90, and 91-365-day mortality) by acute kidney injury stage.

Figure 1. Flow chart and acute kidney injury definition.

Figure 2. Number of patients who developed acute kidney injury, by day after surgery for all patients. Abbreviations: AKI, Acute Kidney Injury.

Figure 3. Cumulative one-year mortality by acute kidney injury stage within seven days after colorectal cancer surgery, Northern Denmark, January 2005 - December 2011. Abbreviations: Acute Kidney Injury, AKI; Colorectal Cancer, CRC.

Figure 1. Flow Chart.



[a] Within seven days after surgery.
[b] Or a 26,5 µmol/l increase within two days after surgery.
[c] Or a PCr above 353.6 µmol/l, with an acute increase of at least 44 µmol/l or with acute administration of dialysis.
Abbreviations: AKI, Acute Kidney Injury ; CRC, colorectal cancer; PCr, Plasma Creatinine.

Figure 2. Number of patients who developed acute kidney injury, by day after surgery for all patients. Abbreviations: AKI, Acute Kidney Injury.

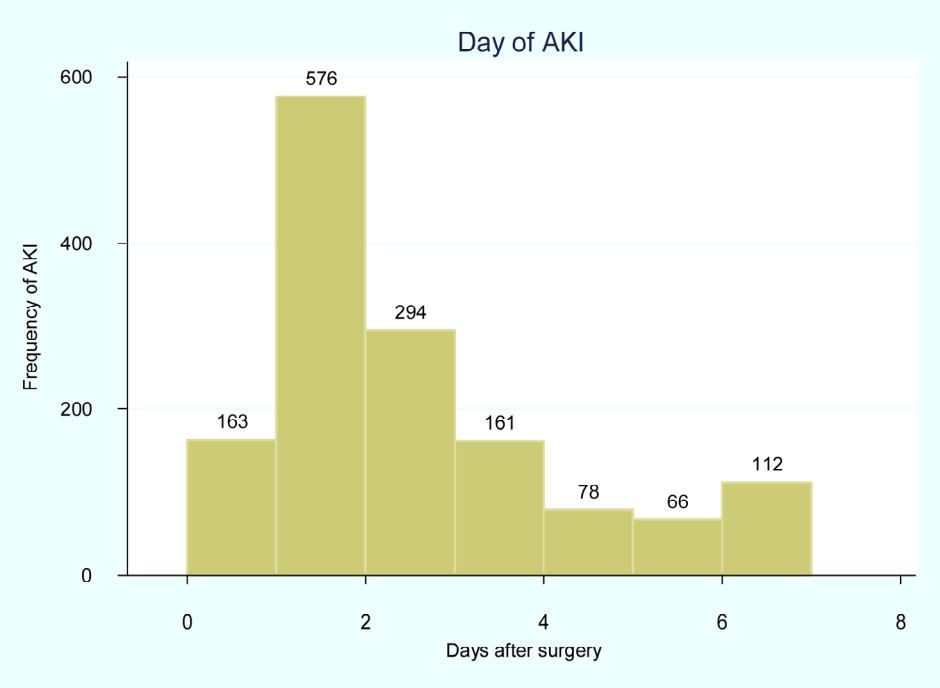
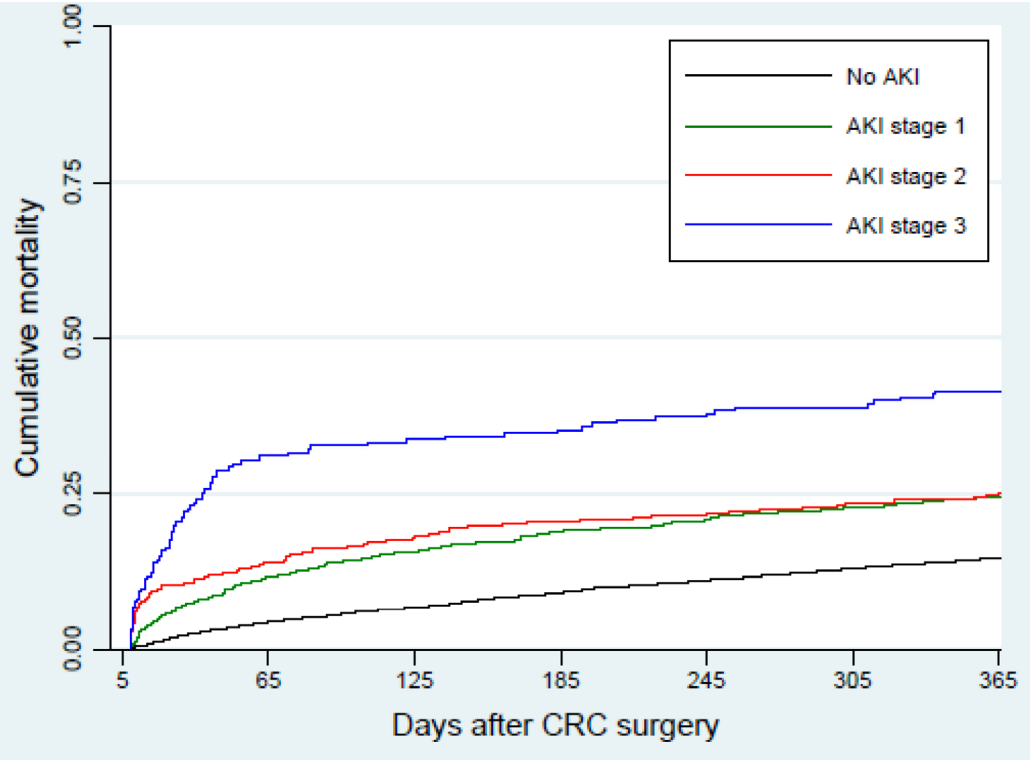


Figure 3. Cumulative one-year mortality by acute kidney injury stage within seven days after colorectal cancer surgery, Northern Denmark, January 2005 - December 2011. Abbreviations: Acute Kidney Injury, AKI; Colorectal Cancer, CRC.



Supplementary material (study I)

Figure S1. Frequency of acute kidney injury by day until 30 days after colorectal cancer surgery.

Figure S2. Creatinine examples of applying the definition and staging of AKI of figure 3.1. Blue circles are examples of baseline definition, back circles are examples of AKI definition and staging.

Figure S3. Stratified analyses of postoperative acute kidney injury and mortality within 8-30 days after surgery.

Figure S4. Frequency of patients who developed acute kidney injury, by day after colorectal cancer surgery for all patients, and divided into patients developing fascial dehiscence, ileus, anastomotic leakage, or no late complications.

Table S1. Patients demographics tabulated by acute kidney injury stage with missing in a separate category

Table S2. Codes used to retrieve data from the Danish National Patient Registry, the LABKA Laboratory Database, and National Health Service Prescription Database (NHSPD)

Table S3. Postoperative complications within 30 days following surgery, by acute kidney injury stage.

Table S4. Cox proportional hazards regression repeated on multiple imputation dataset.

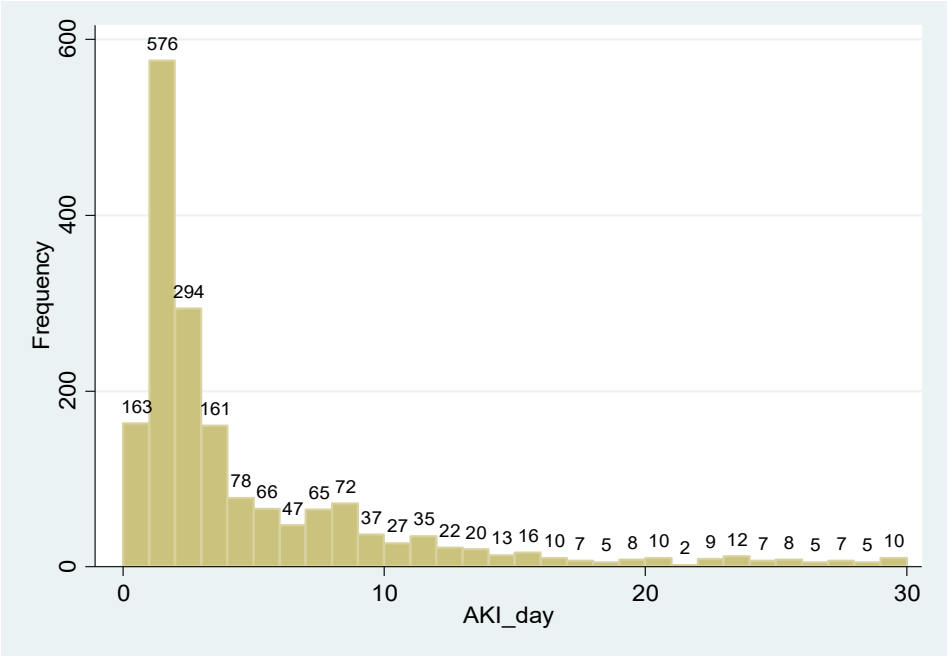
Table S5. Postoperative mortality risk by acute kidney injury stage following colorectal cancer surgery. Complete case analysis.

Table S6. Postoperative mortality risk by acute kidney injury stage following colorectal cancer surgery. Acute kidney injury defined within 3 days

Table S7. Postoperative mortality risk by acute kidney injury stage following colorectal cancer surgery. Acute kidney injury defined within 10 days.

Table S8. Postoperative mortality risk by acute kidney injury stage following colorectal cancer surgery. Acute kidney injury defined within 30 days**.**

Figure S1. Frequency of acute kidney injury by day until 30 days after colorectal cancer surgery.



Abbreviations: Acute Kidney Injury, AKI; first day with AKI after colorectal cancer surgery, AKI_day.

Figure S2. Creatinine examples of applying the definition and staging of AKI of figure 3.1. Blue circles are examples of baseline definition, back circles are examples of AKI definition and staging.

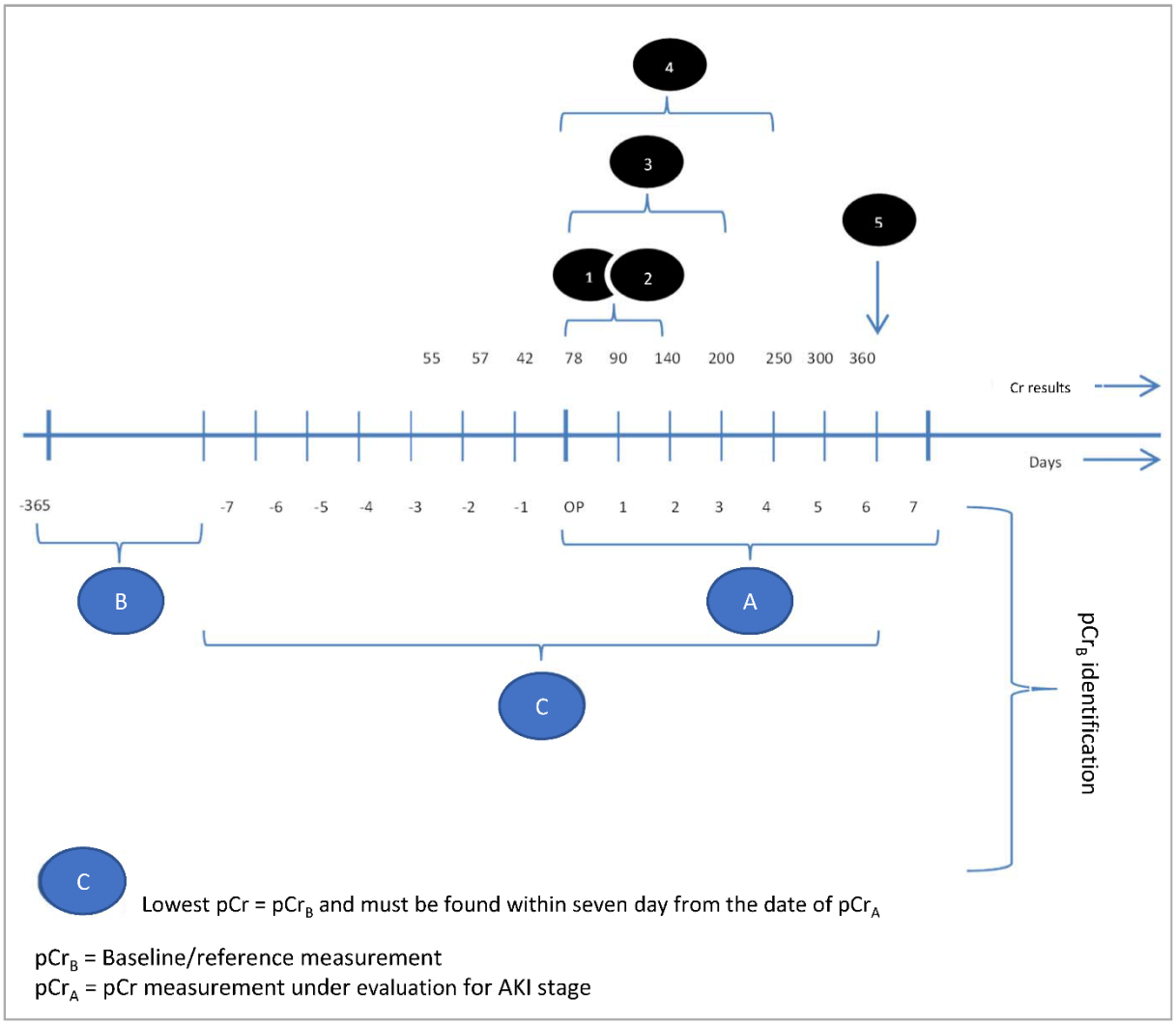
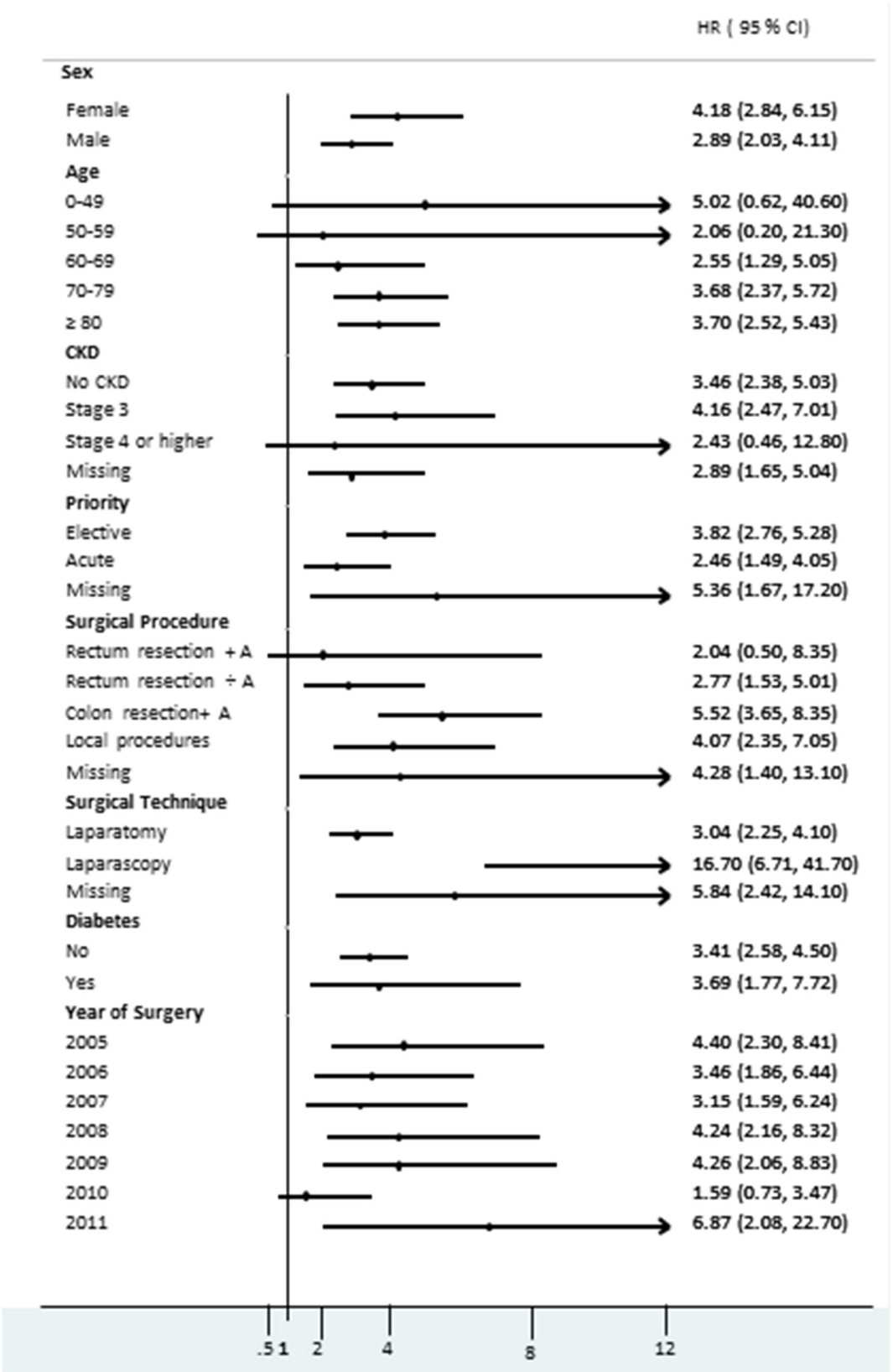
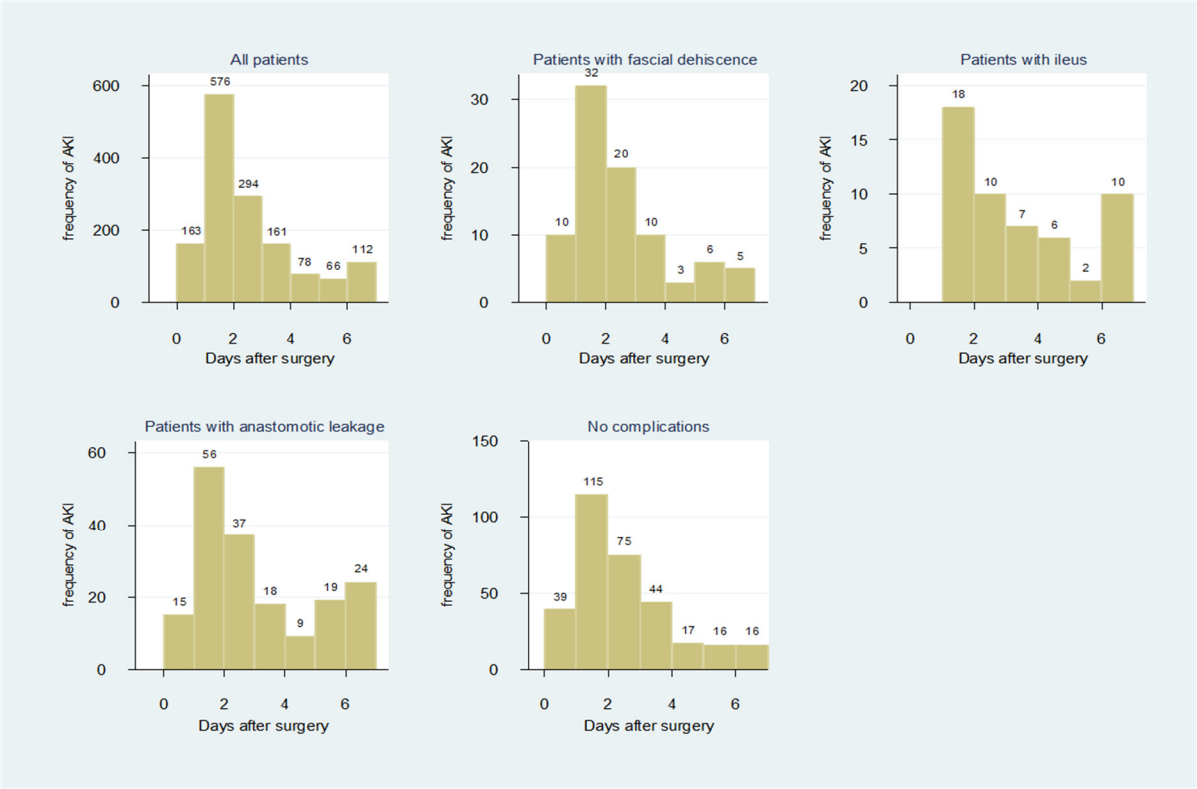


