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Post-operative acute kidney injury and five-year risk of death, myocardial infarction, and stroke among elective cardiac surgical patients:
A cohort study

Research year report

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Preface

This research year report is based on a study carried out during my research year at the Department of Clinical Epidemiology, Aarhus University Hospital, from September 2012 to August 2013. During this year, I have been introduced to epidemiology and the methods used in the field.

I am sincerely thankful to my main supervisor Søren Paaske Johnsen for giving me the opportunity to experience what health research can be like. It has been great to try *hands-on* how health research is conducted and I am honored by the trust you've shown me.

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Abbreviations

AKI	Acute Kidney Injury
AKIN	Acute Kidney Injury Network
BMI	Body Mass Index
CABG	Coronary Artery Bypass Grafting
CCI	Charlson Comorbidity Index
CRS	Central Registration System
CI	Confidence Interval
DNRP	Danish National Registry of Patients
GFR	Glomerular Filtration Rate
HR	Hazard Ratio
ICD	International Classification of Disease
KI	Konfidens Interval
LABKA	Clinical Laboratory Information System
MI	Myocardial Infarction
PS	Propensity Score
RCT	Randomized Controlled Trial
sCr	Serum Creatinine

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Extract

Introduction

Acute kidney injury (AKI) occurs in up to 30% of patients undergoing cardiac surgery and has been reported to be associated with increased short-term mortality [1,2]. AKI is defined as an abrupt decline of kidney function with severity ranging from mild kidney dysfunction to complete renal failure with the need for acute dialysis. Recent classification systems divide AKI into three severity levels based on changes in serum creatinine level and/or urine output [3].

Previous studies in cardiac surgical patients have mainly focused on severe AKI requiring dialysis [4]. Lately, focus has shifted towards the mortality impact of less severe AKI as defined by either the Risk, Injury, Failure, Loss of function, and End-stage renal disease (RIFLE) criteria or the Acute Kidney Injury Network (AKIN) criteria. Only three studies have examined the long-term prognosis (i.e. beyond 90 days) of cardiac surgery complicated by less severe AKI [5-7]. These studies have found that AKI is associated with a 40-50% increase in long-term mortality and that AKI is associated with a higher one-year risk of major adverse cardiac events compared to patients without AKI. The studies were limited by baseline serum creatinine (sCr) being estimated by the Modification of Diet in Renal Disease equation rather than measured, inclusion of both acute and elective surgical patients, and incomplete follow-up data [6,7].

More insight into the prognostic role of AKI in elective cardiac surgical patients is needed, as AKI occurs frequently and may have devastating consequences for the patient. Increased awareness of AKI could therefore potentially facilitate a more effective prophylactic treatment strategy among high-risk patients.

We therefore conducted a cohort study of elective cardiac surgical patients with detailed pre-, peri-, and post-operative information to examine the prognostic role of early AKI on long-term risk of major adverse clinical outcomes including death, myocardial infarction (MI), and stroke.

Materials and methods

Design and setting

We conducted the study at the Department of Cardiothoracic and Vascular Surgery, Aarhus University Hospital, Denmark. The hospital provides cardiothoracic surgery for a mixed rural-urban population of approximately 1.2 million inhabitants (20% of the total Danish population) in the Central

Denmark Region. The Danish National Health Service provides tax-funded medical care for all Danish residents. Due to the unique Central Personal Registry number assigned to each Danish citizen at birth and to residents on immigration, it is possible to make accurate record linkages at an individual level [8]. The study was approved by the Regional Ethics Committee and the Danish Data Protection Agency (record number: 2013-41-1516).

Elective cardiac surgical patients

During the period from 1 April 2005 to 8 October 2007 a total of 2215 patients underwent acute and elective cardiac surgery at the Department of Cardiothoracic and Vascular Surgery, Aarhus University Hospital, Denmark. Patient screening and recruitment was done with the assistance of a project nurse working half-time, thus approximately 50% of the total population could be screened consecutively. Patients were included in the study database on the basis of: 1) age (≥18 years old); and 2) elective cardiac surgery (surgery performed more than two days after planning the procedure) including valve surgery, on- and off-pump coronary artery bypass grafting, thoracic aortic surgery, pulmonary thromboendarterectomy, ventricular aneurysm, adult congenital heart disease procedures, or combined procedures. Exclusion criteria were: 1) severe pre-existing chronic kidney disease (sCr >200μmol/L (2.3mg/dL)); and/or 2) previous heart or renal transplant surgery. The nurse prospectively collected information and completed a case-report-form for each patient included in the study containing baseline characteristics such as: smoking; body mass index (BMI); diabetes mellitus; dyslipidemia; blood pressure, and in-hospital peri-operative information.

Acute kidney injury

We used the regional laboratory database to obtain pre- and post-operative laboratory measurements. This population-based database contains information on all patient tests analyzed since 1997, including analyses codes, measurement units, dates of test collection and results [9]. Measurements of plasma creatinine - equivalent to serum creatinine - were used to classify patients as either AKI or non-AKI according to the sCr criteria in the AKIN classification (Table 1) [3,10]. We did not include the urine output criteria. The term AKI included all AKIN stages, and was further subdivided according to the individual AKIN stages. For each patient, a pre-operative blood sample was collected 10 days prior to surgery. Accordingly, the baseline sCr was available for all study participants. The peak post-operative measurement of sCr from surgery start until day five was compared to baseline sCr to assign AKI status.

Study endpoints

Information on all-cause death was obtained through linkage to the Danish Civil Registration System [8]. This system includes information on all changes in vital status, migration and exact date of death for the Danish population since 1968 and is electronically updated daily.

Causes of death (both immediate and underlying) were studied through linkage to the Danish Registry of Causes of Death which contains date and causes of death according to the International Classification of Diseases 10th revision (ICD-10) classification (Supplementary table 1) [11].

Data regarding hospitalization with MI and hospitalization with stroke (including both ischemic and hemorrhagic stroke) were obtained from the Danish National Registry of Patients (DNRP) (Supplementary table 1) [12]. The DNRP is a nationwide hospital discharge registry established in 1977 and includes civil registration number, hospital, department, discharge diagnosis, as well as surgical and diagnostic procedures for all admissions. Since 1994, diagnoses have been coded using the ICD-10 classification. We included all first-time hospitalizations with a discharge diagnosis of the specified outcome, occurring after index admission for surgery. Date of diagnosis was defined as the date of hospitalization (not including out-patient visits). Outcomes occurring during index admission for surgery, i.e. from admission date until discharge date, were excluded for the concerned analysis.

Covariates

Information on potential confounding factors was obtained from a pre-operative interview and medical records [13]. The included covariates were: gender; age; smoking habits (present, never, previous); BMI; history of ischemic peripheral disease; previous stroke; previous myocardial infarction; history of arrhythmias; diabetes; dyslipidemia; and hypertension. In addition, we obtained data on pre-existing comorbidity based on diagnoses from the DNRP (ICD-8 and ICD-10) since 1977 to compute the Charlson Comorbidity Index (CCI) scores. The CCI includes 19 disease categories with an assigned weight, and the sum of the weights defines the level of comorbidity. Patients were categorized as having low (score 0), medium (score 1-2), and high (score ≥ 3) levels of comorbidity (Supplementary table 2) [14]. The Western Denmark Heart Registry established in 1999 is a regional administrative and clinical register including detailed records on baseline patient characteristics and data regarding all cardiac procedures as well as corresponding covariates [15]. From this registry we obtained procedural characteristics including type of surgery, extra-corporal circulation,

and the EuroSCORE (European System for Cardiac Operative Risk). The EuroSCORE assigns the patient an operative mortality risk based on patient-, cardiac- and operation related factors [16].

Statistical analyses

We followed patients from day five after surgery (i.e. after assignment of AKI status) until death or emigration occurred or up to five years.

For the full cohort the cumulative incidence method was used to compute one- and five-year absolute risk of death, MI, and stroke. Death was considered a competing risk in the estimation of the risk of MI and stroke. We computed five-year unadjusted and adjusted hazard ratios (HRs) for death, MI, and stroke using a Cox proportional hazards regression model. The assumption of proportional hazards was examined graphically and fulfilled for the whole time period and for every outcome. Sensitivity analyses were performed by repeating the analysis on MI and stroke after excluding patients with a previous MI or stroke.

We computed a propensity score, which predicted the probability of developing AKI conditional on the observed baseline covariates, using multivariable logistic regression. By modeling the exposure rather than the outcome propensity scores efficiently allow for simultaneous control for a large number of potentially confounding factors in studies such as ours where we have few outcomes but many exposed [17]. The included covariates were: gender; age; smoking; BMI; history of ischemic peripheral disease; previous stroke; previous myocardial infarction; history of arrhythmias; diabetes mellitus; dyslipidemia; hypertension; CCI; baseline creatinine; EuroSCORE; type of surgical procedure (valve, CABG, combined valve and CABG, others); and extra corporal circulation.

