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DISSERTATION

Long-term Survival After Cardiac Surgery-Induced Acute Kidney Injury: A Prospective Observational Study

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Acute kidney injury (AKI)

Cardiac surgery-associated acute kidney injury (CSA-AKI)

Akutes Nierenversagen (ANV)

Intensive care unit (ICU)

Coronary artery bypass grafting (CABG)

Kidney disease: Improving global outcome (KDIGO)

Acute Kidney Injury Networks (AKIN)

Risk, Injury, Failure, Loss, End Stage Kidney Disease (RIFLE)

Estimated glomerular filtration rate (eGFR)

Transcatheter aortic valve implantation (TAVI)

Interleukin-6 (IL-6)

Interleukin-10 (IL-10)

Tumor necrosis factor alpha (TNF- α)

Apolipoprotein E (APOE)

Renin-angiotensin-aldosterone-system (RAAS)

Glomerular filtration rate (GFR)

Neutrophil gelatinase-associated lipocalin (NGAL)

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Insulin-like growth factor-binding protein 7 (IGFBP7)

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European system for cardiac operative risk evaluation II (EuroSCORE II)

Chronic Kidney Disease Epidemiology Collaboration (CKDepi)

Myocardial infarction (MI)

Cardiopulmonary bypass (CPB)

Acute Physiology and Chronic Health Evaluation II (APACHE II)

Simplified Acute Physiology Score II (SAPS II)

Sepsis-related Organ failure Assessment (SOFA)

Standard deviation (SD)

Interquartile range (IQR)

Body mass index (BMI)

Abstract (English)

Background

Postoperative acute kidney injury (AKI) is one of the most common and severe complications in cardiac surgery. Cardiac surgery-associated acute kidney injury (CSA-AKI) is associated with increased morbidity, as well as increased short- and long-term mortality. The aim of this study is to identify risk factors for acute kidney injury and to assess the long-term mortality.

Materials and methods

This was a prospective study with 119 patients who underwent cardiac surgery between 2014 and 2015. Acute kidney injury was determined according to the KDIGO 2012 classification, which is defined by an increase in serum creatinine of at least 50% and urine output parameters. Accordingly, patients were stratified into 3 levels of AKI. Risk factors for CSA-AKI were determined by a logistic regression model. Patient survival was determined by telephone survey. Long-term survival was analyzed with a Kaplan-Meier algorithm and a risk-adjusted Cox proportional hazards regression model.

Results

36.1% (n=43) of the study population developed CSA-AKI. More than two thirds of these patients (71.1%) developed a stage 1 CSA-AKI. Important risk factors for CSA-AKI were a preoperatively impaired kidney function (HR: 0.77; 95% CI: 0.61 – 0.95; p=0.016), the preoperative use of diuretics (HR: 3.71; 95% CI: 1.50 – 9.20; p=0.005) and diabetes mellitus (HR: 2.74; 95% CI: 1.01 – 7.46; p=0.048). CSA-AKI was an independent risk factor for an increased 3-year mortality (HR 13.58 (3.89 – 47.41); p<0.001). Overall 3-year mortality in this study was 20.5% (n=24). 3-year mortality for patients without acute kidney injury was 4% (n=3) and 49.4% (n=21) for patients with CSA-AKI (p<0.001). 3-year mortality in patients with mild CSA-AKI was 48.4 % (n=15).

Conclusion

All-cause mortality was significantly increased in patients with CSA-AKI compared to patients without CSA-AKI, regardless of the severity. Even mild CSA-AKI increased all-cause long-term mortality drastically. Preventive strategies regarding the important risk factors are only of limited use. Therefore, we should focus on closer monitoring during

hospitalization and follow-up check-ups, especially for patients with any degree of CSA-AKI and as well for those with an already impaired kidney function preoperatively or other relevant comorbidities.