Figure S3. Stratified analyses of postoperative acute kidney injury and mortality within 8-30 days after surgery.



Abbreviations: Anastomosis, A; Chronic Kidney Disease, CKD.

Figure S4. Frequency of patients who developed acute kidney injury, by day after colorectal cancer surgery for all patients, and divided into patients developing fascial dehiscence, ileus, anastomotic leakage, or no late complications.



Abbreviations: AKI, Acute Kidney Injury. No late complications = fascial dehiscence, ileus, anastomotic leakage

Table S1. Patients demographics tabulated by acute kidney injury stage with missing in a separate category.

	Without AKI	**AKI**	**Missing PCr**	**All Patients**
	(n = 4640)	(n = 1337)	(n = 603)	(n = 6580)
	No. (%)	No. (%)	No. (%)	No. (%)
Sex				
Female	2 305 (49.7)	513 (38.4)	260 (43.1)	3 078 (46.8)
Male	2 335 (50.3)	824 (61.6)	343 (56.9)	3 502 (53.2)
Age (years)				
0-49	238 (5.1)	40 (3.0)	39 (6.5)	317 (4.8)
50-59	655 (14.1)	130 (9.7)	98 (16.3)	883 (13.4)
60-69	1 395 (30.1)	323 (24.2)	160 (26.5)	1 878 (28.5)
70-79	1 455 (31.4)	497 (37.2)	188 (31.2)	2 140 (32.5)
≥ 80	897 (19.3)	347 (26.0)	118 (19.6)	1 362 (20.7)
BMI				
Normal	1 595 (34.4)	375 (28.0)	160 (26.5)	2 130 (32.4)
Underweight	116 (2.5)	26 (1.9)	8 (1.3)	150 (2.3)
Overweight	1 677 (36.1)	512 (38.3)	158 (26.2)	2 347 (35.7)
Missing	1 252 (27.0)	424 (31.7)	277 (45.9)	1 953 (29.7)
ASA score				
1	1 055 (22.7)	152 (11.4)	157 (26.0)	1 364 (20.7)
2	2 357 (50.8)	650 (48.6)	229 (38.0)	3 236 (49.2)
3	910 (19.6)	425 (31.8)	80 (13.3)	1 415 (21.5)
4	83 (1.8)	45 (3.4)	32 (5.3)	160 (2.4)
5	2 (0.0)	2 (0.1)	1 (0.2)	5 (0.1)
Missing	233 (5.0)	63 (4.7)	104 (17.2)	400 (6.1)
CCI score				
0	1 429 (30.8)	348 (26.0)	273 (45.3)	2 050 (31.2)
1-2	2 206 (47.5)	608 (45.5)	221 (36.7)	3 035 (46.1)
≥ 2	1 005 (21.7)	381 (28.5)	109 (18.1)	1 495 (22.7)
Heart				
No	4 583 (98.8)	1 314 (98.3)	593 (98.3)	6 490 (98.6)
Yes	57 (1.2)	23 (1.7)	10 (1.7)	90 (1.4)
Diabetes				
No	4 202 (90.6)	1 152 (86.2)	562 (93.2)	5 916 (89.9)
Yes	438 (9.4)	185 (13.8)	41 (6.8)	664 (10.1)
Liver disease				
No	4 596 (99.1)	1 318 (98.6)	597 (99)	6 511 (99)
Yes	44 (0.9)	19 (1.4)	6 (1.0)	69 (1.0)
Hypertension				
No	3 495 (75.3)	858 (64.2)	488 (80.9)	4 841 (73.6)
Yes	1 145 (24.7)	479 (35.8)	115 (19.1)	1 739 (26.4)
OPD				
No	4 183 (90.2)	1 171 (87.6)	548 (90.9)	5 902 (89.7)
Yes	457 (9.8)	166 (12.4)	55 (9.1)	678 (10.3)
CKD				
No CKD	293 (62.8)	779 (58.2)	398 (66.1)	4 174 (63.4)
Stage 3	756 (16.3)	347 (26.0)	78 (12.9)	1 181 (17.9)
Stage 4 or higher	31 (0.7)	48 (3.6)	8 (1.3)	87 (1.3)
Missing	930 (20.2)	163 (12.2)	119 (19.7)	1 138 (17.4)
Cancer type				
Colon	3 070 (66.2)	862 (64.5)	411 (68.2)	4 343 (66)
Rectum	1 570 (33.8)	475 (35.5)	192 (31.8)	2 237 (34)
Urgency of surgery				
Elective	4 040 (87.1)	1 102 (82.4)	500 (82.9)	5 642 (85.7)
Acute	494 (10.6)	208 (15.6)	48 (8)	750 (11.4)
Missing	106 (2.3)	27 (2.0)	55 (9.1)	188 (2.9)

Abbreviations: Acute Kidney Injury, AKI; Body Mass Index, BMI; Charlson Comorbidity Index, CCI; Chronic Kidney Disease, CKD; Obstructive Pulmonary Disease, OPD; plasma Creatinine, PCr.

Table S2. Codes used to retrieve data from the Danish National Patient Registry, the LABKA Laboratory Database, and National Health Service Prescription Database (NHSPD).

Description	**Type of Code**			
	Diagnoses	**ATC**	**Procedure**	**Laboratory** (NPU- and local codes)
Exposure				
Acute kidney injury Acute RRT Chronic RRT Plasma creatinine measurements			 BJFD0 BJFD2	 NPU: 18016, 01807, 04998. ASS: 00356, 00354, 00355
Covariates				
Charlson comorbidities[a]	s1-s19			
Diabetes mellitus (DM) Diagnosis of DM Reimbursed diabetic medication	 ICD-10: E10-14	 A10B		
Obstructive pulmonary disease COPD Asthma Reimbursed OPD medication	 ICD-10: DJ44 ICD-10: DJ45	 R03B, QR03B		
Heart disease[a] Myocardial infarction Congestive heart failure	S1-S2 ICD-10: I21;I22;I23 ICD-10: I50;I11.0;I13.0; I13.2			
Hypertension	ICD-10: I10-I15			
Liver disease	ICD-10: DK70-77			
Chronic kidney disease Plasma creatinine measurements				NPU: 18016, 01807, 04998. ASS: 00356, 00354, 00355

Abbreviations: Angiotensin-Converting Enzyme Inhibitors, ACE; Angiotensin Receptor Blocker, ARB; Chronic Obstructive Pulmonary Disease, COPD, Non-Steroidal Anti-Inflammatory Drugs, NSAID; Renal Rlacement Therapy, RRT.

[a] Thygesen S, Christiansen C, Christensen S, Lash T, Sørensen HT. The predictive value of ICD-10 diagnostic coding used to assess Charlson comorbidity index conditions in the population-based Danish National Registry of Patients. BMC Medical Research Methodology [serial online]. January 2011;11(1):83-88.

Table S3. Postoperative complications within 30 days following surgery, by acute kidney injury stage.

Postoperative Complication	Without AKI	AKI	All patients	PRR[a] (95% CI)
Total	5,243 (100.0)	1,337 (100.0)	6,580 (100.0)	
Anastomotic leakage				3.71 (3.03–4.53)
With reoperation	144 (2.7)	152 (11.4)	296 (4.5)	
Without reoperation	29 (0.6)	20 (1.5)	49 (0.7)	
Bleeding				3.04 (2.08–4.39)
With reoperation	51 (1.0)	40 (3.0)	91 (1.4)	
Without reoperation	8 (0.2)	7 (0.5)	15 (0.2)	
Missing	3,638 (69.4)	916 (68.5)	4,554 (69.2)	
Fascial dehiscence				2.24 (1.75–2.89)
With reoperation	130 (2.5)	83 (6.2)	213 (3.2)	
Without reoperation	9 (0.2)	2 (0.1)	11 (0.2)	
Missing	3,575 (68.2)	882 (66.0)	4,457 (67.7)	
Ileus				2.29 (2.05–4.14)[a]
With reoperation	37 (0.7)	38 (2.8)	75 (1.1)	
Without reoperation	31 (0.6)	14 (1.0)	45 (0.7)	
Missing	3,645 (69.5)	919 (68.7)	4,569 (69.3)	
AMI	44 (0.8)	48 (3.6)	92 (1.4)	
Stroke	21 (0.4)	22 (1.6)	43 (0.7)	
Deep venous thrombosis	5 (0.1)	4 (0.3)	9 (0.1)	
Heart failure	29 (0.6)	40 (3.0)	69 (1.0)	
Missing	3,660 (69.8)	941 (70.4)	4,601 (69.9)	
Infectious conditions[a]	158 (3.0)	104 (7.8)	262 (4.0)	
Missing	3,517 (67.1)	843 (63.1)	4,360 (66.3)	
Pulmonary embolism	8 (0.2)	6 (0.4)	14 (0.2)	
Pulmonary insufficiency				
Yes	47 (0.9)	100 (7.5)	147 (2.2)	
Missing	155 (3.0)	27 (2.0)	182 (2.8)	
Pneumonia	149 (2.8)	151 (11.3)	300 (4.6)	
Sepsis	49 (0.9)	104 (7.8)	153 (2.3)	

[a] Prevalence rate ratios of postoperative AKI and other complications within 30 days after CRC surgery (exact date unknown)
Abbreviations: Acute Kidney Injury, AKI; Acute Myocardial Infarction, AMI; plasma Creatinine, PCr.

Table S4. Cox proportional hazards regression repeated on multiple imputation[b] dataset.