In the analyses of the full cohort, the HR was adjusted for the propensity score as a continuous variable. Furthermore, we performed a propensity score matched analyses which aimed to match each AKI patient with the non-AKI patient with the nearest propensity score within a maximum caliper range of ± 0.025 and without replacement. In this manner we were able to match 257 (89.5%) of 287 AKI patients with a non-AKI patient. Covariates were adequately balanced after propensity score matching, as evidenced by a standardized difference of each covariate to values below 0.1 [18]. In the matched cohort we also computed the cumulative risk and HRs for each outcome, stratified on the matched pairs.

We examined the causes of death for the full cohort including both immediate and underlying causes of death. Hence, a patient may be registered with more than one cause of death. Causes were

listed in disease categories and estimates given as percentages of the total number of causes of death according to AKI status.

Analyses were performed using the statistical software package Stata® 12.0 package (StataCorp LP, Texas, US).

Results

The study population comprised 1030 patients (Figure 1). A total of 27.9% (287 of 1030) had an episode of AKI during the first five post-operative days; these included 82.9% (238 of 287) patients in AKI stage 1 and 17.1% (49 of 287) patients in AKI stage 2 or 3. AKI patients were older, more likely to have a history of stroke, arrhythmias, and diabetes, had a higher comorbidity score and a higher EuroSCORE. Mean baseline sCr value was 94.2 µmol/L for AKI patients and 81.4 µmol/L for non-AKI patients (Table 2). In the matched cohort the covariates were equally distributed.

Three patients emigrated during follow-up. Total follow-up time was 4699 person-years with a median duration of five years. In the full cohort, a total of 166 patients died during the five years of follow-up (76 AKI patients and 90 non-AKI patients). We found a five-year cumulative risk of death of 26.5% (95% CI: 21.2–32.0) among AKI patients compared with 12.1% (95% CI: 10.0–14.7) among non-AKI patients. Adjusted HR was 1.6 (95% CI: 1.1–2.2). When stratifying according to AKI stage we found a progressively higher mortality with advancing AKI stage: Five-year cumulative risk of death in AKI stage 1 of 24.8% (95% CI: 19.5–31.2) and AKI stage 2 and 3 of 34.7% (95% CI: 23.2–49.7) (Figure 2). The adjusted HRs were 1.4 (95% CI: 1.0–2.1) for AKI stage 1 and 2.3 (95% CI: 1.4–3.9) for AKI stage 2 and 3 compared to non-AKI patients (Table 3).

Heart disease was registered as cause of death in 55% of causes among AKI patients and 47% of causes among non-AKI patients (Figure 3). MI was registered as the cause of death in 10% of causes among AKI patients and 4% of causes among non-AKI patients. Kidney insufficiencies and cerebrovascular diseases (including stroke) were equally distributed between the two groups. Data on cause of death was not available on seven patients.

When analyzing the risk of MI, we excluded 35 non-AKI patients and nine AKI-patients because they received their MI diagnosis during the index admission for surgery. We found a five-year cumulative risk of MI of 5.0% (95% CI: 2.9–8.1) among AKI patients and 3.3% (95% CI: 2.1–

4.8) among non-AKI patients. The adjusted HR was 1.5 (95% CI: 0.7–3.2) (Table 3). The risk estimates were lowered when restricting to patients with no previous MI (Supplementary table 3).

When analyzing the risk of stroke, we excluded seven non-AKI patients and five AKI-patients because they received their stroke diagnosis during the index admission for surgery. We found a five-year cumulative risk of stroke of 5.0% (95% CI: 2.8–7.9) among AKI patients and 4.2% (95% CI: 2.9–5.8) among non-AKI patients. The adjusted HR was 0.9 (95% CI: 0.5–1.8) for AKI patients compared with non-AKI patients (Table 3). When restricting to patients with no previous stroke, the estimates did not change notably (Supplementary table 3).

Results for the matched cohort are listed in Supplementary table 4. The results were in accordance with the findings of the full cohort.

Discussion

Key results

We found that more than one out of four adult elective cardiac surgical patients without pre-existing severe kidney impairment developed AKI according to the AKIN criteria within five days after surgery. AKI was associated with increased mortality up to five years after elective cardiac surgery. On the basis of the available data, AKI may also be associated with an increased risk of MI, whereas we found no association with the risk of stroke.

Existing studies

Only three studies have examined the long-term impact of RIFLE/AKIN defined AKI following cardiac surgery [5-7]. In a US cohort of 2973 acute and elective cardiac surgical patients a total of 1265 patients (43%) experienced an episode of AKI during admission. They found a 10-year adjusted HR for death of 1.39 (95% CI: 1.23–1.57) [6]. They observed a higher proportion of patients who developed AKI compared to our findings (27.9%), which may partly be explained by the estimation of baseline sCr by the Modification of Diet in Renal Disease equation rather than measuring sCr. Studies have reported that the Modification of Diet in Renal Disease equation overestimates the incidence of AKI [19]. This misclassification may bias the association between AKI and death towards a lower risk of death among AKI patients. Furthermore, the inclusion of acute patients will tend towards a higher proportion of patients developing AKI. However, the HR estimate was in

concordance with our findings (adjusted HR of 1.6 (95% CI: 1.1–2.2). Tsai et al. studied the long-term impact of RIFLE-defined AKI after surgery for aortic dissection. AKI occurred in 135 (52.7%) of 256 patients and they found an adjusted one-year HR for death of 2.6 (95% CI: 1.0–6.3) [7]. Finally, Gallagher et al. found in a propensity score matched cohort an adjusted five-year HR for death of 1.52 (95% CI: 1.19–1.93) after CABG [5].

Suggested short- and long-term pathophysiologic mechanisms between AKI and cardiovascular events include fluid retention leading to unstable heart function and inflammation leading to apoptosis and fibrosis at cardiac level [20]. However, clinical studies of adverse cardiac events after AKI are sparse and no studies have used time-to-event analysis to examine the prognostic impact of AKI on the risk of MI in cardiac surgical patients. The aforementioned study by Tsai et al. found a higher risk of major adverse cardiac events after one year among AKI patients (40% (54 of 135)) compared with non-AKI patients (15% (18 of 121)) [7]. Similarly they found a higher risk of stroke among AKI patients. Studies of patients undergoing coronary angiography and percutaneous coronary intervention have also found a substantially higher risk of MI during long-term follow-up [21-23]. This indicates that the long-term prognostic impact of AKI appears consistent, although the prevalence of AKI differs according to population under study. Differences in the prevalence of AKI may be explained by characteristics of the procedure. Open cardiac surgery releases a massive inflammatory response and hemodynamic stress, whereas PCI is a less invasive procedure with a low surgical stress. Moreover, the radiographic contrast used in PCI and CAG patients, might alter pathophysiologic mechanisms and the patients' risk of both AKI and MI, thus making direct comparisons difficult.

Strengths and limitations

The strengths of our study include a well-defined study population with uniform access to health care which minimizes selection bias. Our study population consisted of solely elective surgical patients, thereby making a homogenous cohort of patients. It is therefore reasonable to assume that the patients' pre-conditions and immediate risks of AKI were more alike than if the study population also included acute patients. We had complete pre-operative plasma creatinine measurements as estimate of baseline kidney function and due to the elective properties of the study population, this measured baseline sCr was reliable as a good estimate of the patients' real baseline level. Furthermore, we had detailed pre-, peri-, and post-operative data.

We were not able to include all patients undergoing surgery in the study period, but patient screening and recruitment was done by a project nurse whose working schedule was independent of which patients who were on the surgery schedule for the day, hence minimizing selection bias.

The urine output criteria were not applied in the classification of AKI status. The accuracy of this parameter has been less well studied than have changes in sCr levels. In addition 6 hour and 12 hour urine output can only be assessed accurately in patients with a urinary catheter and is largely influenced by use of diuretics [24]. This is a huge disadvantage in using the urine output criteria.

We defined the outcomes MI and stroke by ICD-10 codes. The positive predictive value was above 92% for MI and 80% for stroke [25,26]. Overall, these indicate that we most likely encountered few false positive outcomes; hence the risk of information bias was limited. However, if present, this misclassification would presumably be non-differential, and bias the association towards unity.

Due to lack of registration of an exact event date a patient receives the code of diagnosis at hospital discharge. For the purpose of a causal interpretation between AKI and MI/stroke, we only included the MI/stroke events if the outcome of interest occurred after discharge from the index admission for surgery. In this manner we assured that the outcome occurred after the AKI, which is required for a causal interpretation.

For every patient follow-up began on the fifth post-operative day. Due to the definition of the outcomes for MI/stroke (only encountering outcomes at a new hospitalization after the index admission for surgery) an immortal person-time bias is introduced, where the object of study is not able to experience an outcome. Particularly this may be the case for patients with long hospitalizations. Our estimates may therefore be underestimated. However, the median length of hospital stay for AKI patients was only seven days and five days for non-AKI patients.