Abstract (deutsch)

Einleitung

Das akute Nierenversagen (ANV) nach herzchirurgischen Eingriffen ist eine der wichtigsten Komplikationen dieses Fachgebietes. Ein postoperatives ANV ist ein unabhängiger Risikofaktor für eine erhöhte postoperative Morbidität und Mortalität. Ziel dieser Studie ist es wichtige Risikofaktoren für die Entwicklung eines postoperativen ANV zu identifizieren sowie die Langzeitmortalität dieser Patienten zu bestimmen.

Material und Methoden

In dieser zwischen 2014 und 2015 durchgeführten prospektiven Observationsstudie wurden 119 Patienten auf das Auftreten eines ANV nach herzchirurgischen Operationen untersucht. Die Einteilung erfolgte dabei entsprechend der verschiedenen Schweregrade der KDIGO-Klassifikation, bestehend aus einem Anstieg des Serumkreatinins um mindestens 50% zum Ausgangswert oder einer akuten Verringerung der Urinausscheidung. Risikofaktoren für das Auftreten eines kardiochirurgisch-assoziierten Nierenversagens wurden mittels logistischer Regression bestimmt. Das Langzeitüberleben wurde mittels Kaplan-Meier-Algorithmus analysiert. Zusätzlich wurde mittels Cox-Regression das relative Risiko in Bezug auf die 3-Jahresmortalität ermittelt.

Ergebnisse

Von den 119 untersuchten Patienten entwickelten 36.1% (n=43) postoperativ ein ANV. Mehr als zwei Drittel dieser Patienten (71.1%) entwickelten ein ANV des Schweregrades 1. Die wichtigsten unabhängigen Risikofaktoren bezüglich des Auftretens eines postoperativen ANV waren die präoperative glomeruläre Filtrationsrate (HR: 0.77; 95% CI: 0.61 – 0.95; p=0.016), die präoperative Einnahme von Diuretika (HR: 3.71; 95% CI: 1.50 – 9.20; p=0.005), sowie ein vorbestehender Diabetes mellitus (HR: 2.74; 95% CI: 1.01 – 7.46; p=0.048). Weiterhin konnte gezeigt werden, dass es sich bei dem herchirurgisch-assoziierten ANV um einen unanhängigen Risikofaktor für eine erhöhte 3-Jahresmortalität nach erfolgter Intervention handelt (HR 13.58 (3.89 – 47.41); p<0.001). Die 3-Jahresmortalitätsrate aller Patienten betrug in dieser Studie 20.5% (n=24). Von den Patienten ohne klinisch nachgewiesenes ANV verstarben 4% (n=3). Wohingegen 49.4% (n=21) der Patienten mit postoperativem ANV

innerhalb dieser Zeitperiode verstarben (p>0.001). Die 3-Jahresmortalitätsrate von Patienten mit nur mildem postoperativen ANV betrug 48.4 % (n=15).

Diskussion

Die Mortalität bei Patienten mit kardiochirigisch-assoziiertem ANV war zu jedem Zeitpunkt des Beobachtungszeitraums höher als bei den Patienten ohne ANV, unabhängig von der Schwere des akuten Nierenversagens. Da mögliche präventive Strategien in Bezug auf die Risikofaktoren nur limitiert möglich sind, sollte das Hauptaugenmerk auf einer engmaschigen postinterventionellen Nachkontrolle von Risikopatienten liegen. Insbesondere von Patienten mit postoperativem ANV, unabhängig vom Schweregrad, sowie von Patienten mit einer schon präoperativ bestehenden Nierenfunktionsstörung oder anderen relevanten Komorbiditäten.

1 Introduction

Acute kidney injury (AKI) is an important complication in cardiac surgery. It is not only the most common postoperative complication in cardiac surgery, but also the second leading cause for AKI in the intensive care unit (ICU) after septic shock (1,2). The incidences for cardiac surgery-associated acute kidney injury (CSA-AKI) in the literature vary between 5% and 53% depending on the study and the definition of AKI being used (3–8). CSA-AKI is an independent risk factor for an increased postoperative morbidity and mortality (9–11). It not only affects the short-term outcome of patients undergoing cardiac surgery, but also has an important impact on long-term mortality in these patients (6,7,9,12). It was shown that long-term mortality in patients with CSA-AKI is increased for up to 10 years after the intervention, compared to patients without CSA-AKI (6). Every year, up to 2 million coronary artery bypass grafting (CABG) operations are performed worldwide (13). Therefore, CSA-AKI is an important problem for the individual patient as well as a financial issue for the health care system (14). With regard to this, there are several studies assessing the association between CSA-AKI, using only the serum creatinine criteria of the Kidney Disease: Improving Global Outcome (KDIGO) guidelines and patient survival (9,15–18), but there are only a few studies examining the association between CSA-AKI, defined by the complete KDIGO criteria including changes in baseline serum creatinine as well as urine output, and long-term mortality (19,20).