	Adjusted HR[a] (95% CI)
Postoperative Mortality (8 to 30 days)	
Without AKI	Ref.
AKI	3.92 (3.00–5.12)
Stage 1	2.62 (1.90–3.60)
Stage 2	4.73 (3.14–7.13)
Stage 3	10.38 (7.06–15.25)
Postoperative Mortality (31 to 90 days)	
Without AKI	Ref.
AKI	2.21 (1.70–2.87)
Stage 1	2.01 (1.45–2.77)
Stage 2	1.86 (1.11–3.09)
Stage 3	4.37 (2.72–7.02)
Postoperative Mortality (91 to 365 days)	
Without AKI	Ref.
AKI	1.18 (0 .96–1.44)
Stage 1	1.16 (0.92–1.47)
Stage 2	1.09 (0 .73–1.64)
Stage 3	1.40 (0.85–2.30)

[a]Adjusted for age (categories: 0–49, 50–59, 60–69, 70–79, and ≥80 years), sex, BMI, CKD stage (3–5), diabetes mellitus (yes/no), obstructive pulmonary disease, hypertension, liver disease, heart disease, tumor site, and urgency of surgery.
[b]Multiple imputation was applied to missing data for the following variables: AKI stage, CKD stage, acute/elective surgery, BMI, smoking, and alcohol intake.
Abbreviations: AKI, Acute Kidney Injury; BMI, body mass index; CKD, chronic kidney disease; CI, Confidence Interval; COPD, chronic obstructive pulmonary disease; HR, Hazard Ratio.

Table S5. Postoperative mortality risk by acute kidney injury stage following colorectal cancer surgery. Complete case analysis.

	Person time (days)	Number of outcomes	Cumulative Mortality % (95% CI)	Crude HR (95% CI)	Adjusted HR[a] (95% CI)
Postoperative Mortality (8 to 30 days)					
Without AKI	100,997	97	2.1 (1.8–2.6)	Ref.	Ref.
AKI	27,465	116	8.9 (7.4–10.5)	4.37 (3.34–5.73)	3.68 (2.79–4.86)
Stage 1	18,058	57	6.7 (5.2–8.6)	3.27 (2.36–4.54)	2.55 (1.83–3.57)
Stage 2	5,705	22	8.0 (5.4–11.9)	4.00 (2.52–6.35)	3.70 (2.32–5.90)
Stage 3	3,702	37	19.6 (14.6–26.0)	10.3 (7.03–15.0)	9.32 (6.24–13.9)
Postoperative Mortality (31 to 90 days)					
Without AKI	263,438	134	3.0 (2.5–3.5)	Ref.	Ref.
AKI	67,741	92	7.7 (6.3–9.4)	2.66 (2.04–3.47)	2.31 (1.76–3.04)
Stage 1	45,161	55	7.0 (5.4–9.0)	2.39 (1.75–3.27)	2.04 (1.48–2.81)
Stage 2	14,488	16	6.3 (4.0–10.1)	2.17 (1.29–3.64)	1.98 (1.18–3.33)
Stage 3	8,092	21	13.9 (9.3–20.4)	5.08 (3.21–8.04)	4.18 (2.59–6.75)
Postoperative Mortality (91 to 365 days)					
Without AKI	1,145,029	409	9.3 (8.5–10.2)	Ref.	Ref.
AKI	283,176	131	12.1 (10.3–14.1)	1.31 (1.08–1.60)	1.18 (0.96–1.44)
Stage 1	188,251	91	12.4 (10.2–15.0)	1.35 (1.08–1.70)	1.19 (0.94–1.50)
Stage 2	61,323	25	10.6 (7.3–15.2)	1.14 (0.76–1.71)	1.11 (0.74–1.66)
Stage 3	33,602	17	13.0 (8.3–20.1)	1.41 (0.87–2.30)	1.19 (0.72–1.97)

[a] Adjusted for age (categories: 0–49, 50–59, 60–69, 70–79, and ≥80 years), sex, BMI, CKD stage (3–5), diabetes mellitus (yes/no), obstructive pulmonary disease, hypertension, liver disease, heart disease, tumor site, and urgency of surgery.

Abbreviations: AKI, Acute Kidney Injury; BMI, Body Mass Index; CKD, Chronic Kidney Disease; CI, Confidence Interval; HR, Hazard Ratio

Table S6. Postoperative mortality risk by acute kidney injury stage following colorectal cancer surgery. Acute kidney injury defined within 3 days.

	Person days	Outcomes (n)	Cumulative Mortality % (95% CI)	Crude HR (95% CI)	Adjusted HR[a] (95% CI)
Postoperative Mortality (4 to 30 days)					
Without AKI	151,800	176	3.2 (2.8–3.7)	Ref.	Ref.
AKI	29,148	154	13.5 (11.7–15.7)	4.57 (3.62–5.58)	3.55 (2.84–4.43)
Stage 1	18,899	66	9.2 (7.3–11.6)	2.99 (2.25–3.96)	2.31 (1.73–3.09)
Stage 2	6,127	41	16.4 (12.4–21.6)	5.67 (4.04–7.97)	4.67 (3.31–6.60)
Stage 3	4,122	47	26.9 (20.9–34.1)	9.54 (6.91–3.16)	8.16 (5.82–11.43)
Postoperative Mortality (31 to 90 days)					
Without AKI	319,764	183	3.4 (3.0–4.0)	Ref.	Ref.
AKI	57,376	79	8.0 (6.5–10.0)	2.40 (1.84–3.12)	2.03 (1.54–2.66)
Stage 1	38,039	46	7.1 (5.4–9.4)	2.11 (1.53–2.91)	1.79 (1.29–2.50)
Stage 2	12,268	15	7.2 (4.4–11.6)	2.13 (1.26–3.61)	1.87 (1.10–3.18)
Stage 3	7,069	18	14.1 (9.1–21.4)	4.42 (2.72–7.17)	3.56 (2.15–5.88)
Postoperative Mortality (91 to 365 days)					
Without AKI I	1,347,647	510	9.9 (9.1–10.7)	Ref.	Ref.
AKI	234,044	111	12.2 (10.3–14.6)	1.25 (1.02–1.54)	1.09 (0.88–1.35)
Stage 1	155,012	76	12.6 (10.2–15.6)	1.29 (1.02–1.65)	1.13 (0.89–1.45)
Stage 2	50,777	19	9.8 (6.4–14.9)	0.99 (0.63–1.56)	0.90 (0.57–1.42)
Stage 3	28,255	95	14.6 (9.2–22.6)	1.49 (0.91–2.46)	1.20 (0.72–2.00)

[a] Adjusted for age (categories: 0–49, 50–59, 60–69, 70–79, and ≥80 years), sex, BMI, CKD stage (3–5), diabetes mellitus (yes/no), obstructive pulmonary disease, hypertension, liver disease, heart disease, tumor site, and urgency of surgery.
Abbreviations: AKI, Acute Kidney Injury; BMI, Body Mass Index; CKD, Chronic Kidney Disease; CI, Confidence Interval; HR, Hazard Ratio

Table S7. Postoperative mortality risk by acute kidney injury stage following colorectal cancer surgery. Acute kidney injury defined within 10 days.

	Person days	No. of outcomes	Cumulative Mortality % (95% CI)	Crude HR (95% CI)	Adjusted HR[a] (95% CI)
Postoperative Mortality (31 to 90 days)					
Without AKI	446,718	204	3.6 (3.2–4.1)	1 (ref.)	1 (ref.)
AKI	72,471	67	7.2 (5.7–9.1)	2.05 (1.55,2.70)	1.94 (1.47,2.57)
Stage 1	43,102	31	5.7 (4.0–8.0)	1.58 (1.09,2.31)	1.49 (1.02,2.19)
Stage 2	18,118	15	6.5 (4.0–10.5)	1.83 (1.08,3.10)	1.82 (1.08,3.09)
Stage 3	11,251	21	14.2 (9.5–20.9)	4.24 (2.71,6.65)	4.03 (2.51,6.46)
Outcome: Postoperative Mortality (91 to 365 days)					
Without AKI	1,415,466	555	10.2 (9.4–11.0)	1 (ref.)	1 (ref.)
AKI	222,362	95	11.1 (9.1–13.3)	1.09 (0.88,1.35)	1.07 (0.86,1.33)
Stage 1	133,767	57	11.3 (8.6–14.1)	1.09 (0.83,1.43)	1.03 (0.78,1.36)
Stage 2	55,517	25	11.6 (8.0–16.7)	1.15 (0.77,1.71)	1.14 (0.76,1.70)
Stage 3	33,078	13	10.2 (6.1–17.0)	1.00 (0.58,1.74)	1.10 (0.63,1.91)

[a] Adjusted for age (categories: 0–49, 50–59, 60–69, 70–79, and ≥80 years), sex, BMI, CKD stage (3–5), diabetes mellitus (yes/no), obstructive pulmonary disease, hypertension, liver disease, heart disease, tumor site, and urgency of surgery.
Abbreviations: AKI, Acute Kidney Injury; BMI, Body Mass Index; CKD, Chronic Kidney Disease; CI, Confidence Interval; HR, Hazard Ratio

Table S8. Postoperative mortality risk by acute kidney injury stage following colorectal cancer surgery. Acute kidney injury defined within 30 days.

	Person days	**No. of events**	**Cumulative Mortality %** (95% CI)	**Crude HR** (95% CI)	**Adjusted HR[a]** (95% CI)
Postoperative Mortality (31 to 90 days)					
Non–AKI	280,678	137	2.84 (2.4–3.3)	1 (ref.)	1 (ref.)
AKI	84,064	117	7.8 (6.6–9.3)	2.84 (2.22–3.64)	2.52 (1.95–3.24)
Stage 1	53,157	62	6.6 (5.2–8.4)	2.38 (1.77–3.22)	2.08 (1.53–2.82)
Stage 2	17,301	23	7.5 (5.1–11.1)	2.72 (1.75–4.22)	2.62 (1.68–4.08)
Stage 3	13,606	32	12.8 (9.2–17.5)	4.79 (3.26–7.04)	4.25 (2.85–6.35)
Postoperative Mortality (91 to 365 days)					
Non–AKI	1,219,026	453	9.7 (8.9–10.5)	1 (ref.)	1 (ref.)
AKI	351,150	164	11.9 (10.3–13.8)	1.26 (1.05–1.50)	1.13 (0.94–1.36)
Stage 1	141,071	111	12.7 (10.7–15.1)	1.35 (1.09–1.66)	1.17 (0.95–1.44)
Stage 2	63,550	28	9.9 (6.9–14.0)	1.03 (0.70–1.51)	1.06 (0.72–1.56)
Stage 3	44,072	25	11.4 (7.9–16.4)	1.20 (0.81–1.79)	1.06 (0.70–1.61)

[a] Adjusted for age (categories: 0–49, 50–59, 60–69, 70–79, and ≥80 years), sex, BMI, CKD stage (3–5), diabetes mellitus (yes/no), obstructive pulmonary disease, hypertension, liver disease, heart disease, tumor site, and urgency of surgery.

Abbreviations: AKI, Acute Kidney Injury; BMI, Body Mass Index; CKD, Chronic Kidney Disease; CI, Confidence Interval; HR, Hazard Ratio

- **Appendix II:**

Paper II

ACE-I/ARB and the risk of acute kidney injury after colorectal cancer surgery: A population-based cohort study

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Running head
ACE-I/ARB and AKI risk after colorectal surgery

Abstract

Background and objectives: It is unknown whether preoperative use of the potentially nephrotoxic angiotensin-converting enzyme inhibitors (ACE-I) or angiotensin-receptor blockers (ARB) affects the risk of acute kidney injury (AKI) after colorectal cancer (CRC) surgery. We assessed the impact of preoperative ACE-I/ARB use on AKI risk after CRC surgery.

Design, setting, participants, and measurements: All incident CRC surgery patients during 2005-2014 in northern Denmark were identified from the Danish Colorectal Cancer Group Database. Patients were defined as current, former and non-users of users of ACE-I/ARB based on redeemed prescriptions within the 365 days before surgery. AKI within seven days after surgery was defined according to the KDIGO criteria. We computed incidence proportions (risk) of AKI with 95% confidence intervals (CI) 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. We stratified the analyses of ACE-I/ARBs users to address any difference in impact within subgroups.

Results: We included 9932 patients, among whom 21.3% were ACE-I/ARB current users, 6.4% were former users, and 72.3% were non-users. The 7-day AKI risk after surgery for current, former, and non-users was 26.4% (95% CI: 24.6%-28.3%), 25.2% (95% CI: 21.9%-28.6%), and 17.8% (95% CI: 17.0%-18.7%), respectively. The aRRs of AKI were 1.20 (95% CI: 1.09-1.32) and 1.16 (95% CI: 1.01-1.34) for current and former users, compared to non-users. The relative risk of AKI in current compared to non-users was higher in patients without hypertension than in patients with hypertension.

Conclusions: Users of ACE-I/ARBs, in particular, non-hypertensive patients, are at higher risk of postoperative AKI compared with non-users.

Introduction

Angiotensin-converting enzyme inhibitors (ACE-I) and angiotensin-receptor blockers (ARB) are commonly prescribed drugs targeting the regulation of water and salt retention in the kidneys (1).

ACE-I/ARBs are potentially nephrotoxic drugs 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). 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 colorectal cancer (CRC) diagnosis is 72 years, the prevalence of ACE-I/ARB use is high in CRC patients (4).

Despite the beneficial long-term effects of ACE-I/ARBs, the literature on the potential consequences of preoperative administration of ACE-I/ARB on the risk of postoperative acute kidney injury (AKI) is limited and recommendations regarding discontinuation of preoperative ACE-I/ARBs are based on institutional policies and guidelines without class I and III recommendations (5–7). Interestingly, for most ACE-I/ARBs some effect may extend beyond 24 hours (8). Thus, withholding ACE-I/ARB on the day of surgery may not be sufficient to eliminate the effect of ACE-I/ARB during surgery. We hypothesize that ACE-I/ARB use in CRC surgery patients is associated with increased risk of AKI potentially through their inhibition of angiotensin II leading to renal vasodilatation and consequently decreased glomerular filtration rate (GFR) (9). Prior studies have been limited by inconsistency in staging of AKI, definition of ACE-I/ARB use, and the inclusion of heterogeneous surgical populations (10–12). 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 (10,13–17).

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 health care 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 (18).

Study Population

The study included all patients registered in the Danish Colorectal Cancer Group (DCCG.dk) database (reported patient completeness of 98%-99%)(19), 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, e.g., demographics, treatments, postoperative complications (<31 days), and mortality (19). In the database, 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 one year before surgery. Laboratory data were retrieved from the clinical laboratory information system (LABKA) research database at Aarhus University (20). Registration of laboratory results from general practice and hospitals in northern Denmark was initiated around the 1990s. Data completeness of creatinine was above 90% in most hospitals after 2004. Some hospitals started reporting to LABKA

at a later time point. Therefore, 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 (20).

We excluded patients with chronic renal replacement therapy (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 according to Figure 1. The NHSPD contains data on all dispensed prescriptions for reimbursable drugs in community pharmacies in Denmark since 2004 (Supplementary, Table S1)

Acute Kidney Injury

AKI was defined by applying the creatinine (Cr) criteria of the Kidney Disease Improving Global Outcome (KDIGO) consensus criteria (21). Data on plasma Cr (PCr, equivalent to serum creatinine) (22) were retrieved from the LABKA database (20). Patients were defined as having AKI if they met one of the following four criteria within seven days after surgery: 1) an increase in PCr of 50% or more from baseline, 2) an increase in PCr of ≥ 0.3mg/dl (26.4µmol/l) within 48 hours, 3) PCr ≥ 4.0 mg/dl (353.6µmol), with an acute increase of at least 0.5mg/dl (44 µmol/l, 4) initiation of RRT. Baseline PCr was defined as either the mean outpatient PCr within 7-365 days before surgery or, if unavailable, the lowest PCr value within the last seven days (23). If neither measurement was available, it was estimated using the Modification of Diet in Renal Disease (MRDR) formula as recommended by the RIFLE, AKIN and KDIGO consensus criteria (21,24).