When adjusting for propensity score we were able to control for the potential confounding caused by the covariates included in the propensity score (although residual confounding can persist). But this method does not adjust for unmeasured covariates, leaving the possibility of unmeasured confounding.

Finally, our study population was of limited size, thus some of our estimates are accompanied by broad confidence intervals.

Clinical perspectives

This study demonstrates the impact of early post-operative AKI on mortality, specifically in elective cardiac surgery patients without pre-operative severe kidney disease. This finding should en-

courage initiatives towards developing prophylactic strategies for patients who develop even mild reductions in kidney function. However, additional data on the risk of MI and stroke is still warranted. Whether the potentially increased risk reflects the effect of AKI or whether AKI acts as a marker of vulnerability remain unclear. The study is most likely generalizable throughout the setting of elective cardiac surgery.

Conclusion

AKI following elective cardiac surgery was associated with increased five-year mortality, and the risk increased with increasing AKI stage. AKI may be associated with an increased risk of MI, but there was no association with the risk of stroke.

Dansk resumé

Formål

Den langtidsprognostiske betydning af akut nyrepåvirkning er endnu uafklaret. Vi undersøgte femårs risikoen for død, myokardieinfarkt (blodprop i hjertet) og apopleksi efter planlagt hjertekirurgi kompliceret af akut nyrepåvirkning (AKI).

Metoder

Vi udførte kohortestudiet blandt voksne, planlagte hjertekirurgiske patienter uden alvorlig nyresygdom og/eller tidligere hjerte- eller nyretransplantation via populationsbaserede registre. AKI var defineret som en stigning i serum kreatinin med 50 % fra udgangsværdien, akut kreatininstigning på ≥26,5 µmol/L indenfor 48 timer og/eller renal erstatningsterapi indenfor fem dage efter hjertekirurgi. Vi fulgte patienterne fra femte post-operative dag indtil indtrædelse af myokardieinfarkt, apopleksi eller død fem år frem. Femårs risiko blev beregnet ved kumuleret incidens-metoden og sammenlignet ved hazard ratio (HR) under anvendelse af Cox regressionsmodel justeret for propensity score.

Resultater

287 ud af 1030 patienter fik AKI. Femårs risiko for død var 26,5 % (95 % KI: 21,2–32,0) og 12,1 % (95 % KI: 10,0–14,7) blandt AKI og ikke-AKI patienter. Justeret HR var 1,6 (95 % KI: 1,1–2,2). Femårs risiko for myokardieinfarkt var 5,0 % (95 % KI: 2,9–8,1) og 3,3 % (95 % KI: 2,1–4,8) blandt AKI og ikke-AKI patienter, for apopleksi 5,0 % (95 % KI: 2,8–7,9) og 4,2 % (95 % KI: 2,9–5,8) blandt AKI og ikke-AKI patienter. Justeret HR var 1,5 (95 % KI: 0,7–3,2) og 0,9 (95 % KI: 0,5–1.8) for myokardieinfarkt og apopleksi.

Konklusion

Akut nyrepåvirkning efter planlagt hjertekirurgi var associeret med øget femårs dødelighed. Akut nyrepåvirkning kan være forbundet med øget risiko for myokardieinfarkt, men der var ingen sammenhæng med risikoen for apopleksi.

English summary

Objectives

The prognostic impact of acute kidney injury (AKI) on long-term clinical outcomes remains controversial. We examined the five-year risk of death, myocardial infarction, and stroke after elective cardiac surgery complicated by AKI.

Methods

We conducted a cohort study among adult elective cardiac surgical patients without severe chronic kidney disease and/or previous heart or renal transplant surgery using data from population-based registries. AKI was defined by the Acute Kidney Injury Network (AKIN) criteria as a 50% increase in serum creatinine from baseline level, acute creatinine rise of ≥26.5 µmol/L (0.3mg/dL) within 48 hours, and/or initiation of renal replacement therapy within five days after surgery. We followed patients from the fifth post-operative day until myocardial infarction, stroke or death within five years. Five-year risk was computed by the cumulative incidence method and compared with hazards ratios (HR) from a Cox proportional hazards regression model adjusting for propensity score.

Results

A total of 287 of 1030 patients developed AKI. Five-year risk of death was 26.5% (95% CI: 21.2–32.0) and 12.1% (95% CI: 10.0–14.7) among AKI and non-AKI patients. Adjusted HR was 1.6 (95% CI: 1.1–2.2). Five-year risk of myocardial infarction was 5.0% (95% CI: 2.9–8.1) and 3.3% (95% CI: 2.1–4.8) among AKI and non-AKI patients, of stroke; 5.0% (95% CI: 2.8–7.9) and 4.2% (95% CI: 2.9–5.8) among AKI and non-AKI patients. Adjusted HRs were 1.5 (95% CI: 0.7–3.2) and 0.9 (95% CI: 0.5–1.8), respectively.

Conclusion

AKI following elective cardiac surgery was associated with increased five-year mortality. AKI may be associated with an increased risk of MI, but there were no association with the risk of stroke.

Supplementary information

Introduction

Acute kidney injury

The acute kidney injury (AKI) syndrome is characterized by the rapid (hours to days) loss of the kidneys excretory function [27]. This loss of function manifests clinically as a decline in urine output and biochemically as the accumulation of nitrogen metabolism waste products. The decline in urine output reflects the reduction in glomerular filtration rate (GFR) and the accumulated nitrogen waste products are e.g. creatinine and urea. GFR and serum creatinine are reciprocally related; when GFR falls, serum creatinine rises. This relationship between the functional parameter GFR and biochemical parameter serum creatinine is used to diagnose AKI. Hence, measurement of serum creatinine is a surrogate marker for loss of kidney function.

AKI covers a continuum from minor changes in markers of renal function to requirement of renal replacement therapy. AKI is thus a syndrome that encompasses patients with severe renal tubular damage causing failure and ultimately death, but also patients with functional impairment without actual damage to the renal tubules. The latter patients are indeed the ones who may benefit from early intervention [28]. However, there are flaws using serum creatinine as marker of AKI. Serum creatinine increases only when GFR is reduced with more than 50% [29]. This has opened for a research field in novel biologic markers of tubular injury. Findings suggest that changes in biomarker levels occur significantly earlier than do changes in serum creatinine. This may have the therapeutic implication of being able to deliver therapy earlier than with usage of serum creatinine [29]. Despite the flaws of using serum creatinine to define AKI, it holds important advantages; it is universally available; inexpensive to measure; and easy to apply in various clinical- and research settings, which is required for a good consensus definition [24].

The causes of AKI are many. In developing countries the most frequent cause for AKI is hypovolemia following diarrhea, whereas in developed countries AKI is frequent in hospitalized patients and especially the critically ill [27]. Sepsis is the most common cause accounting for 47.5% of AKI cases in critically ill patients followed by major surgery, especially open-heart surgery, accounting for 23.2% of AKI cases [30]. In the setting of sepsis or cardiac surgery reduced renal blood flow causes prerenal azotemia, but no satisfying model explains the pathophysiology leading to AKI. Animal models have shown that renal artery occlusion leading to stop of renal blood flow

causes ischemia, inflammation, and parenchymal injury. Unfortunately, this model is of little clinical relevance with regard to sepsis or cardiac surgery where no renal occlusion exists [27].

Through history more than 30 separate definitions of AKI has been used [31]. Comparison of studies and extraction of knowledge on how to enhance management of these patients were hence extremely difficult. In 2004 the Acute Dialysis Quality Initiative Group proposed a new consensus definition of AKI known as RIFLE (acronym indicating Risk of renal dysfunction, Injury to the kidney, Failure of kidney function, Loss of kidney function, and End-stage renal disease) [32]. In 2007 a modified version of RIFLE was published by the Acute Kidney Injury Network and the criteria are now known as the AKIN criteria [3]. AKI is defined as a 50% increase in serum creatinine from baseline level, acute creatinine rise of ≥26.5 µmol/L (0.3 mg/dL) within 48 hours, and/or initiation of renal replacement therapy, or less than 0.5 ml urine/kg/hour for 6 hours (Table 1). The AKIN criteria are categorical with three stages from mild to severe. This gives the advantage of being highly sensitive in one end (stage 1) and highly specific in the other end (stage 3). Sensitivity is the proportion of patients who in fact have the disease being categorized as diseased and specificity is the proportion of patients who in fact are not diseased being categorized as non-diseased [33]. Of this follows that stage 1 contains the greatest proportion of patients but also some who are misdiagnosed, whereas stage 3 contains a smaller proportion due to the more strict criteria, but some patients will be missed [31]. However, these properties may be more of a theoretical advantage since there is no gold standard of determining AKI stage, thus the true distribution of patients is unknown.