Mortality

We obtained data on mortality from date of CRC surgery to seven 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 (18).

Potential Confounders

Age and gender were determined from the CPR number provided by the CRS (18). Preexisting comorbidities were chosen based on their potential association with use of ACE-I/ARBs and risk of AKI (10,21,25). 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 pulmonary disease (including chronic obstructive pulmonary disease and asthma), hypertension, diabetes, heart disease (myocardial infarction and congestive heart failure), and liver disease (26). The DNPR contains information on all hospitalizations since 1977, outpatient visits since 1994, and emergency room visits since 1995. It includes among others information on diagnoses, procedures, and admission/discharge (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 (27). Chronic kidney disease (CKD), a strong predictor for AKI (21), was identified using PCr measurements from LAKBA (20) and defined as an estimated glomerular filtration rate (eGFR) <60 ml/min/1.73 m^2 lasting at least three months within two years before CRC surgery. [4] Data on smoking, weekly alcohol intake and body mass index (BMI, defined as: 'underweight' if kg/m^2 was < 18.5, 'normal weight' if kg/m^2 was 18.5-25, and 'overweight' if kg/m^2 was >25) were retrieved from the DCCG database (28).

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 (29). These drugs were chosen based on their potential role as nephrotoxin and frequent use in elderly patients for chronic conditions such as hypertension, heart disease, diabetes, CKD or for infection (30).

Statistical Methods

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

We computed seven-day post-operative cumulative incidence proportions (risk) of AKI with 95% confidence intervals for patients with current, former, and no use of ACE-I/ARBs, including death as a competing risk (31,32).

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 CRC patients, 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 non-steroidal anti-inflammatory drugs (NSAIDs), and diuretic use.

In ten percent of our cohort, outcome data were missing. Based on two rationales, and a sensitivity analysis, they were categorized as patients without AKI. First, the indication threshold is low. Second, the hospitals that contributed the most patients lacking PCr 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 (33–35).

Multiple imputations of the covariates (CKD, smoking, BMI, weekly alcohol intake) with missing data (~20%) was performed using the mi impute chained procedure in Stata 13.1 to create five imputed datasets and included in the log-binomial regression (36,37). We addressed the impact on our results of potential misclassification associated with missing covariates in a complete case analysis of relative risk.

All analyses were conducted using the software package Stata, version 13.1 (StataCorp, College Station, TX, USA). All data were obtained from Danish registries and, according to Danish law, their use does not require ethics approval or informed consent. The study was approved by the Danish Data Protection Agency (record no.2015-67-0002) through Aarhus University (record no. 2016-051-000001-423). According to Danish law, non-interventional registry-based studies do not require ethics approval or informed consent.

Results

Study Population

We identified 10,713 CRC patients living in northern Denmark who underwent CRC surgery during 2005-2014. Of these, we excluded 781 patients for the following reasons: on RRT (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 percent of the included patients were current ACE-I/ARB users, 6.4% former users, and 72.3% were non-users.

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 (ASA) score and Charlson comorbidity index (CCI) than non-users of ACE-I/ARB (38,39). Moreover, current users more frequently were female, had diabetes mellitus, CKD, or hypertension compared to 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. (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 (Supplementary, Table S3).

Seven-day risk of AKI

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

Sensitivity Analyses

The complete case analysis yielded aRR estimates similar to those obtained in the primary analyses, although the confidence intervals, as expected, were wider. Changing the exposure period from 90 to 30, 60, or 100 days resulted only in minor changes (Supplementary, Table S3).

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: 1.23-1.59; absolute risk: 25.7% for current users, 16.2% for non-users) than in patients with hypertension (aRR 1.03 95% CI: 0.90-1.17, 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).

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 CRC patients as opposed to the mixed surgical populations in the current literature (16,17,40–44).

Strengths of our study include a minimal 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 health care 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 were exposed to their medication on the day of surgery. However, a majority (619/1113) of the patients with in-hospital data continued took 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. 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 that the lack of difference in association for current and former user may be explained by to unmeasured confounding by indication and residual confounding. For example, we lack data on potential mechanisms explaining the results,

e.g., blood pressure, fluid balance and administration, or timing of other postoperative complications.

Interpretation

The debate of whether ACE-I/ARBs are potentially harmful or beneficial on outcomes after non-cardiac surgery is ongoing, due to conflicting results (12,45). The conflicting results may be due to the heterogeneity of the methodology across the studies. Some studies retrieved data from redeemed prescriptions (16,40,41) while others used perioperative databases (17,43). Additionally, different definitions of AKI were used: dialysis within 14 days after surgery (16), creatinine increase of 0.5mg/dL (44), AKIN (43), RIFLE (42), and KDIGO (40,41). Some studies have based the definition on creatinine measurements (40–42,44,46) others on ICD-9 (17) codes or ICD-10 codes (16), 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 – 0.82 and aRR 0.83 95 % CI: 0.71-0.98) (16,40). Shah et al. conducted a large multicenter retrospective cohort study of 273,208 patients undergoing major elective surgery (16). 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 seven days before surgery from an electronic prescription system (40). The short interval for identifying users may explain their lower prevalence of ACE-I/ARB compared with our analyses. In line with their results (aOR 0.68; 95% CI: 0.57–0.82 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. preoperative

One study of major abdominal surgeries resembled ours regarding AKI and ACE-I/ARB definition(41). This study also found an increased risk of AKI (aRR 1.20 95% CI: 1.16-1.23). The prevalence of current ACE-I/ARB users was 34%, comparable to the prevalence in our study. In contrast, two studies found no association (42,43). These studies included non-cardiac surgery patients and were focused on whether the use of ACE-I/ARB on the day of surgery was associated with AKI, whereas we in our study defined ACE-I/ARB use from information on redeemed prescriptions.

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

With the aging population, the frequency of ACE-I/ARB use, and the number of CRC surgeries are expected to rise. As users of ACE-I/ARB represent a group of CRC patients at increased risk of AKI, an increased awarenes 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 CRC surgery patients.

Disclosures

None.

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Tables

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

	ACE-I/ARB use			
	Non-user (n = 7181) No. (%)	Former user (n = 639) No. (%)	Current user (n = 2112) No. (%)	All Patients (n = 9932) No. (%)
Sex				
Female	3464 (48)	286 (45)	891 (42)	4641 (47)
Male	3717 (52)	353 (55)	1221 (58)	5291 (53)
Age, yrs.				
mean	69 (±11.7)	73.4 (±9.4)	72.8 (±9.0)	70.1 (±)
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				
smoker	1197 (16)	90 (14)	271 (13)	1558 (16)
Former smoker	2373 (33)	257 (40)	872 (41)	3502 (35)
Never smoker	2092 (29)	179 (28.0)	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)
BMI*				
Underweight (BMI < 18.5)	224 (3)	19 (3)	30 (1)	273 (3)
Normal weight (BMI 18.5-25)	2781 (39)	198 (31)	644 (31)	3623 (37)
Overweight (BMI > 25)	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**				
No CKD	5193 (72)	439 (69)	1457 (69)	7089 (71)
CKD	508 (7)	120 (19)	366 (17)	994 (10)
Cancer type				
Colon	4699 (65)	461 (72)	1413 (68)	6573 (66)
Rectum	2482 (35)	178 (28)	699 (33)	3359 (34)
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)

Abbreviations: A, anastomosis; AKI, Acute Kidney Injury; ASA American Society of Anesthesiology; BMI Body Mass Index; CKD, chronic kidney disease; OPD Obstructive Pulmonary Disease; CCI, Charlson Comorbidity Index. Missing data: alcohol, BMI, CKD, smoking ~20%; ASA (3.1%).
* (kg/m^2)
** CKD was defined as an estimated glomerular filtration rate (eGFR) <60 ml/min/1.73 m2 lasting at least 3 months within 2 years before CRC surgery. The mean and median preoperative GFR was higher in patients without CKD information (~20%).

Table 2. Seven-day acute kidney injury risk by angiotensin-converting enzyme inhibitor (ACE-I) and/or angiotensin-receptor blocker (ARB) use.

AKI risk outcomes	No. of outcomes	7-day Incidence proportion % (95% CI)	Crude RR (95% CI)	Adjusted RR[1] (95% CI)
Non-user	1281	17.8% (17.0-18.7)	Ref.	Ref.
Former user	161	25.2% (21.9-28.6)	1.41 (1.22-1.63)	1.16 (1.01-1.19)
Current user	558	26.4% (24.5-28.3)	1.48 (1.36-1.61)	1.20 (1.09-1.32)

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

Figures

Figure 1. Definition of exposure to angiotensin-converting enzyme inhibitors (ACE-I) and/or angiotensin-receptor blockers (ARB).

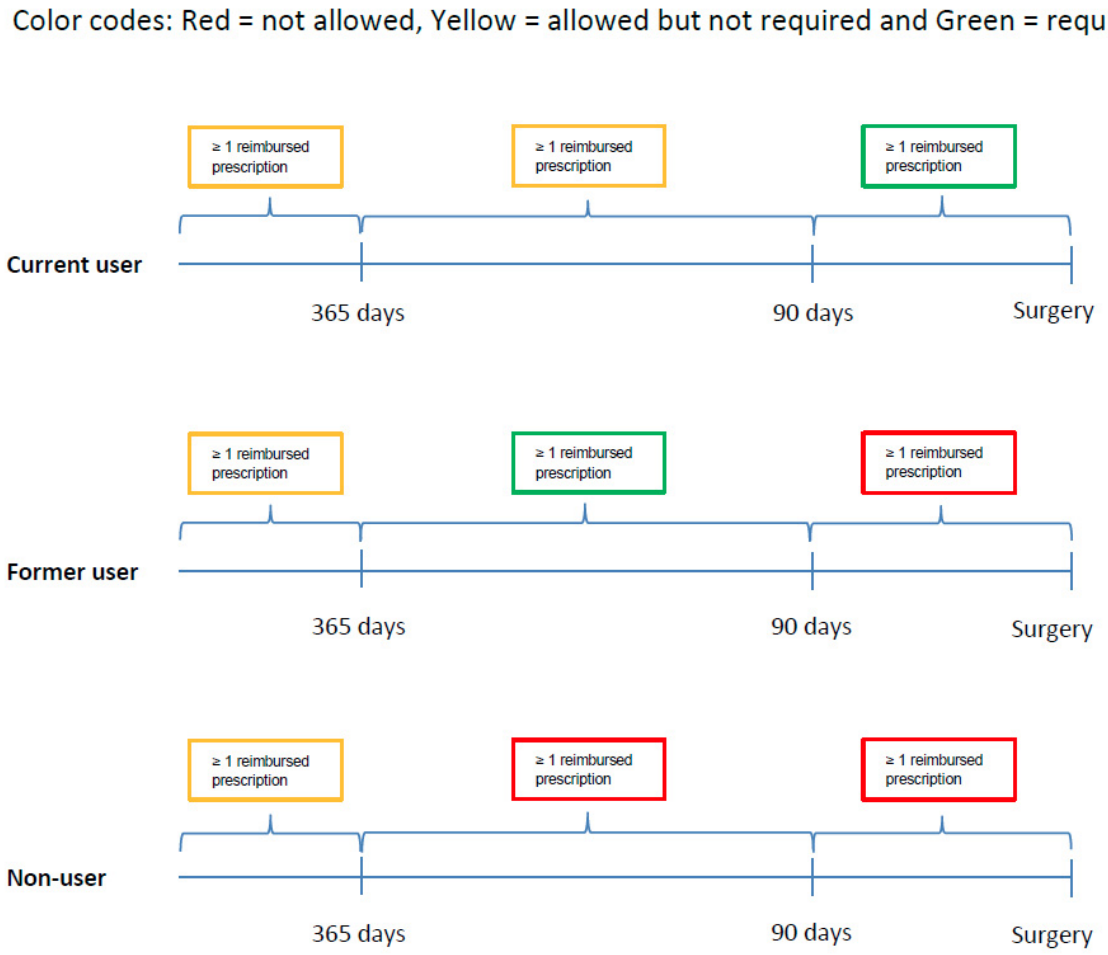
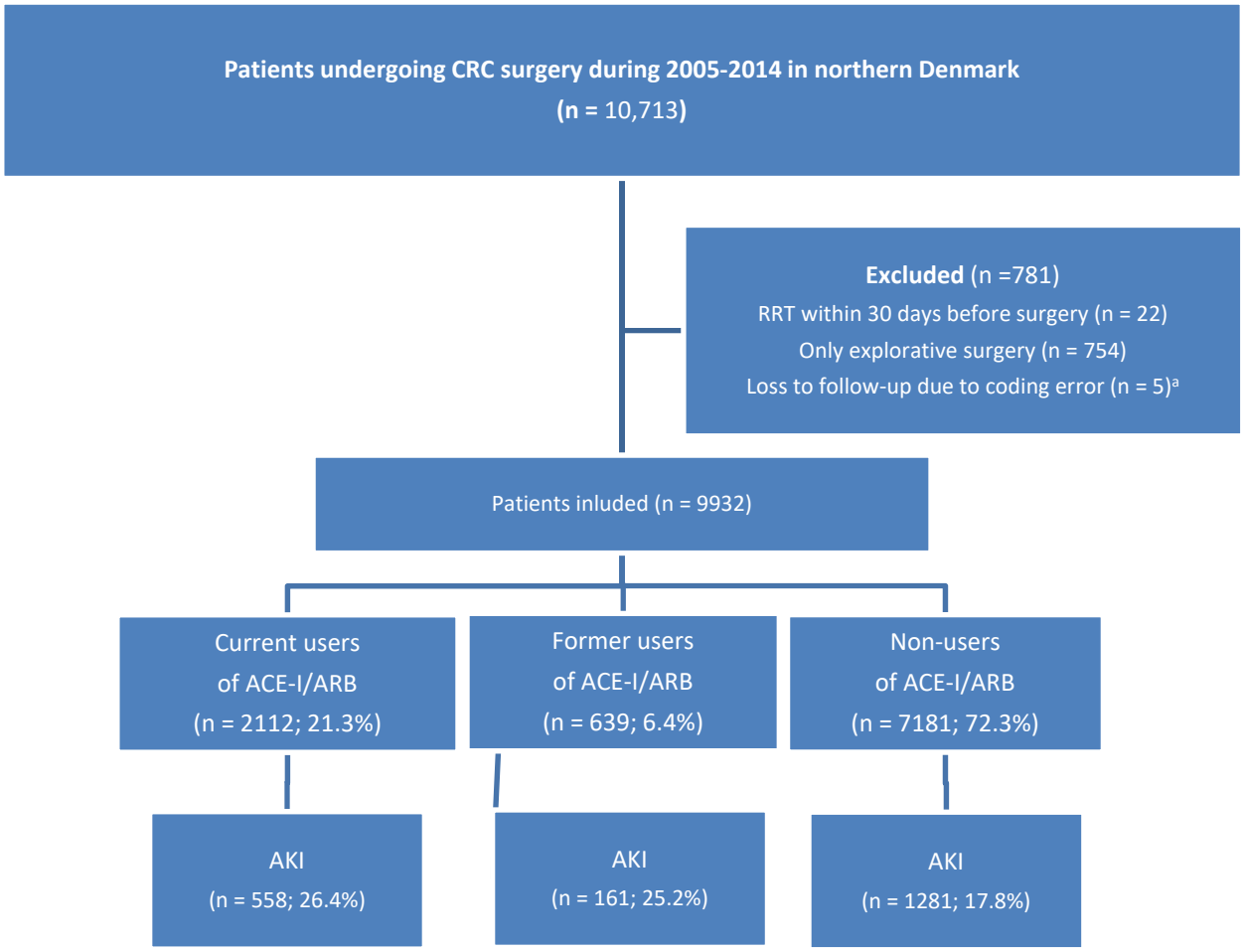
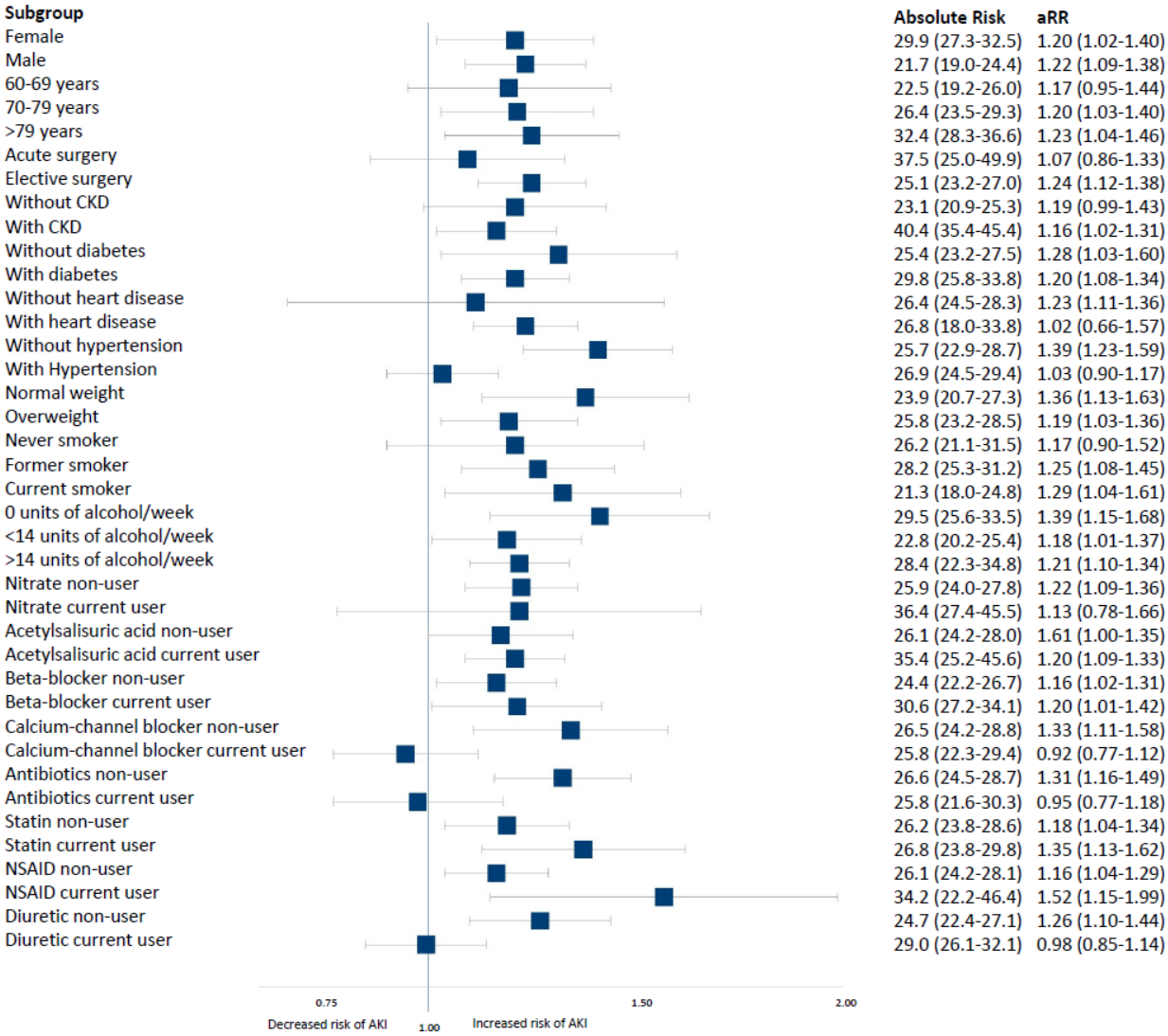