Characteristics of cardiac surgical patients

AKI occurs in up to 30% of patients undergoing cardiac surgery and has been reported to be associated with increased mortality [1,2]. Hence, these patients were chosen to investigate the prognosis after AKI.

Patients undergoing coronary artery bypass grafting (CABG) are suffering from ischemic heart disease due to atherosclerosis causing partial occlusion of the coronary arteries. The aim of a CABG procedure is to reestablish the supply of oxygen to areas with insufficient oxygen. This is done by making a bypass using most frequently the left internal mammary artery and/or the great saphenous vein. The procedure can be executed both on and off extra corporal circulation. The main risk factors for atherosclerosis and ischemic heart disease are life-style related factors such as smoking, diabetes, genetics, hypertension, and hyperlipidemia. In the setting of elective cardiothoracic surgical patients most CABG patients will have stable angina [34,35]. Among valve diseases aortic

stenosis is the most frequent accounting for 75% of all valve surgeries [34]. Risk factors are congenital bicuspid valve that gradually degenerates or a tricuspid valve which calcify due to hypertension, elevated cholesterol, smoking or diabetes [34]. Following aortic stenosis mitral insufficiency is the most frequent valve disease requiring treatment [34]. Combinations of surgical procedures are frequent.

Ischemic heart disease can be considered as a chronic disease and recommendations on healthy life-style should be provided. Life-long treatment with anti-thrombotic and lipid-lowering drugs is mandatory [36]. Treatment of hypertension and diabetes should be initiated when indicated. Atherosclerosis is a slowly developing condition and remains subclinical for a long time. The rate of progression to clinical evident disease is highly determined by life-style factors. As atherosclerosis can be considered a systemic condition, ischemic heart disease is often associated with a variety of atherosclerotic comorbidities, e.g. atherosclerotic kidney disease and cerebral atherosclerosis.

Methods

Cohort design for studying prognosis

The goal of the study was to examine the effect of exposure (AKI) on long-term prognosis with regard to three outcomes; death, myocardial infarction (MI), and stroke. We wanted to estimate the absolute cumulative risk for the specified outcomes for patients with and without AKI and compare the risk of the outcome events (expressed as hazard ratio) AKI patients versus non-AKI patients. Therefor a study design with a specified period of follow-up was required.

The concept of a cohort study is to passively observe what happens to the people in a cohort during a certain amount of time. The design is logically built up in the same way as the clinical question is asked: "If you have AKI, are you then at higher risk of getting an MI than if you didn't have AKI?" The basis of the study design is the study population sampled from a parent population [37]. The study population can be the total population of a country; people living in a specific region; all admitted patients to a hospital; people with a certain disease. The choices are many. The choice of study population is of great importance since it composes the source of data information in which you will examine the study question. Also, choice of study population can threaten extern validity if it does not represent the parent population it was sampled from [37]. After all you want to make an inference that the results from the study population resemble those of the parent population. On the other hand, for scientific inference the external validity can be neglected in favor of internal validity. The goal is here to infer a - perhaps abstract - theory of how exposure affects out-

come that is not tied for a specific population [33]. To enable the conduct of scientific inference regardless of population one must control for confounding by e.g. restriction (see later).

The analyses are conducted using the study population. Specific requirements, i.e. inclusion and exclusion criteria, can be set up for the study population. We chose cardiac surgical patients as our parent population. The inclusion criteria "elective patients" was made to assure pre-operative steady conditions and hence reduce the influence of pre-operative conditions on immediate post-operative risk of AKI. Similarly we excluded patients with severe chronic kidney disease as chronic kidney disease was considered to be a strong confounder of the association between AKI and death. Inclusion and exclusion criteria increase homogeneity of patients in the study population and strengthen internal validity. They make it easier to distinguish the effect of exposure from surrounding "noise", i.e. confounding bias.

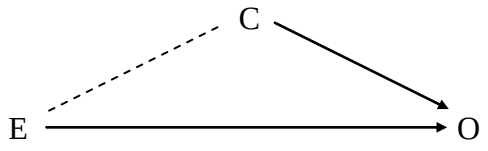
At the beginning of study the people who are in the study population are characterized by exposure status (determined by a set of criteria e.g. AKIN) making two groups (or more) for comparison. A great strength of the cohort design is that the exposure status is measured without knowing the outcome, hence avoid recall bias.

An essential part of a cohort design is the choice of time line to determine both start- and end of follow-up. The time of start must be the same for all in the study population and the length of follow-up sufficient for the outcome to be observed. We used Danish population-based registries to examine the date and type of outcome during the follow-up period [8,12]. We examined long-term (five-year) prognosis. When doing so it is likely that one cannot be able to follow all patients in the study population for five full years as emigration can occur. Survival analysis are capable of dealing with this problem, under the assumption that those emigrated (censored) are at the same risk of the outcome as those remaining in the study population.

Propensity scores as a way to control for confounding

When the goal of a study is to examine whether a single factor is independently related to an outcome the ideal is to compare two groups where the only difference between them is the presence of the factor in one group and not in the other (as the random assignment of exposure in randomized controlled trials (RCT) of a sufficient size). In a study like ours it would not be possible to conduct a RCT, since the exposure AKI would have to be assigned by chance to the patients. Actually, this is usually not the case in observational studies and one must consider if confounding is present and how to handle it. If not handled properly confounding can lead to a misinterpretation of the data – confounding bias.

When determining whether a variable is a confounder three criteria must be fulfilled: 1) The variable is not on the causal pathway between exposure and outcome; 2) The variable is an independent risk factor (or a proxy) for the outcome; and 3) The variable is imbalanced across exposure categories [33]. A traditional way to depict the relationship between exposure, outcome and confounder is by the "confounder-triangle" cartoon [38].



C: Confounder
E: Exposure
O: Outcome

To control for confounding one must remove the association between either confounder and exposure, or confounder and outcome. There are principally two ways to control for confounding; by study design (restriction, matching and randomization) and analysis (stratification, single and multivariable adjustment, and propensity score estimation). As an example traditional multivariable adjustment removes the arrow from the confounder to outcome by controlling for the effect of each confounder on the outcome. Dealing with selection bias must be considered in the design phase of the study, whereas confounding can be handled during the data analysis part.

As mentioned propensity score (PS) methods are a way to control for confounding. PS methods were developed by Rosenbaum and Rubin and the technique has become popular in particular in epidemiologic studies assessing outcomes of drug and medical procedures [17].

The PS is an estimate of the probability (propensity) of being exposed conditional of the baseline covariates.

$$\text{Prob}\,(E = 1 \mid X)$$

E: Exposure
X: Covariates

Thus, PS combines multiple covariates and reduces dimensionality of confounders into a single variable. The PS is often computed using multivariable logistic regression where you model the exposure rather than the outcome, i.e. the dependent variable is the exposure and the independent variables are the confounders. Covariates to be included in the model should be associated with both the exposure and the outcome (the covariate is a true confounder) or the covariates are only associated the outcome [39]. Since the PS shares the properties of probability, the propensity score lies between 0 and 1.

Figure 4 shows the distributions of PS by exposure status in our study. There is a great overlap between exposed and unexposed indicating exchangeability. This is a key property of the PS that given the same PS the exposed and unexposed tend to have the same distribution of covariates and are thus exchangeable. This allow for the hypothesis that the observed outcome in the exposed stands in for the unobserved potential outcome in the unexposed with the same PS – the counterfactual goal. Also, the figure shows that the curves of the exposed are skewed to the right compared to the unexposed. This was also expected that the in fact exposed people have a higher propensity of being exposed than the unexposed.

The PS can be applied in several ways, e.g. adjustment, matching, and weighting (inverse probability of treatment weight (IPTW) and standardized mortality ratio (SMR) weights). By applying PS methods one can theoretically achieve balance of covariates by, metaphorically speaking, erasing the dotted line between the confounder and the exposure in the "confounder triangle" and hence control for confounding.

In the main analysis of our study we adjusted for PS as a continuous variable. In this manner we simultaneously controlled for a large number of potential confounding factors. This is a great advantage in a study such as ours, where we have few outcomes but many exposed. Furthermore, we performed a PS matched analysis which aimed to match each AKI patient with the non-AKI patient with the nearest PS. In this manner a restricted study population was created with the ability to estimate the effect of exposure in the exposed. By matching on PS the distribution of the covariates included in the PS model tends to be similar in the two exposure groups (Table 2). PS matching methods has been compared to RCTs. However, there is an important difference in regard to confounding. In RCT all confounders, both measured and unmeasured, known and unknown, are theoretically balanced since exposure is assigned by chance [33]. When using PS matching only the confounders included in the PS model will be balanced.

Results

Additional results

As a sensitivity analysis we changed the beginning of follow-up to day 10 (Supplementary table 5). These results did not differ from the main results (Table 3).

Discussion

Strengths and limitations

The strengths of our study include a well-defined study population with uniform access to health care which minimizes selection bias. Equal access to health care is secured by the tax-funded Danish National Health Service that ensures equal opportunities to professional medical assistance for all Danish citizens.

Our study population consisted of solely elective surgical patients, thereby making a homogenous cohort of patients assuring internal validity.

By linkage to a population-based laboratory registry (LABKA) we were able to achieve complete plasma creatinine measurements to estimate baseline kidney function and post-operative kidney function. This was an essential source to gather information on plasma creatinine and obligate when using the AKIN criteria to define AKI. It has been shown that coding of acute renal failure by the International Classification of Disease 9-revision (ICD-9) fails to identify AKI as evidenced by a sensitivity of less than 35% [40]. This means that the burden of acute renal failure is substantially underestimated when using ICD-9. It is thus considered an advantage to use serum creatinine as marker of AKI status. Furthermore, due to the elective properties of the study population, this measured baseline creatinine was reliable as a good estimate of the patients' real baseline level not modified by acute illness [24].

Patient screening and recruitment was done by a project nurse whose working schedule was independent of which patients who were on the surgery schedule for the day, hence minimizing selection bias. Twelve patients did not accept the invitation to participate in the study. These patients were a potential source of bias, but we do not have any reason to believe, that these patients were more likely to have developed AKI, why our estimate is not biased.

We defined the outcomes MI and stroke by ICD-10 codes. The code/diagnosis itself is not the disease, but an indication of an assessment of the patient's illness [38]. This assessment was at the clinical discretion of physicians – and consequently, can hold some misclassification. Therefore, when using register codes one must consider whether a diagnostic code actually represents that an event has occurred and/or if the code is carried over from a previous event. By only using in-hospital diagnosis codes (excluding out-patient diagnosis) we tried to oblige this concern aiming for a high positive predictive value. A high positive predictive value may be guarded by the properties of both the symptomatic manifestation of the diseases and the strict diagnostic criteria. Previous studies have shown that the positive predictive value is above 92% for MI and 80% for stroke

[25,26]. Overall, these indicate that we most likely encounter few false positive outcomes hence risk of information bias is reduced. However, if present, this misclassification would presumably be non-differential, and bias the association towards unity. The completeness of the diagnosis and the risk of false negatives are of lesser concern due to the symptomatic manifestation of MI/stroke leading to hospital admission and treatment and thus being diagnosed. However if present, this misclassification would presumably also be non-differential, and bias the results towards the null.

For every patient follow-up began on the fifth post-operative day. Due to the definition of the outcomes for MI/stroke (only encountering outcomes at a new hospitalization after the index admission for surgery) immortal person-time is introduced. This may lead to immortal time bias [41]. Of this follows, that an object of study is not able to experience an outcome until they are discharged. This may be the case for patients with hospitalizations beyond five days, which would be more likely to be patients with AKI. We therefore may understate the association. However, the median length of hospital stay for AKI patients was only seven days and five days for non-AKI patients suggesting that only a limited amount of the person-time was actual immortal. In a sensitivity analysis we postponed begin of follow-up until day 10 and this did not change the estimates suggesting that bias is of very limited size (Supplementary table 5). A way to avoid introducing immortal time could be by starting follow-up at discharge. But this solution is not preferable in our study, since length of hospital stay does vary between AKI and non-AKI patients. When comparing exposed to non-exposed; the difference in the immediate risk of an MI/stroke might be greater after discharge than after day five. Thus the risk of MI/stroke after discharge might be lower for AKI-patients with a long hospitalization than for non-AKI patients who are discharged directly after surgery. Furthermore, it may diminish a dose-response association between AKI stages.

When adjusting for propensity score, we were able to control for the potential confounding caused by the covariates included in the propensity score. But this method does not adjust for unmeasured and unknown confounders, in contrast to a well conducted RCT. However, we do believe that we have encountered the most important confounders in our analyses[1].

In a sensitivity analysis we restricted to patients who did not have a previous MI (Supplementary table 3). In this analysis the risk estimates lowered for MI. This suggests that MI was a confounder of the association between AKI and a new hospitalization with MI. However, numbers were small in this sensitivity analysis and interpretation must be done with caution.

[1] The included covariates in the propensity score; gender; age; smoking; BMI; history of ischemic peripheral disease; previous stroke; previous myocardial infarction; history of arrhythmias; diabetes mellitus; dyslipidemia; hypertension; Charlson comorbidity index; baseline creatinine; EuroSCORE; type of surgical procedure (valve, CABG, combined valve and CABG, others); and extra corporal circulation.

To analyze the causes of death we used the Danish Registry of Causes of Death. The quality of data in this registry relies mainly on the correctness of the physician who issues the death certificate and hence correctness of the recorded underlying and contributory causes of death. Due to declining autopsy rates, the validity of this register is threatened [11]. However, it can still be used as an indicator of the presumed cause of death. Our results indicate that heart disease is more often stated as an important contributor to the cause of death in patients with AKI than in patients without AKI (Figure 3).

In fact, the topic of the reliability of the registries is ever present in epidemiological research. One will always be limited by the quality of the data. Our study comprises data from both population-based registries (Civil Registration System, Danish National Registry of Patients, Danish Register of Causes of Death, and the Regional Laboratory Database) as well as clinically gathered information at the Department of Cardiothoracic and Vascular Surgery, Aarhus University Hospital. By using the unique civil registration number we were able to link all the information. Data from the Civil Registration System are highly accurate, whereas data from the Danish National Registry of Patients depends on the diagnosis used, and hence the validity of the codes differs. The positive predictive value can be used as guidance to discuss the validity. Clinically gathered information, e.g. by a nurse, enables the possibility of getting information that is almost impossible to achieve elsewhere. A drawback is the cost.

Clinical perspective

This study demonstrates the impact of early post-operative AKI on mortality, specifically in elective patients without pre-operative severe kidney disease. This finding should encourage initiatives towards developing preventive strategies for AKI and prophylactic strategies for patients who develop even mild reductions in kidney function. However, the risk of MI and stroke remain uncertain and further studies are needed. Whether the potentially increased risk of long-term adverse outcomes reflects the effect of AKI or whether AKI acts as a marker of vulnerability remain unclear. The study is most likely generalizable throughout the setting of elective cardiac surgery.

Conclusion

Acute kidney injury following elective cardiac surgery was associated with increased five-year mortality, and the risk increased with increasing acute kidney injury stage. Acute kidney injury may be associated with an increased risk of myocardial infarction, but there was no association with the

risk of stroke. We argue that the results are not affected by selection bias, however residual confounding might be present.

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Tables

Table 1. AKIN serum creatinine classification of AKI.

Stage 1	Increase in sCr by 26.5µmol/L (0.3mg/dL) within 48 hours or increase in baseline sCr by ≥150-199% within the prior 7 days.
Stage 2	Increase in baseline sCr by ≥200-299%.
Stage 3	Increase in baseline sCr by ≥300% or increase in sCr to 354µmol/L (4.0mg/dL) with an acute rise of 44 µmol/L (0.5mg/dL) or initiation of renal replacement therapy.

Abbreviations: AKI: Acute Kidney Injury, AKIN: Acute Kidney Injury Network, sCr: serum creatinine

Table 2. Descriptive data of patients undergoing elective cardiac surgery in the full cohort and matched cohort.