Figure 2. Flow Chart.



[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 3. Forest plot (subgroup analyses). Current use of angiotensin-converting enzyme inhibitors (ACE-I) and/or angiotensin-receptor blockers (ARB) and the risk of acute kidney injury within seven days after colorectal cancer surgery across subgroups of demographics and comorbidities.



Abbreviations: aRR, adjusted relative risk; CKD, chronic kidney disease. NSAID, Non-steriodal anti-inflammatory drugs; Underweight = <18.5kg/m^2, normal weight = 18.5-25kh/m^2, and overweight >25kg/m^2.

Supplemental Material

Table S1. Codes used to retrieve data from NHSPD, LABKA, and DNPR.

Description	Type of Code			
	Diagnoses	ATC	Procedure	Laboratory (NPU- and local codes)
Exposure				
ACE-I		C09A, C09BA, C09BB		
ARB		C09CA, C09DB		
Outcome				
Acute kidney injury				
Acute RRT			BJFD0	
Chronic RRT			BJFD2	
Plasma creatinine measurements				NPU: 18016, 01807, 04998. ASS: 00356, 00354, 00355
Covariates				
Charlson comorbidities[a]	s1-s19			
Diabetes mellitus				
Diagnosis of DM	ICD-10: E10-14			
Reimbursed diabetic medication		A10B		
Obstructive pulmonary disease				
COPD				
Asthma	ICD-10: DJ44			
Reimbursed OPD medication	ICD-10: DJ45	R03B, QR03B		
Heart disease[a]	S1-S2			
Myocardial infarction	ICD-10: I21;I22;I23			
Congestive heart failure	ICD-10: I50;I11.0;I13.0; I13.2			
Hypertension	ICD-10: I10-I15			
Liver disease	ICD-10: DK70-77			
Chronic kidney disease				
Plasma creatinine measurements				NPU: 18016, 01807, 04998. ASS: 00356, 00354, 00355
Diuretics		C03		
NSAIDs		M01A		
Antibiotics		J01		
Statins		C10AA		
Beta-blockers		C07		
Acetylsalicylic acid		B01AC06, N02BA01		
Calcium-Channel blockers		C08		
Nitrates		C01DA, C01DX		

Abbreviations: Angiotensin-Converting Enzyme Inhibitors, ACE; Angiotensin Receptor Blocker, ARB; Chronic Obstructive Pulmonary Disease, COPD, Non-Steroidal Anti-Inflammatory Drugs, NSAIDs; the Danish National Patient Registry, DNPR; the Laboratory Database, LABKA, and the National Health Service Prescription Database (NHSPD); Renal Replacement Therapy, RRT.

[a] Thygesen S, Christiansen C, Christensen S, Lash T, Sørensen HT. The predictive value of ICD-10 diagnostic coding used to assess Charlson comorbidity index conditions in the population-based Danish National Registry of Patients. BMC Medical Research Methodology [serial online]. January 2011;11(1):83-88.

Table S2. Preoperative use of medication tabulated by angiotensin-converting enzyme inhibitor (ACE-I) and/or angiotensin-receptor blocker (ARB) user status.

		ACE-I/ARB use			
Type of medication		Non-user (n = 7181) No. (%)	Former user (n = 639) No. (%)	Current user (n = 2112) No. (%)	All Patients (n = 9932) No. (%)
Diuretics					
	Non-user	6177 (86)	450 (70)	1272 (60)	7899 (79)
	Current user	1004 (14)	189 (29)	840 (40)	2033 (21)
Non-steroidal Anti-inflammatory Drugs					
	Non-user	6692 (93)	589 (92)	1956 (93)	9237 (93)
	Current user	489 (7)	50 (8)	156 (7)	695 (7)
Antibiotics					
	Non-user	6015 (84)	524 (82)	1725 (82)	8264 (83)
	Current user	1166 (16)	115 (18)	387 (18)	1668 (17)
Statins					
	Non-user	6201 (86)	469 (73)	1272 (60)	7942 (80)
	Current user	980 (14)	170 (27)	840 (40)	199 (20)
Acetylsalicylic Acid					
	Non-user	707 (98)	625 (98)	203 (96)	9725 (98)
	Current user	111 (2)	14 (2)	82 (4)	207 (2)
Beta-blockers					
	Non-user	6309 (88)	525 (82)	1429 (68)	8263 (83)
	Current user	872 (12)	114 (18)	683 (32)	1669 (17)
Calcium-Channel Blockers					
	Non-user	6506 (91)	518 (81)	1526 (72)	8550 (86)
	Current user	675 (9)	121 (19)	586 (28)	1382 (14)
Nitrates					
	Non-user	7016 (98)	612 (96)	2005 (95)	9633 (97)
	Current user	165 (2)	27 (4)	107 (5)	299 (3)

Table S3. Postoperative complications tabulated by angiotensin-converting enzyme inhibitor (ACE-I) and/or angiotensin-receptor blocker (ARB) *user status.*

	ACE-I/ARB use			
Type of complication	Non-user (n = 7181) No. (%)	Former user (n = 639) No. (%)	Current user (n = 2112) No. (%)	All Patients (n = 9932) No. (%)
Bleeding	134 (2)	10 (2)	58 (3)	202 (2)
Fascial Dehiscience	248 (4)	24 (4)	77 (4)	349 (4)
Ileus	180 (3)	21 (3)	71 (3)	272 (3)
Anastomosis Leakage	419 (8)	21 (5)	130 (9)	570 (8)

Table S4. Sensitivity analyses of the exposure window for angiotensin-converting enzyme inhibitors (ACE-Is) and angiotensin-receptor blockers (ARBs) current use defined as 30, 60 or 100 days.

ACE-I/ARB user definition		Risk outcomes	
		Crude RR (95% CI)	**Adjusted RR[1] (95% CI)**
Current user 30 days			
	Non-user	Ref.	Ref.
	Former user	1.38 (1.34-1.43)	1.09 (1.06-1.13)
	Current user	1.48 (1.42-1.54)	1.09 (1.05-1.14)
Current user 60 days			
	Non-user	Ref.	Ref.
	Former user	1.41(1.35-1.46)	1.13 (1.08-1.17)
	Current user	1.42 (1.37-1.42)	1.07 (1.04-1.11)
Current user 100 days			
	Non-user	Ref.	Ref.
	Former user	1.35 (1.15-1.60)	1.10 (0.93-1.30)
	Current user	1.49 (1.37-1.62)	1.17 (1.06-1.28)
Complete case			
	Non-user	Ref.	Ref.
	Former	1.41 (1.22-1.63)	1.12 (0.96-1.30)
	current	1.48 (1.36-1.62)	1.16 (1.04-1.28)

[1] Adjusted for: age (0-59, 60-69, 70-79, ≥80 years), gender, CKD, diabetes, obstructive pulmonary disease, hypertension, liver disease, heart disease, cancer type, urgency of surgery, smoking, BMI, and alcohol

Abbreviations: BMI, body mass index; CI, confidence interval; CKD, Chronic Kidney Disease; Ref., reference; RR, relative risk.

Supplementary material (study II)

Table S1. Sensitivity analysis of angiotensin-converting enzyme inhibitor (ACE-I) and angiotensin-receptor blocker (ARB) exposure definition (alternative definition: redeemed enough medication to be treated at the day of surgery).

Table S1. Sensitivity analysis of angiotensin-converting enzyme inhibitor (ACE-I) and/or angiotensin-receptor Blocker (ARB) exposure definition (Alternative definition: redeemed enough medication to be treated at the day of surgery).

Exposure group	**ACE-I/ARB use** No. (%)	**Patients with AKI** No.	**Seven-day Incidence Proportion % (95% CI)**	**Crude RR**	**aRR[a]**
Non-user	7,181 (72.3)	1,281	17.8% (17.0–18.7)	Ref.	Ref.
Former user	438 (4.4)	107	24.4% (20.5–28.5)	1.37 (1.15–1.63)	1.13 (0.96–1.34)
Current user	2,312 (23.3)	612	26.5% (24.7–28.3)	1.48 (1.36–1.61)	1.20 (1.10–1.32)

[a] adjusted for age (0–59, 60–69, 70–79, ≥80) sex, CKD, diabetes, obstructive pulmonary disease, hypertension, liver disease, heart disease, cancer type, urgency of surgery, smoking, BMI, and alcohol

- **Appendix III:**

Paper III

Renin–angiotensin system blockers and one-year mortality in patients with postoperative acute kidney injury

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Acute kidney injury; Angiotensin-converting enzyme inhibitor; Angiotensin-receptor blocker, Colorectal neoplasm; Colorectal surgery; Mortality; Post-operative complication; Cohort study

ABSTRACT

Background: Limited data address the association between angiotensin-converting enzyme inhibitor (ACE-I) and angiotensin-receptor blocker (ARB) use and mortality in patients with postoperative acute kidney injury (AKI). We studied whether preoperative use of ACE-I/ARBs in patients with AKI after colorectal cancer surgery (CRC) was associated with increased mortality up to a year after AKI.

Methods: This population-based cohort study in Northern Denmark included all patients with AKI within 7 days after CRC surgery during 2005–2014. Based on reimbursed prescriptions, patients were classified as current ACE-I/ARB users (≥1 prescription within 90 days before surgery), former users (≥1 prescription in the 91–365 days before surgery only), or non-users (no prescriptions within 365 days before surgery). We computed the cumulative mortality with 95% confidence intervals (CIs) for days 0–30, 31–90, 91–365, and 0–365 post-AKI using the Kaplan–Meier method (1 – survival function). Hazard ratios (HRs) comparing mortality in current and former ACE-I/ARB users with non-users were computed by Cox proportional hazards regression analyses, controlling for potential confounders.

Results: Among the 2000 included patients, the one-year mortality rates were 26.4% (95% CI: 22.9–30.4), 29.8% (95% CI: 23.2-37.8), and 24.7% (95% CI: 22.4-27.2) in current, former, and non-users, respectively. Compared with non-users, the adjusted HR for one-year mortalities for current and former users were 1.26 (95% CI: 0.96–1.65) and 1.19 (0.78–1.82), respectively.

Conclusion: Being a user of ACE-I/ARBs was not substantially associated with elevated mortality during the first year after postoperative AKI in CRC surgery patients.

INTRODUCTION

Acute kidney injury (AKI), a sudden decline in kidney excretory function, is a frequent complication after major non-cardiac surgery,[1,2] including colorectal cancer (CRC) surgery.[3–5] Patients developing AKI after colorectal or CRC surgery have an increased in-hospital and 30-day mortality compared with patients without AKI.[2,6]

Preventing AKI is crucial because treatment options are limited to discontinuation of nephrotoxic drugs, ensuring adequate fluid balance, and supportive care with renal replacement therapy (RRT).[7] Identifying patients at risk for AKI is important for targeting prevention. One potential target is the preoperative use of angiotensin-converting enzyme inhibitors (ACE-Is) and angiotensin-receptor blockers (ARBs), which are commonly prescribed for hypertension, heart failure, to preserve kidney function in chronic kidney disease (CKD), or to delay the development of diabetic nephropathy.[8,9] Evidence is limited for the association of ACE-I/ARB with increased postoperative mortality after major non-cardiac surgery, and current results are conflicting.[10–12] The association between postoperative AKI and mortality could result from a decreased ability of the kidneys to maintain homeostasis and acidity levels or through refractory hypotension in patients using ACE-I/ARBs.[13]

No studies have investigated the impact of ACE-I/ARBs on mortality in patients with AKI after major non-cardiac surgery. An association of ACE-I/ARB use with increased mortality in these patients would have clinical implications for postoperative monitoring. Therefore, we examined the association between preoperative use of ACE-I/ARB and mortality within the first year after AKI.

METHODS

Study design and setting

We conducted a cohort study in Northern Denmark (North and Central Denmark Regions, 2,074,956 inhabitants in the study period). Surgery for CRC was performed at nine hospitals in the study area, and data were prospectively recorded in medical and administrative databases.[14–17] All Danish residents are provided with tax-supported health care by the Danish National Health Service. Since 1968, all residents have been assigned a unique 10-digit civil registration number, which allows unambiguous individual-level linkage among medical and administrative databases.[14]

Study Population

The study included all patients registered in the Danish Colorectal Cancer Group (DCCG.dk) database, who underwent surgery for incident CRC from 1 January 2005 to 31 December 2014 and developed AKI within 7 days after surgery.[18,19]

The DCCG database, established in May 2001, contains information for CRC patients on demographics, treatments, complications, survival, and mortality.[18] We required residency in the study area for at least one year before surgery to ensure availability of baseline laboratory data. Moreover, all but two hospitals had greater than 90% creatinine data completeness during the entire study period. Patients from the remaining two hospitals were included after 2005 and 2009 because these centers achieved creatinine data completeness above 90% in 2006 and in 2010, respectively.[17]

We identified all patients who developed AKI within 7 days after CRC surgery according to the serum creatinine criteria in the Kidney Disease Improving Global Outcome (KDIGO) consensus criteria.[19] Data on plasma creatinine (PCr) (equivalent to serum creatinine)[20] were retrieved from

the clinical laboratory information system (LABKA) research database at Aarhus University.[17] This database contains PCr results collected by general practices and hospitals in the study area.

ACE-I and ARB

Preoperative use of ACE-I/ARBs was identified through the National Health Service Prescription Database (NHSPD). Since 2004, all reimbursable drugs dispensed in community pharmacies in Denmark have been registered in the NHSPD. Patients were characterized as current users of ACE-Is/ARBs (≥1 prescription within 90 days before surgery), former users (≥1 prescription in the period 90-365 days before surgery), or non-users (no prescriptions during 365 days before surgery). The current users with in-hospital information on ACE-I/ARB use were confirmed as having continued with treatment if a registration of ACE-I/ARB was made in the electronic patient chart on the day of surgery; otherwise, they were defined at having withheld their medication on the day of surgery.

Mortality

We obtained data on mortality from the date of AKI to one year after AKI from the Danish Civil Registration System (CRS). The CRS has maintained information on all changes in vital status and migration for the entire Danish population since 1968.[14]

Covariates

We obtained data on potential confounders associated with ACE-I/ARB use and post-operative mortality.[19,21,22] Data on age and sex were obtained from the CRS.[14] Data on comorbidity within 10 years before CRC surgery were identified from the Danish National Patient Registry (DNPR) based on diagnoses from any inpatient or outpatient hospital contact for obstructive pulmonary disease, hypertension, diabetes, heart disease, or liver disease. These date were age, sex, obstructive

pulmonary disease, hypertension, diabetes, heart disease, and liver disease.[16] Among other data recorded, the DNPR includes information on diagnoses, procedures, and admission/discharge dates on all hospitalizations since 1977, outpatient visits since 1994, and emergency room visits since 1995. The presence of CKD, a strong predictor for AKI and mortality, was assessed using PCr results from the LABKA database converted to estimated glomerular filtration rate with the CKD Epidemiology Collaboration equation.[17,23] CKD was defined by an estimated glomerular filtration rate <60 ml/min/1.73 m^2 lasting at least 3 months within the 2 years before the CRC surgery.[24]

In addition to diagnoses from the DNPR, we captured patients with diabetes and obstructive pulmonary disease by including previous (within 1 year before surgery) prescriptions of medications used to treat these conditions, as recorded in the NHSPD.[15] Body mass index (BMI; computed from weight and height), alcohol consumption, and tobacco use were retrieved from the DCCG database. [21] Preoperative use of statins, calcium-channel blockers, beta-blockers, antibiotics, and nitrates was identified according to the definition used for ACE-I/ARB current users. Non-steroidal anti-inflammatory drug (NSAID) use was defined as one or more prescriptions redeemed within 60 days before surgery, because these prescriptions are typically redeemed every 60 days.[25]

Statistical methods

Patient characteristics, including demographics, preexisting comorbidities, medication use, and information from the hospitalization associated with the CRC surgery, were tabulated relative to use of ACE-I/ARB. We followed patients from the day they developed AKI after surgery until death, emigration, or up to one year after AKI, whichever came first. The Kaplan–Meier method was used to compute cumulative mortality curves (1 – survival function) with 95% confidence intervals (CIs) for current, former, and non-users of ACE-I/ARB.[26] Using a Cox proportional hazards regression

model adjusted for potential confounding, we compared mortality at 30, 31 to 90, 91 to 365, and 0 to 365 days in current and former users with the mortality among non-users. Confounders included age (0–59, 60–69, 70–79, ≥80 years), sex, BMI, tobacco use, alcohol consumption, CKD, diabetes, obstructive pulmonary disease, hypertension, heart disease, cancer type, and urgency of surgery. Because of the limited number of events, medications were not included in the multivariate Cox proportional hazard regression but examined for their potential role as effect modifiers in stratified analyses.

To examine for potential effect modification, analyses were repeated for the following subgroups: sex, age (0–59, 60–69, 70–79, ≥80), BMI category, alcohol use, smoking status, CKD, diabetes, hypertension, heart disease, urgency of surgery, calcium-channel blockers, beta-blockers, statins, antibiotics, NSAIDs, and diuretic use. The assumption of proportional hazards was checked graphically and found to be appropriate within all follow-up periods. We imputed missing data for four categorical variables (BMI, tobacco use, alcohol consumption, CKD) using all covariates, the exposure and outcome, and the Nelson–Aalen estimator of the cumulative hazard.[27] We expected data to be missing at random, whereby multiple imputation is preferable to complete case analysis.[27] Therefore, multiple imputation was included in our primary analyses, and a complete case analysis was included as an additional analysis to address the potential bias from missing data. Misclassification of the exposure was addressed in sensitivity analyses where the window for being a current user (primary analysis 90 days) was changed to 30, 60, and 100 days.

All analyses were conducted using the software package Stata, version 13.1 (StataCorp, College Station, TX, USA). All data were obtained from Danish registries, and according to Danish law, their use did not require ethical approval or informed consent. The study was approved by the Danish

Data Protection Agency (Record no. 2015-57-0002, Aarhus University record number 2016-051-000001-423).

RESULTS

Study population and ACE-I/ARB prevalence

We identified 2000 patients with AKI after CRC surgery living in Northern Denmark who underwent CRC surgery from 1 January 2005 to 31 December 2014 after exclusion of patients with chronic dialysis (n = 22), no follow-up data (n = 5), only exploratory surgery (n = 754), or without postoperative AKI (n = 7933) (Figure 1). “Figure 1 about here” Of the included patients, 27.9% (n = 558) were current users, 8.1% were former users, and 64.0% non-users. In-hospital information on the use of ACE-I/ARB was available for 65% (n = 363) of current users. Of these 65%, 33% were confirmed to have taken their ACE-I/ARB on the day of surgery. “

Descriptive data

Total follow-up time was 1554 person-years, with no loss to follow-up. Median age was 74.1 years, and 1221 (61.1%) patients were men. A total of 1285 (64.3%) patients had colon cancer, while 715 (35.7%) had rectal cancer (Table 1). Information on CKD, BMI, tobacco use, and alcohol was missing for around 20% of the patients, whereas 3% of the patients did not have information on American Society of Anesthesiology score (Table 1). “Table 1 about here”

Current and former users of ACE-I/ARBs were older, had a higher BMI, and had more comorbidities compared with non-users (Table 1). Thus, patients with ACE-I/ARB use more often had preoperative CKD, diabetes, and hypertension than non-users. Postoperative bleeding and surgical lesions were more frequent in current users than non-users (Supplementary Table S1).

Mortality

30-day mortality

The 30-day mortalities were 16.5% (95% CI: 13.7–19.8) for current users, 16.2% (95% CI: 11.3–22.8) for former users, and 13.4% (95% CI: 11.6–15.4) for non-users (Table 2). The adjusted hazard ratio (aHR) was 1.26 (95% CI: 0.96–1.65) for current users and 1.19 (95% CI: 0.78–1.82) for former users compared with non-users (Table 2). “Table 2 around here”

Mortality at 31–90 days

Former users of ACE-I/ARBs did not have a higher 31–90-day cumulative mortality (Table 2). At 31 to 90 days, current users had a cumulative mortality of 6.7% (95% CI: 4.7–9.3); among former users, it was 9.6% (95% CI: 5.7–16.0), and for non-users, it was 5.4 % (95% CI: 4.2–6.9). After adjusting for potential confounding, we found aHRs of 1.22 (95% CI: 0.76–1.96) for current users and 1.87 (95% CI: 1.00–3.51) for former users (Table 2).

Mortality at 91–365 and 0–365 days

For current users, mortality at 91–365 days was 9.0% (95% CI: 6.6–12.1); for former users, it was 12.3% (95% CI: 7.6–19.6), and it was 11.3% (95% CI: 9.5–13.3) for non-users (Table 2). Neither crude nor adjusted HRs showed an association between use of ACE-I/ARBs and mortality (Table 2). Cumulative mortality at 0–365 days was 26.4% (95% CI: 22.9–30.4) for current users, 29.8% (95% CI: 23.2–37.8) for former users, and 24.7% (95% CI: 22.4–27.2) for non-users. The aHR for current versus non-users was 1.11 (95% CI: 0.91–1.35) (Table 2 and Figure 2).

Sensitivity and subgroup analyses

To address the potential bias from missing data, we conducted a complete case analysis in addition to the primary analysis (where missing data were imputed) and found a slightly higher

adjusted relative one-year mortality after AKI for both current and former users compared with non-users (Supplementary Table S2). Misclassification of the exposure was addressed in sensitivity analyses where the window for being a current user (primary analysis 90 days) was changed to 30, 60, and 100 days. This approach also did not change the results markedly (Supplementary Table S2).

Analyses yielded no signs of effect modification upon repeating them across subgroups of sex, age (0–59, 60–69, 70–79, ≥80), BMI category, alcohol use, smoking status, CKD, diabetes, hypertension, heart disease, urgency of surgery, calcium-channel blockers, beta-blockers, statins, antibiotics, NSAIDs, and diuretic use (Supplementary Figure S1).

DISCUSSION

Key results

In this prospective cohort study of 2000 patients with AKI after surgery for CRC, we found that being a user of ACE-I/ARBs was not substantially associated with elevated mortality risk during the first year after postoperative AKI.

Limitations and strengths

The strength of this study is the use of Danish national population-based registries where data are collected for administrative and clinical quality monitoring purposes.[14–17] These registries are largely complete with regard to the Danish population because of a tax-based health care system. Moreover, there is virtually complete follow-up.

Some important limitations must be considered when interpreting our results, however. In an observational study, confounding by indication is an inherent issue that must be reflected upon and reduced if possible. Therefore, we adjusted for comorbidities and co-medication and included

a former user category to eliminate and evaluate the size of confounding. Despite these precautions, we cannot exclude some residual confounding and unmeasured confounding. A key issue of this study was defining the exposure window of current ACE-I/ARB use with the highest possible sensitivity with due consideration of specificity. The lack of notable changes in the estimates from adjusting the exposure window from 90 days to 30, 60, or 100 days supports the robustness of our definition.

The non-association of ACE-I/ARB use and one-year mortality of CRC surgery patients with AKI identified here may be a result of the small sample size. If ACE-I/ARB use is truly associated with increased mortality in patients with AKI after CRC surgery, the explanation could be inhibition of angiotensin-II, resulting in a worsening of hypotension or decreased circulatory volume. This effect may contribute to reduced arterial pressure beyond the auto-regulatory range of the kidneys. Consequently, refractory hypotension could develop and AKI severity increase, further worsening the hypotension by the kidney's decreased ability to maintain homeostasis through regulation of electrolyte concentration, blood pressure, and acidity.[28,29]

If all current users of ACE-I/ARBs withheld their ACE-I/ARB on the day of surgery, that could explain the non-association we found. However, we could confirm medication withholding or continuation on the day of surgery only for patients undergoing their procedure in the Central Denmark Region (~65%). Thirty-three percent of the current users with in-hospital information were registered in the electronic patient chart as continuing the medication on the day of surgery. Additionally, some patients may have been advised to take the medication at home, which would not have been registered. Moreover, most ACE-I/ARBs affect blood pressure for at least 24 hours, so withholding medication on the day of surgery might not be expected to exclude its effects on that day. Thus, there may be a risk of information bias in our study. That said, we would expect

this information bias to be non-differential because it is not evident whether use of ACE-I/ARB in patients undergoing non-cardiac surgery is associated with AKI risk or if ACE-I/ARBs are associated with increased mortality after surgery. Thus, we would not expect clinicians to be more likely to advise withholding than continuing in a systematic way depending on the patient's current medical status. Also, the hospitals included in the study did not seem to have guidelines for advising patients to continue or withhold ACE-I/ARBs before surgery.