		Full cohort		Matched cohort	
	Total [a]	AKI [a]	non-AKI [a]	AKI [a]	non-AKI [a]
Clinical features	n=1030	n=287	n=743	n=257	n=257
Pre-operative characteristics					
Male gender	750 (72.8)	209 (72.8)	541 (72.8)	190 (73.9)	189 (73.5)
Age (years), mean (IQR)	65.8 (59–75)	70.0 (64–78)	64.1 (58–73)	69.4 (63–77)	69.3 (65–76)
Smoker					
Present	487 (47.3)	147 (51.2)	340 (45.8)	130 (50.6)	129 (50.2)
Never	357 (34.7)	88 (30.7)	269 (36.2)	82 (31.9)	83 (32.3)
Previous	186 (18.1)	52 (18.1)	134 (18.0)	45 (17.5)	45 (17.5)
BMI (kg/m^2)					
<25	287 (27.9)	85 (29.6)	202 (27.2)	72 (28.0)	63 (24.5)
25-30	425 (41.3)	110 (38.3)	315 (42.4)	103 (40.0)	100 (38.9)
>30	318 (30.9)	92 (32.1)	226 (30.4)	82 (31.9)	94 (36.6)
Previous ischemic peripheral disease	57 (5.5)	19 (6.6)	38 (5.1)	17 (6.6)	13 (5.1)
Previous stroke	104 (10.1)	37 (12.9)	67 (9.0)	32 (12.5)	29 (11.3)
Previous myocardial infarction	256 (24.9)	66 (23.0)	190 (25.6)	63 (24.5)	65 (25.3)
History of arrhythmias	154 (15.0)	60 (20.9)	94 (12.7)	49 (19.1)	51 (19.8)
Diabetes Mellitus	166 (16.1)	58 (20.2)	108 (14.5)	50 (19.5)	55 (21.4)
Dyslipidemia	570 (55.3)	156 (54.3)	414 (55.7)	141 (54.9)	147 (57.2)
Hypertension	585 (56.8)	166 (57.8)	419 (56.4)	146 (56.8)	153 (59.5)
Normal <140 and <90 [b]	455 (44.2)	121 (42.2)	324 (43.6)	111 (43.2)	104 (40.5)
Grade I 140-159 or 90-99 [b]	306 (29.7)	80 (27.9)	226 (31.4)	70 (27.2)	91 (23.7)
Grade II 160-179 or 100-109 [b]	189 (18.4)	61 (21.3)	128 (17.2)	56 (21.8)	42 (16.3)
Grade III >=180 or >=110 [b]	90 (8.7)	25 (8.7)	65 (8.8)	20 (7.8)	20 (7.8)
Charlson Comorbidity Index					
Low (score 0)	396 (38.5)	91 (31.7)	305 (41.5)	86 (33.5)	91 (35.0)
Medium (score 1-2)	456 (44.3)	135 (47.0)	321 (43.2)	119 (46.3)	112 (43.6)
High (score >3)	178 (17.3)	61 (21.3)	117 (15.7)	52 (20.2)	54 (21.0)
Baseline creatinine (µmol/L), mean (IQR)	85.0 (68–98)	94.2 (73–109)	81.4 (66–92)	90.9 (72–107)	91.3 (73–105)
euroSCORE, mean (IQR) [c]	5.2 (3–7)	6.4 (4–8)	4.7 (3–7)	6.1 (4–8)	6.1 (4–8)
low risk (score 0-2)	199 (19.3)	30 (10.5)	169 (22.8)	30 (11.7)	28 (10.9)
medium risk (score >2-5)	369 (35.8)	82 (28.6)	287 (38.6)	78 (30.4)	81 (31.5)
high risk (score >5)	462 (44.9)	175 (70.0)	287 (38.6)	149 (58.0)	148 (57.6)
Surgical procedure characteristics					
Type of surgery					
Valve [d]	313 (30.4)	84 (29.3)	229 (30.8)	77 (30.0)	78 (30.4)
CABG	372 (36.1)	85 (29.6)	287 (38.6)	80 (31.1)	71 (27.6)
Valve and CABG	158 (15.3)	59 (20.6)	99 (13.3)	51 (19.8)	54 (17.1)
Other [e]	187 (18.2)	59 (20.6)	128 (17.2)	49 (19.1)	54 (17.1)
Extra corporal circulation	910 (88.4)	255 (88.9)	655 (88.2)	227 (88.3)	223 (86.8)

[a] Values are expressed as counts (percentage) unless otherwise indicated.

[b] Measured in mmHg.

[c] EuroSCORE: A risk score for the operative mortality.

[d] Valve: Aortha, mitral, tricuspidal.

[e] Other: Pulmonary valve surgery, coarctatio, subvalvular membrane, ventricular aneurysme, ventricular septum defect, atrial septum defect, pulmonary thromboendatrerectomi, thoracic aortha.

Abbreviations: AKI: Acute Kidney Injury, BMI: Body Mass Index, CABG: Coronary Artery Bypass Grafting, IQR: Inter Quartile Range.

Table 3. One- and five-year risks, five-year unadjusted and adjusted hazard ratios for death, myocardial infarction, and stroke by AKI status in the full cohort.

Endpoint	Events n	Number at period start n	One-year risk % (95% CI)	Five-year risk % (95% CI)	Unadjusted HR (95% CI)	Adjusted HR[a] (95% CI)
Death						
Non-AKI	90	743	2.3 (1.4–3.7)	12.1 (10.0–14.7)	1 (reference)	1 (reference)
AKI	76	287	9.4 (6.6–13.4)	26.5 (21.2–32.0)	2.4 (1.8–3.3)	1.6 (1.1–2.2)
Stage 1	59	238	8.8 (5.8–13.2)	24.8 (19.8–30.8)	2.3 (1.6–3.1)	1.4 (1.0–2.1)
Stage 2+3	17	49	12.2 (5.7–25.2)	34.7 (23.2–49.7)	3.4 (2.0–5.7)	2.3 (1.4–3.9)
Myocardial infarction						
Non-AKI	23	708	1.4 (0.7–2.5)	3.3 (2.1–4.8)	1 (reference)	1 (reference)
AKI	14	278	1.8 (0.7–3.9)	5.0 (2.9–8.1)	1.7 (0.9–3.3)	1.5 (0.7–3.2)
Stage 1	11	230	1.7 (0.6–4.1)	4.7 (2.6–7.6)	1.6 (0.8–3.3)	1.4 (0.7–3.1)
Stage 2+3	3	48	2.1 (0.2–9.6)	6.3 (1.6–15.4)	2.2 (0.7–7.4)	2.0 (0.6–6.9)
Stroke						
Non-AKI	31	736	1.6 (0.9–2.8)	4.2 (2.9–5.8)	1 (reference)	1 (reference)
AKI	14	282	2.1 (0.9–4.4)	5.0 (2.8–7.9)	1.3 (0.7–2.4)	0.9 (0.5–1.8)
Stage 1	10	236	1.8 (0.7–3.9)	5.0 (2.8–7.9)	1.1 (0.5–2.2)	0.8 (0.4–1.6)
Stage 2+3	4	46	2.1 (0.9–4.4)	3.2 (1.6–5.7)	2.5 (0.9–7.0)	1.8 (0.6–5.3)

[a] Adjusted for propensity score

Abbreviations: AKI: Acute Kidney Injury, CI: Confidence Interval, HR: Hazard Ratio