Existing studies

To the best of our knowledge, no existing literature addresses the association between ACE-I/ARB use and mortality in patients with AKI after non-cardiac surgery. Two studies of intensive care unit (ICU) patients assessed the association between ACE-I/ARB use and mortality in patients with AKI and found a reduced one-year mortality, but results were given for all patients and not surgical patients separately.[30,31] In one of the studies, a cohort study of 1551 ICU patients treated with mechanical ventilation or vasopressor, in patients with AKI, a prescription of ACE-I/ARB at discharge was associated with decreased one-year mortality (aHR=0.45; 95% CI: 0.27–0.75; one-year mortality was 28% for non-users and 15% for users).[31] Compared with CRC surgery patients, these patients had a higher average Charlson comorbidity index[32] and greater circulatory and respiratory instability as per the need/indication for treatment with vasopressors and mechanical ventilation; thus, the results may not be generalizable to CRC surgery patients.[31] The other cohort study of 1463 ICU patients with AKI requiring RRT found no association between use of ACE-I/ARBs and mortality ($aHR_{90\text{-}day}$=0.78; 95% CI: 0.51–1.21).[30]

We believe our results are generalizable to other CRC surgical settings comparable to that of enhanced recovery after surgery. In conclusion, being a current user of ACE-I/ARB was not

substantially associated with an elevated mortality risk during the first year after postoperative AKI.

Competing interests

No competing interests.

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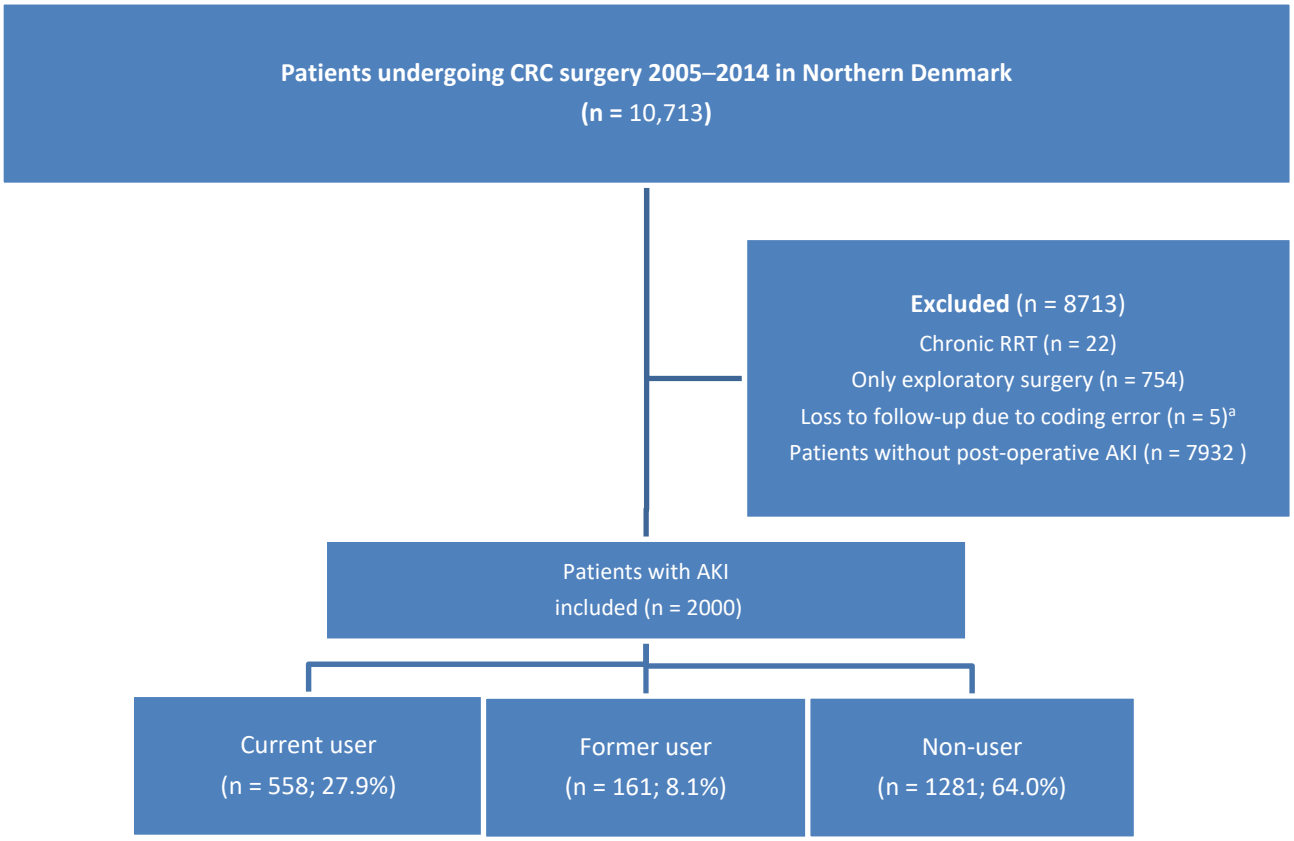
Tables and Figures

Figure 1. Flow chart.



[a] Death date registered as prior to surgical date.
Abbreviations: acute kidney injury, AKI; angiotensin-converting enzyme inhibitor, ACE-I; angiotensin-receptor blocker, ARB; renal replacement therapy, RRT

Figure 2. Cumulative one-year mortality in patients with postoperative AKI according to angiotensin-converting enzyme inhibitor (ACE-I) and angiotensin-receptor blocker (ARB) use.

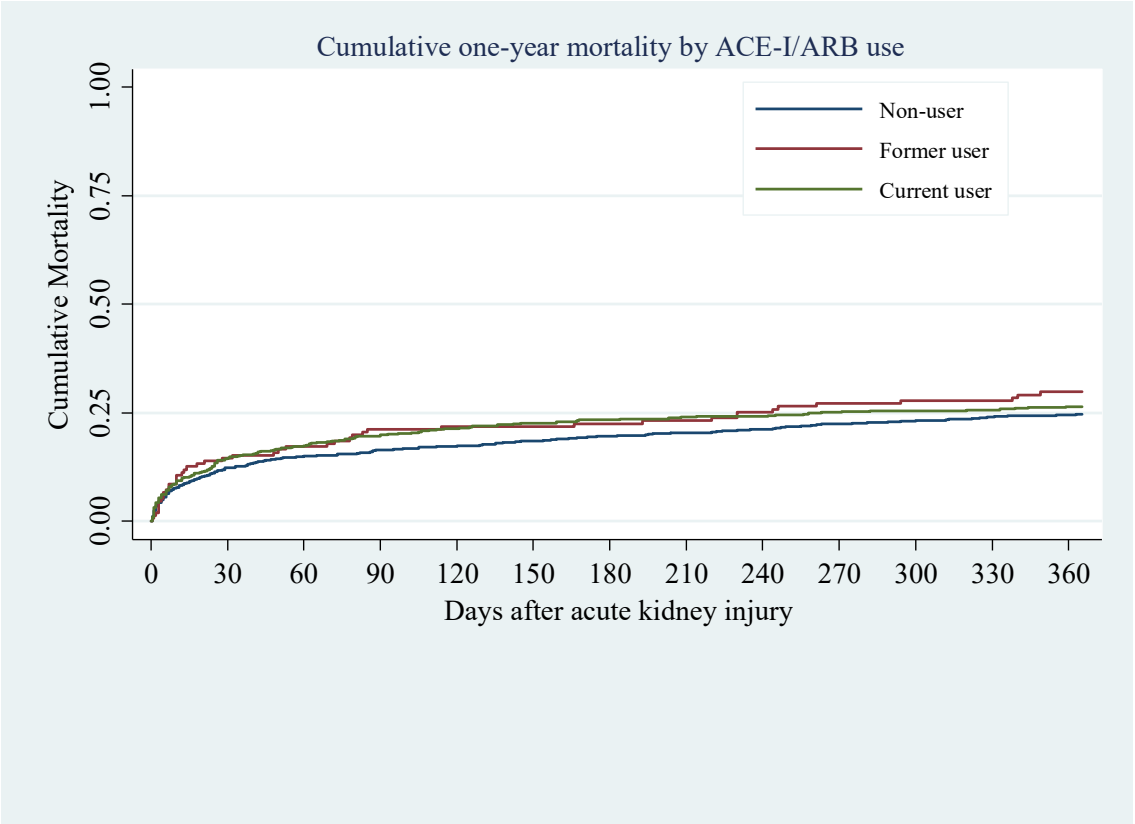


Table 1. Demographics tabulated by use of angiotensin-converting enzyme inhibitor (ACE-I) and angiotensin-receptor blocker (ARB) use.

Patient characteristics	ACE-I/ARB use			
	Non-user (n = 1281) No. (%)	Former user (n = 161) No. (%)	Current user (n = 558) No. (%)	All patients (n = 2000) No. (%)
Sex				
Female	523 (40.8)	63 (39.1)	193 (34.6)	779 (39.0)
Male	758 (59.2)	98 (60.9)	365 (65.4)	1221 (61.1)
Age, y				
Mean	72.1 (±11.0)	75.2 (±8.4)	74.0 (±9.3)	72.9 (±10.4)
0–59	184 (14.4)	6 (3.7)	41 (7.3)	231 (11.6)
60–69	329 (25.7)	38 (23.6)	132 (23.7)	499 (24.9)
70–79	431 (33.6)	66 (41)	228 (40.9)	725 (36.3)
>79	337 (26.3)	51 (31.7)	157 (28.1)	545 (27.3)
Tobacco use				
Smoker	224 (17.5)	15 (9.3)	71 (12.7)	310 (15.5)
Former smoker	434 (33.9)	76 (47.2)	246 (44.1)	756 (37.8)
Never smoker	274 (21.4)	38 (23.6)	118 (21.1)	430 (21.5)
Missing	349 (27.2)	32 (19.9)	123 (22)	504 (25.2)
Alcohol consumption (weekly)				
0 Units/week	274 (21.4)	39 (24.2)	150 (26.9)	463 (23.2)
1–14 Units/week	531 (41.5)	75 (46.6)	223 (40)	829 (41.4)
>14 Units/week	117 (9.1)	12 (7.5)	56 (10)	185 (9.3)
Missing	359 (28)	35 (21.7)	129 (23.1)	523 (26.2)
BMI category				
Normal weight	406 (31.7)	41 (25.5)	154 (27.6)	601 (30)
Underweight	29 (2.3)	6 (3.7)	8 (1.4)	43 (2.1)
Overweight	501 (39.1)	85 (52.8)	274 (49.1)	860 (43.0)
Missing	345 (26.9)	29 (18)	122 (21.9)	496 (24.8)
ASA score				
1	214 (16.7)	6 (3.7)	15 (2.7)	235 (11.8)
2	617 (48.2)	78 (48.4)	266 (47.7)	961 (48)
3	366 (28.6)	64 (39.8)	235 (42.1)	665 (33.3)
4	41 (3.2)	9 (5.6)	26 (4.7)	76 (3.8)
5	3 (0.2)	0 (0)	1 (0.2)	4 (0.2)
Missing	40 (3.1)	4 (2.5)	15 (2.7)	59 (2.9)
Charlson comorbidity index				
0	803 (62.7)	61 (37.9)	246 (44.1)	1110 (55.5)
1-2	322 (25.1)	67 (41.6)	208 (37.3)	597 (29.8)
> 2	156 (12.2)	33 (20.5)	104 (18.6)	293 (14.6)
Heart disease	32 (2.5)	5 (3.1)	29 (5.2)	66 (3.3)
Diabetes mellitus	101 (7.9)	45 (28)	148 (26.5)	294 (14.7)
Liver disease	23 (1.8)	0 (0.0)	12 (2.2)	35 (1.8)
Hypertension	315 (24.6)	98 (60.9)	331 (59.3)	744 (37.2)
Obstructive pulmonary disease	175 (13.7)	24 (14.9)	79 (14.2)	278 (13.9)
Chronic Kidney Disease				
Yes	317 (24.7)	69 (42.9)	235 (42.1)	621 (31.1)
Missing	248 (19.4)	20 (12.4)	74 (13.3)	342 (17.1)
Cancer type				
Colon	822 (64.2)	106 (65.8)	357 (64)	1285 (64.3)
Rectum	459 (35.8)	55 (34.2)	201 (36)	715 (35.8)
Palliative or curative treatment				
Curative	1138 (88.8)	140 (87)	496 (88.9)	1774 (88.7)
Palliative	143 (11.2)	21 (13)	62 (11.1)	226 (11.3)
Elective or acute surgery				
Elective	1040 (81.2)	140 (87)	480 (86)	1660 (83)
Acute	241 (18.8)	21 (13)	78 (14)	340 (17)
Procedure type				
Colon resection + A	714 (55.7)	81 (50.3)	288 (51.7)	1083 (54.1)

Colon resection ÷ A	371 (29)	52 (32.3)	175 (31.4)	598 (29.9)
Rectum resection + A	196 (15.3)	28 (17.4)	95 (17)	319 (16)

Abbreviations: A, anastomosis; AKI, acute kidney injury; ASA, American Society of Anesthesiology; BMI, body mass index; CKD, chronic kidney disease. Missing data: alcohol, BMI, CKD, smoking ~20%; ASA (2.9%).

Table 2. Mortality outcomes (0–30, 31–90, 91–365, and 0–365 days) according to angiotensin-converting enzyme inhibitor (ACE-I) and/or angiotensin-receptor blocker (ARB) use.

Mortality outcomes	**Person-time (days)**	**Number of outcomes**	**Cumulative Mortality % (95% CI)**	**Crude HR (95% CI)**	**Adjusted HR[1] (95% CI)**
0–30 days					
Non-user	35,836	172	13.4 (11.7–15.4)	Ref.	Ref.
Former user	4380	26	16.2 (11.3–22.8)	1.22 (0.80–1.85)	1.19 (0.78–1.82)
Current user	15,283	92	16.5 (13.7–19.8)	1.25 (0.97–1.61)	1.26 (0.96–1.65)
31–90 days					
Non-user	65,281	60	5.4 (4.2–6.9)	Ref.	Ref.
Former user	7858	13	9.6 (5.7–16.0)	1.80 (0.99–3.27)	1.87 (1.00–3.51)
Current user	27,393	231	6.7 (4.7–9.3)	1.23 (0.80–1.90)	1.22 (0.76–1.96)
91–365 days					
Non-user	271,232	118	11.3 (9.5–13.3)	Ref.	
Former user	31,870	15	12.3 (7.6–19.6)	1.08 (0.63–1.85)	1.11 (0.64–1.95)
Current user	113,357	39	9.0 (6.6–12.1)	0.79 (0.55–1.13)	0.81 (0.55–1.20)
0–365 days					
Non-user	370,315	350	24.7 (22.4–27.2)	Ref.	Ref.
Former user	43865	54	29.8 (23.2–37.8)	1.27 (0.96–1.69)	1.29 (0.96–1.73)
Current user	155,183	362	26.4 (22.9–30.4)	1.09 (0.90–1.31)	1.11 (0.91–1.35)

[1] Adjusted for age (0–59, 60–69, 70–79, ≥80), sex, urgency of surgery, cancer type, CKD, diabetes mellitus, hypertension, heart disease, BMI, smoking, and alcohol.

Abbreviations: AKI, acute kidney injury; BMI, body mass index; CKD, chronic kidney disease; CI confidence interval; HR, hazard ratio.

SUPPLEMENTARY

Table S1. Surgical complications after colorectal cancer surgery according to angiotensin-converting enzyme inhibitor (ACE-I) and/or angiotensin-receptor blocker (ARB) use.