Figures

Figure 1. Flowchart

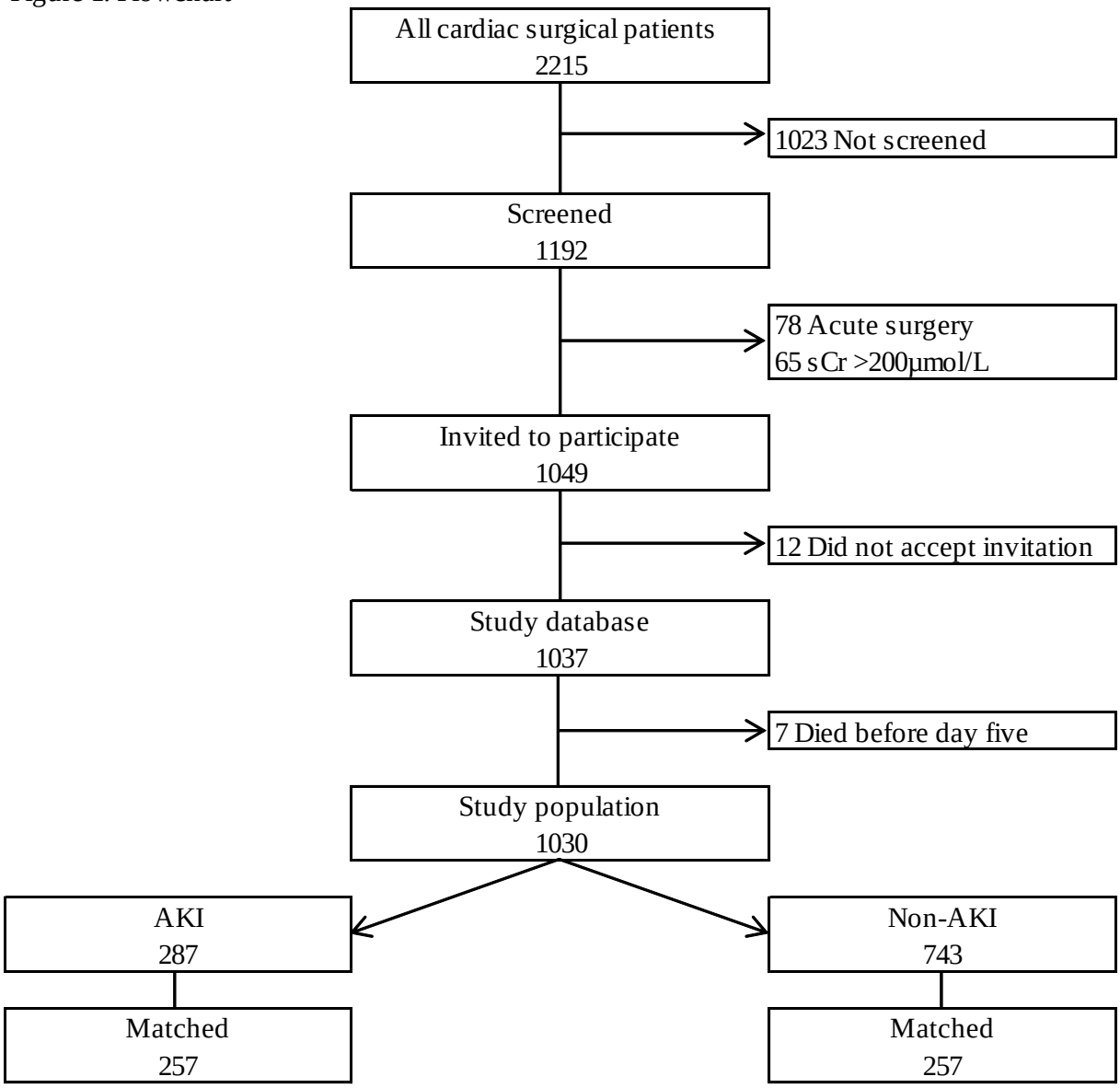
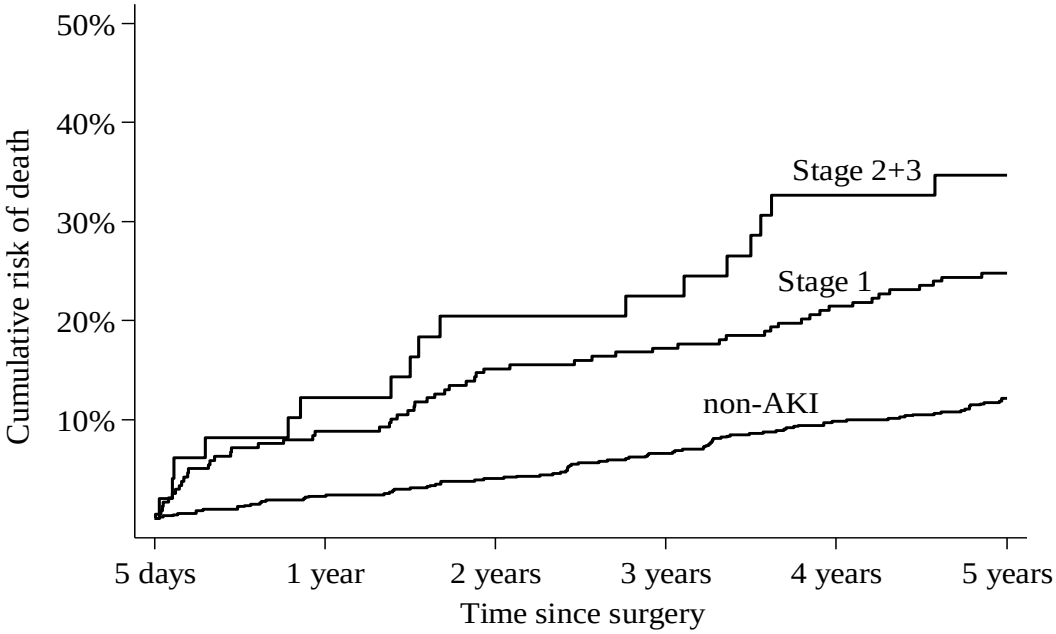


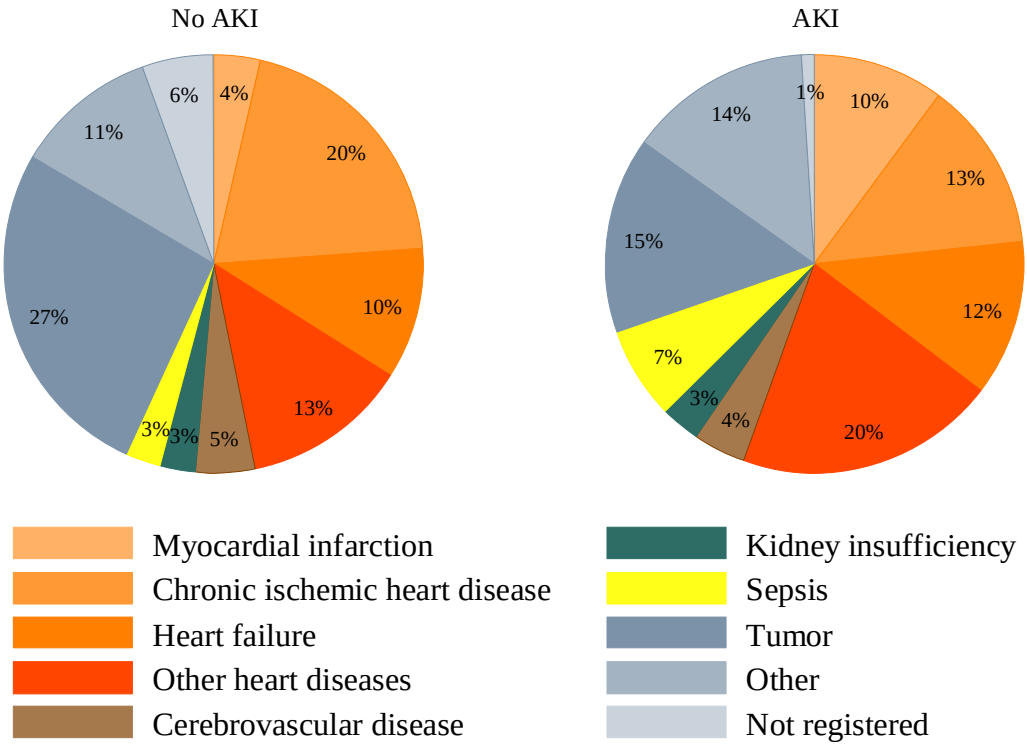
Figure 2. Five-year risk of death by AKI stage



Number at risk						
Non-AKI	743	725	712	693	668	650
AKI stage 1	238	217	202	197	187	179
AKI stage 2+3	49	43	39	38	33	32

Abbreviations: AKI: Acute Kidney Injury

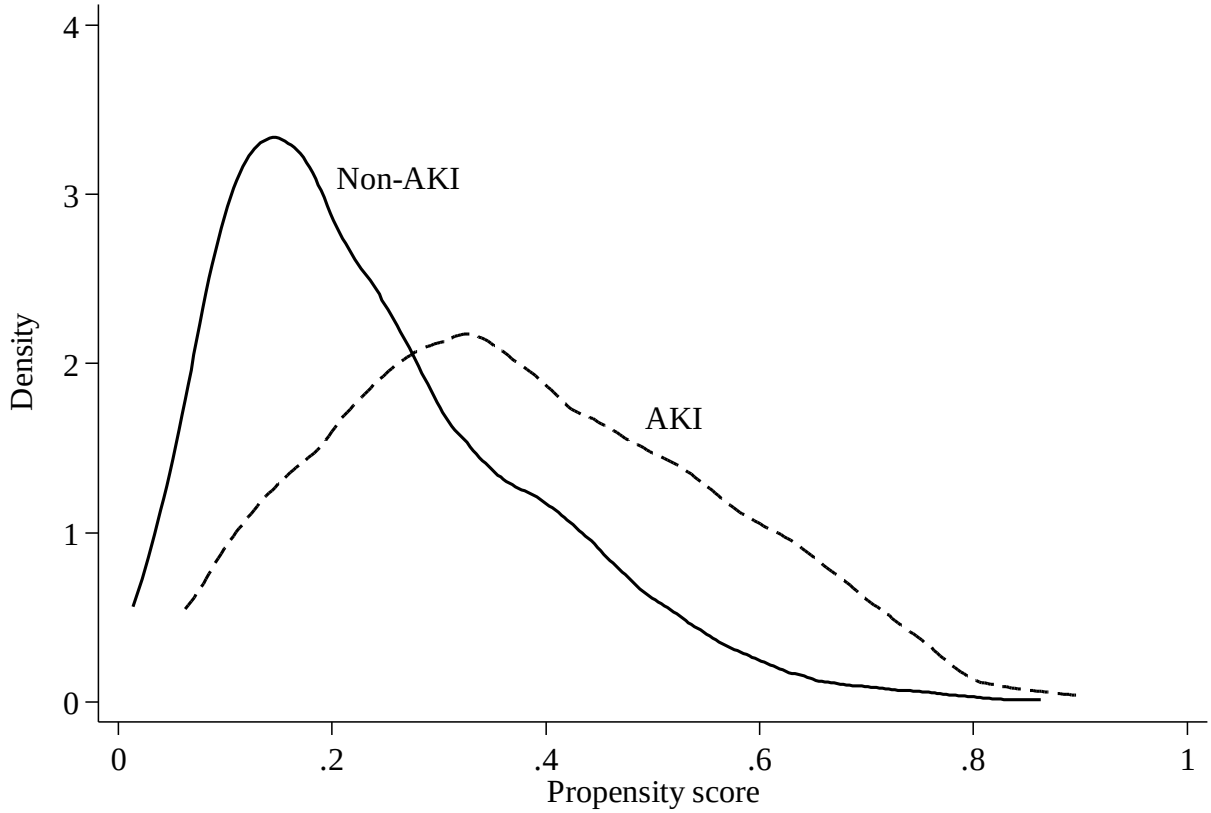
Figure 3. Causes of death by AKI status*



* Patients can be registered with more than one cause of death

Abbreviations: AKI: Acute Kidney Injury

Figure 4. Propensity score distributions by AKI status



Abbreviations: AKI: Acute Kidney Injury

Supplementary tables

Supplementary table 1. Identification of outcomes and causes of death.

Outcome	**ICD-10 code**
Myocardial infarction	I21
Stroke	I61, I63, I64
Cause of death	
Myocardial infarction	I21
Chronic ischemic heart disease	I25
Heart failure	I50
Other heart diseases	I00-20, I23-24, I26-49, I51-52
Cerebrovascular disease	I60-69
Kidney insufficiency	N17-19
Sepsis	A41
Tumor	C00-95, D46-47
Other	All other codes not included above

Abbreviations: ICD: International Classification of Diseases

Supplementary table 2. Charlson conditions and the corresponding International Classification of Disease (ICD) codes, 10th and 8th revision.[a]

Charlson conditions	Corresponding ICD-10 codes	Corresponding ICD-8 codes	Weight
Myocardial infarction	I21, I22, I23	410	1
Congestive heart failure	I50, I11.0, I13.0, I13.2	427.09, 427.10, 427.11, 427.19, 428.99	1
Peripheral vascular disease	I70, I71, I72, I73, I74, I77	782.49, 440, 441, 442, 443, 444, 445	1
Cerebrovascular disease	I60-69, G45, G46	430-438	1
Dementia	F00-F03, F05.1, G30	290.09-290.19, 293.09	1
Chronic pulmonary disease	J40-J47, J60-67, J68.4, J70.1, J70.3, J84.1, J92.0, J96.1, J98.2, J98.3	490-493, 515-518	1
Connective tissue disease	M05, M06, M08, M09, M30, M31, M32, M33, M34, M35, M36, D86	712, 716, 734, 446, 135.99	1
Ulcer Disease	K22.1, K25-28	530.91, 530.98, 531-534	1
Mild liver disease	B18, K70.0-K70.3, K70.9, K71, K73, K74, K76.0	571, 573.01, 573.04	1
Diabetes Mellitus	E10.0, E10.1, E10.9 E11.0, E11.1, E11.9	249.00, 249.06, 249.07, 249.09, 250.00, 250.06, 250.07, 250.09,	1
Hemiplegia	G81, G82	344	2
Moderate/severe renal disease	I12, I13, N00-N05, N07, N11, N14, N17-N19, Q61	403, 404, 580-583, 584, 590.09, 593.19, 753.10-753.19, 792	2
Diabetes Mellitus with chronic complications	E10.2-E10.8 E11.2-E11.8	249.01-249.05, 249.08, 250.01.250.05, 250.08,	2
Any tumor	C00-C75	140-194	2
Leukemia	C91-C95	204, 205, 206, 207	2
Lymphoma	C81-C85, C88, C90, C96	200, 202, 203	2
Moderate/severe liver disease	B15.0, B16.0, B16.2, B19.0, K70.4, K72, K76.6, I85	275.59, 070.00, 070.02, 070.04, 070.06, 070.08, 573.00	3
Metastatic solid tumor	C76-C80	456.00-456.09, 195-198, 199	6
AIDS	B21-B24	079.83	6

[a] Usage of ICD-8 from 1977-1993, usage of ICD-10 since 1994.

Supplementary table 3. One- and five-year risks, five-year unadjusted and adjusted hazard ratios for myocardial infarction and stroke by AKI status in the full cohort. Patients with previous myocardial infarction and previous stroke were excluded for the respective endpoints.

	Events	Number at period start	One-year risk	Five-year risk	Unadjusted HR	Adjusted HR[a]
Endpoint	n	n	% (95% CI)	% (95% CI)	(95% CI)	(95% CI)
Myocardial infarction						
Non-AKI	16	546	1.3 (0.6–2.5)	2.9 (1.7–4.6)	1 (reference)	1 (reference)
AKI	6	220	0.5 (0.0–2.3)	2.7 (1.1–5.5)	1.0 (0.4–2.5)	0.8 (0.3–2.2)
Stage 1	5	184	0.5 (0.1–2.8)	2.3 (0.9–4.9)	1.0 (0.4–2.7)	0.8 (0.3–2.3)
Stage 2+3	1	36	Omitted	2.7 (1.1–5.5)	1.0 (0.1–7.8)	0.8 (0.1–6.6)
Stroke						
Non-AKI	23	671	1.5 (0.8–2.6)	3.4 (2.2–5.0)	1 (reference)	1 (reference)
AKI	12	246	1.6 (0.5–3.9)	4.9 (2.7–8.1)	1.6 (0.8–3.1)	1.0 (0.5–2.2)
Stage 1	8	210	1.2 (0.3–3.3)	4.9 (2.7–8.1)	1.2 (0.5–2.7)	0.8 (0.3–1.9)
Stage 2+3	4	36	1.6 (0.5–3.9)	2.8 (1.3–5.5)	3.8 (1.3–11.1)	2.8 (0.9–8.3)

[a] Adjusted for propensity score

Abbreviations: AKI: Acute Kidney Injury, CI: Confidence Interval, HR: Hazard Ratio

Supplementary table 4. One- and five-year risks and five-year hazard ratios for death, myocardial infarction, and stroke by AKI status in the matched cohort.

Endpoint	Events n	Number at period start n	One-year risk % (95% CI)	Five-year risk % (95% CI)	Unadjusted HR (95% CI)
Death					
Non-AKI	48	257	2.7 (1.3–5.6)	18.7 (14.5–24.1)	1 (reference)
AKI	66	257	9.3 (6.4–13.6)	25.7 (20.8–31.5)	1.6 (1.1–2.4)
Stage 1	53	216	9.7 (6.5–14.5)	24.5 (19.3–30.9)	1.8 (1.1–2.8)
Stage 2+3	13	41	7.3 (2.4–21.0)	31.7 (19.8–48.3)	1.2 (0.5–2.8)
Myocardial infarction					
Non-AKI	7	242	0.4 (0.0–2.1)	2.9 (1.3–5.6)	1 (reference)
AKI	11	248	1.6 (0.5–3.8)	4.4 (2.4–7.5)	1.1 (0.4–3.2)
Stage 1	8	208	1.6 (0.5–3.8)	4.0 (2.1–7.0)	0.7 (0.2–2.3)
Stage 2+3	3	40	1.2 (0.3–3.3)	4.4 (2.4–7.5)	Omitted
Stroke					
Non-AKI	17	252	3.2 (1.5–5.9)	6.7 (4.1–10.3)	1 (reference)
AKI	10	252	2.0 (0.8–4.3)	4.0 (2.0–6.9)	0.5 (0.2–1.2)
Stage 1	7	214	2.0 (0.8–4.3)	4.0 (2.0–6.9)	0.4 (0.1–1.0)
Stage 2+3	3	38	1.6 (0.5–3.8)	3.2 (1.5–5.9)	1.5 (0.3–9.0)

Abbreviations: AKI: Acute Kidney Injury, CI: Confidence Interval, HR: Hazard Ratio

Supplementary table 5. One- and five-year risks, five-year unadjusted and adjusted hazard ratios for death, myocardial infarction, and stroke by AKI status in the full cohort. Begin of follow-up at post-operative day 10.

Endpoint	Events n	Number at period start n	One-year risk % (95% CI)	Five-year risk % (95% CI)	Unadjusted HR (95% CI)	Adjusted HR[a] (95% CI)
Death						
Non-AKI	92	743	2.4 (1.5–3.8)	12.4 (10.2–15.0)	1 (reference)	1 (reference)
AKI	75	286	9.1 (6.3–13.1)	26.2 (21.5–31.7)	2.4 (1.7–3.2)	1.5 (1.1–2.1)
Myocardial infarction						
Non-AKI	22	707	1.3 (0.6–2.3)	3.1 (2.0–4.6)	1 (reference)	1 (reference)
AKI	14	277	1.8 (0.7–3.9)	5.1 (2.9–8.1)	1.8 (0.9–3.5)	1.6 (0.8–3.3)
Stroke						
Non-AKI	30	736	1.6 (0.9–2.8)	4.1 (2.8–5.7)	1 (reference)	1 (reference)
AKI	14	281	2.1 (0.9–4.4)	5.0 (2.9–8.0)	1.3 (0.7–2.5)	1.0 (0.5–1.9)

[a] Adjusted for propensity score

Abbreviations: AKI: Acute Kidney Injury, CI: Confidence Interval, HR: Hazard Ratio