	ACE-I/ARB use			
	Non-user (n = 1281)	Former user (n = 161)	Current user (n = 558)	All patients (n = 2000)
Surgical complications	No. (%)	No. (%)	No. (%)	No. (%)
Bleeding	46 (3.6)	5 (3.1)	32 (5.7)	83 (4.2)
Fascial dehiscence	89 (6.9)	13 (8.1)	30 (5.4)	132 (6.6)
Ileus	65 (5.1)	6 (3.7)	32 (5.7)	103 (5.1)
Anastomosis leakage	180 (14.1)	15 (9.3)	71 (12.7)	266 (13.3)

Table S2. Sensitivity analyses. Mortality outcomes (0–30, 31–90, 91–365, and 0–365 days) according to angiotensin-converting enzyme inhibitor (ACE-I) and angiotensin-receptor blocker (ARB) use.

Mortality outcomes (sensitivity analyses)		**Crude HR (95% CI)**	**Adjusted HR[1] (95% CI)**
Complete case			
	0–30 days		
	Non-user	Ref.	Ref.
	Former user	1.22 (0.81–1.85)	1.83 (0.99–3.36)
	Current user	1.25 (0.97–1.61)	1.68 (1.09–2.58)
	31–90 days		
	Non-user	Ref.	
	Former user	1.80 (0.99–3.27)	3.23 (1.49–7.01)
	Current user	1.23(0.80–1.90)	1.66 (0.89–3.13)
	91–365 days		
	Non-user	Ref.	Ref.
	Former user	1.08 (0.63–1.85)	1.38 (0.71–2.70)
	Current user	0.79 (0.55–1.14)	0.69 (0.41–1.16)
	0–365 days		
	Non-user	Ref.	Ref.
	Former user	1.27 (0.96–1.69)	1.88 (1.28–2.77)
	Current user	1.09 (0.91–1.32)	1.25 (0.93–1.67)
Current user 100 days			
	0–30 days		
	Non-user	Ref.	Ref.
	Former user	1.14 (0.67–1.82)	1.11 (0.67–1.82)
	Current user	1.27 (0.97–1.66)	1.27 (0.97–1.66)
	31–90 days		
	Non-user	Ref.	Ref.
	Former user	2.03 (1.07–3.86)	2.03 (1.03–3.98)
	Current user	1.22 (0.80–1.87)	1.23 (0.77–1.96)
	91–365 days		
	Non-user	Ref.	Ref.
	Former user	1.07 (0.58–1.99)	1.11 (0.58–2.11)
	Current user	0.81 (0.57–1.15)	0.84 (0.57–1.22)
	0–365 days		
	Non-user	Ref.	Ref.
	Former user	1.27 (0.92–1.76)	1.28 (0.91–1.79)
	Current user	1.11 (0.92–1.32)	1.12 (0.92–1.37)
Current user 60 days			
	0–30 days		
	Non-user	Ref.	Ref.
	Former user	1.20 (0.87–1.67)	1.22 (0.87–1.71)
	Current user	1.27 (0.96–1.67)	1.26 (0.94–1.69)
	31–90 days		
	Non-user	Ref.	Ref.
	Former user	1.44 (0.86–2.42)	1.50 (0.87–2.60)
	Current user	1.30 (0.81–2.07)	1.27 (0.76–2.11)
	91–365 days		
	Non-user	Ref.	Ref.
	Former user	1.03 (0.67–1.58)	1.07 (0.68–1.69)
	Current user	0.74 (0.49–1.12)	0.75 (0.48–1.16)
	0–365 days		
	Non-user	Ref.	Ref.
	Former user	1.19 (0.94–1.49)	1.22 (0.96–1.55)
	Current user	1.10 (0.89–1.34)	1.10 (0.88–1.37)

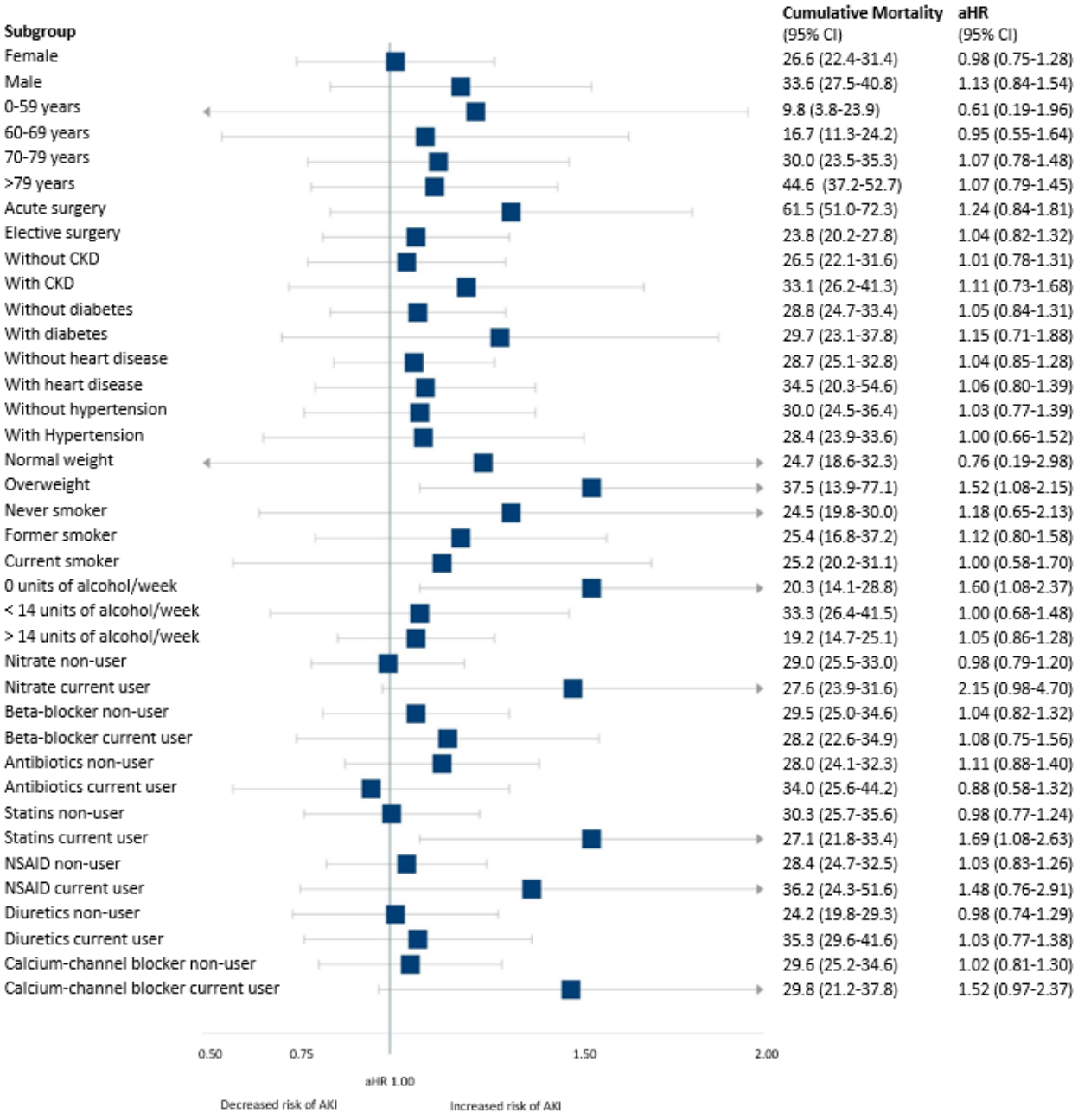
Table S2 (continued). Mortality outcomes (0–30, 31–90, 91–365, and 0–365 days) according to angiotensin-converting enzyme inhibitor (ACE-I) and angiotensin-receptor blocker (ARB) use.

Mortality outcomes (sensitivity analyses)	**Crude HR (95% CI)**	**Adjusted HR[1] (95% CI)**
Current user 30 days		
0–30 days		
Non-user	Ref.	Ref.
Former user	1.17 (0.98–1.53)	1.19 (0.89–1.59)
Current user	1.39 (1.00–1.95)	1.34 (0.94–1.90)
31–90 days		
Non-user	Ref.	Ref.
Former user	1.36 (0.88–2.11)	1.40 (0.87–2.26)
Current user	1.35 (0.75–2.42)	1.28 (0.68–2.39)
91–365 days		
Non-user	Ref.	Ref.
Former user	0.86 (0.60–1.25)	0.90 (0.60–1.34)
Current user	0.84 (0.50–1.39)	0.84 (0.49–1.43)
0–365 days		
Non-user	Ref.	Ref.
Former user	1.10 (0.90–1.34)	1.13 (0.92–1.40)
Current user	1.20 (0.94–1.54)	1.18 (0.90–1.54)
Follow-up start on day 8 after surgery		
0–30 days		
Non-user	Ref.	Ref.
Former user	1.29 (0.70–2.38)	1.21 (0.65–2.26)
Current user	1.36 (0.94–1.97)	1.30 (0.87–1.94)
31–90 days		
Non-user	Ref.	Ref.
Former user	1.63 (0.90–2.96)	1.72 (0.92–3.20)
Current user	1.12 (0.73–1.72)	1.13 (0.71–1.80)
91–365 days		
Non-user	Ref.	Ref.
Former user	1.08 (0.63–1.85)	1.11 (0.63–1.94)
Current user	0.81 (0.57–1.16)	0.83 (0.56–1.22)
0–365 days		
Non-user	Ref.	Ref.
Former user	1.27 (0.95–1.69)	1.29 (0.96–1.74)
Current user	1.09 (0.91–1.32)	1.10 (0.91–1.36)

Table S3. Preoperative use of medication according to angiotensin-converting enzyme inhibitor (ACE-I) and/or angiotensin-receptor blocker (ARB) use.

		ACE-I/ARB use			
Type of medication		Non-user (n = 1281) No. (%)	Former user (n = 161) No. (%)	Current user (n = 558) No. (%)	All patients (n = 2000) No. (%)
Diuretics					
	Non-user	1000 (78.1)	101 (62.7)	314 (56.3)	1415 (70.8)
	Current user	281 (21.9)	60 (37.3)	244 (43.7)	585 (29.3)
Non-steroidal anti-inflammatory drugs					
	Non-user	1192 (93.1)	149 (92.5)	511 (91.6)	1852 (92.6)
	Current user	89 (6.9)	12 (7.5)	47 (8.4)	148 (7.4)
Antibiotics					
	Non-user	1028 (80.2)	132 (82.0)	458 (82.1)	1618 (80.9)
	Current user	253 (19.8)	29 (18.0)	100 (17.9)	382 (19.1)
Statins					
	Non-user	1102 (86.0)	118 (73.3)	333 (59.7)	1553 (77.6)
	Current user	179 (14.0)	43 (26.7)	225 (40.3)	447 (22.4)
Beta-blockers					
	Non-user	1072 (83.7)	130 (80.7)	349 (62.5)	1551 (77.5)
	Current user	209 (16.3)	31 (19.3)	209 (37.5)	449 (22.4)
Calcium-channel blockers					
	Non-user	6506 (90.6)	518 (81.1)	1526 (72.3)	8550 (86.1)
	Current user	675 (9.4)	121 (18.9)	586 (27.7)	1382 (13.9)
Nitrates					
	Non-user	1234 (96.3)	154 (95.7)	519 (93.0)	1907 (95.3)
	Current user	47 (3.7)	7 (4.3)	39 (7.0)	93 (4.7)

Figure S1. Subgroup analyses of the association between current angiotensin-converting enzyme inhibitor (ACE-I) and/or angiotensin-receptor blocker (ARB) use and one-year mortality in patients with AKI after CRC surgery. Demographics, comorbidities, and preoperative medication.



Supplementary Material (study III)

Table S1. Codes used to retrieve data from the Danish National Patient Registry, the LABKA Laboratory Database, and National Health Service Prescription Database (NHSPD)

Table S2. Angiotensin-converting enzyme inhibitors (ACE-I) and/or angiotensin-receptor Blockers (ARB) use and the day of AKI after colorectal cancer surgery.

Table S1. Codes used to retrieve data from the Danish National Patient Registry, the LABKA Laboratory Database, and National Health Service Prescription Database (NHSPD)

Description	Type of Code			
	Diagnoses	**ATC**	**Procedure**	**Laboratory (NPU- and local codes)**
Study population				
Acute kidney injury Acute RRT Chronic RRT Plasma creatinine measurements			 BJFD0 BJFD2	 NPU: 18016, 01807, 04998. ASS: 00356, 00354, 00355
Exposure				
ACE-I ARB		C09A, C09BA,C09BB C09CA, C09DB		
Covariates				
Charlson comorbidities[a]	s1-s19			
Diabetes mellitus (DM) Diagnosis of DM Reimbursed diabetic medication	 ICD-10: E10-14	 A10B		
Obstructive pulmonary disease COPD Asthma Reimbursed OPD medication	 ICD-10: DJ44 ICD-10: DJ45	 R03B, QR03B		
Heart disease[a] Myocardial infarction Congestive heart failure	S1-S2 ICD-10: I21;I22;I23 ICD-10: I50;I11.0;I13.0; I13.2			
Hypertension	ICD-10: I10-I15			
Liver disease	ICD-10: DK70-77			
Chronic kidney disease Plasma creatinine measurements				NPU: 18016, 01807, 04998. ASS: 00356, 00354, 00355
Diuretics NSAIDs Antibiotics Statins Beta-blockers Calcium-Channel blockers Nitrates		C03 M01A J01 C10AA C07 C01DA, C01DX		

Abbreviations: angiotensin-converting enzyme inhibitors, ACE; angiotensin receptor blocker, ARB; chronic obstructive pulmonary disease, COPD;, non-steroidal anti-inflammatory drugs, NSAIDs; the Danish National Patient Registry, DNPR; the Laboratory Database, LABKA; the National Health Service Prescription Database, (NHSPD), renal replacement therapy, RRT.

a Thygesen S, Christiansen C, Christensen S, Lash T, Sørensen HT. The predictive value of ICD-10 diagnostic coding used to assess Charlson comorbidity index conditions in the population-based Danish National Registry of Patients. BMC Medical Research Methodology [serial online]. January 2011;11(1):83-88.

Table S2. Angiotensin-converting enzyme inhibitors (ACE-I) and/or angiotensin-receptor Blockers (ARB) use and the day of AKI after colorectal cancer surgery.

Day of AKI after CRC Surgery	ACE-I/ARB use			
	Non-users (n=1,281) (%)	Former users (n = 161) (%)	Current users (n = 558) (%)	All patients (n = 2,000) (%)
0	137 (11)	14 (9)	68 (12)	219 (11)
1	500 (39)	58 (36)	208 (37)	766 (38)
2	247 (19)	48 (30)	123 (22)	418 (21)
3	145 811)	19 (12)	57 (10)	221 (11)
4	82 86)	8 (5)	32 (6)	122 (6)
5	68 (5)	7 (4)	23 (4)	98 (5)
6	44 (3)	5 (3)	21 (4)	70 (4)
7	58 (5)	8 (1)	26 (5)	86 (4)

Abbreviations: Acute Kidney Injury, AKI; Colorectal Cancer, CRC

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