This study is a prospective analysis of 119 patients undergoing cardiac surgery in the study periods from September 2014 to October 2014 and from April 2015 to July 2015 at the Charité University Medicine Berlin, Campus Mitte. Patients were postoperatively screened for the development of CSA-AKI and 3 years post-intervention patients were reevaluated according to their survival status.

The aim of this study was to identify risk factors for the development of CSA-AKI, defined by the complete KDIGO criteria and to assess if there is an independent association between increased long-term mortality and CSA-AKI. We then compared the collected data with the data of other similar studies to see if the results correspond to those we had obtained.

1.1 Definition of cardiac surgery-associated acute kidney injury

Acute kidney injury is defined as a sudden but potentially reversible deterioration of the kidney´s function, including a decrease in the ability to excrete wastes, concentrate urine, conserve electrolytes and maintain fluid balance (21). To date, there is no generally valid definition for CSA-AKI. Most studies concerning this topic usually use the definitions of the Acute Kidney Injury Networks (AKIN) (22) and the Risk, Injury, Failure, Loss, End Stage Kidney Disease (RIFLE) criteria (23) for diagnosing and categorizing CSA-AKI. The criteria mentioned use changes in patients' baseline serum creatinine and changes in patients' urine output over a specific period of time to diagnose and categorize AKI. Due to typical fluctuations in patients' fluid balance after the use of the cardiopulmonary bypass system, CSA-AKI may be overdiagnosed when AKIN criteria are being used. Therefore, postoperative rises in serum creatinine in these patients need to be adjusted to the changes occurring in patients' fluid balance (24). The RIFLE criteria, on the other hand, classify all patients with the need for renal replacement therapy as “failure”. This can be problematic, due to the different criteria for initiating renal replacement therapy in patients with AKI (24). Other studies have diagnosed CSA-AKI with self-made criteria, which can lead to a lack of comparability between studies (25,26). For these reasons, diagnosing CSA-AKI by using just one of the aforementioned criteria might be problematic and insufficient. This is why the new Kidney Disease: Improving Global Outcomes (KDIGO) criteria are recommended for diagnosing CSA-AKI (27). The KDIGO criteria merge the definitions of AKIN and RIFLE to diagnose and categorize AKI. An AKI is defined by an increase in serum creatinine of at least 0.3 mg/dl within 48 hours, or an increase of at least 50% compared to baseline creatinine within 7 days, or urine output less than 0.5 ml/kg/h over a period of at least 6 hours. In addition, AKI can be divided into 3 different severity levels according to the increase in baseline serum creatinine and the amount of reduction in urine output (27). It has been shown that the KDIGO criteria are more sensitive for diagnosing AKI and for predicting in-hospital mortality in critically ill patients in the ICU (28). Every patient that fulfills these criteria within the first 7 days after surgery can be diagnosed with CSA-AKI (27). In summary, it can be said that the KDIGO criteria are the international standard for diagnosing AKI. Nevertheless, the use of these criteria in cardiosurgical patients is still limited due to particular characteristics of these patients, especially when a cardiopulmonary bypass system is being used.

1.2 Epidemiology and clinical course of CSA-AKI

The observed incidences for CSA-AKI vary between 5% and 53% depending on the criteria for diagnosing AKI, the study populations, the types of surgery performed, the urgency of the operation and whether a cardiopulmonary bypass system was used during the operation (3,4,7,17,22–32). The lack of a consistent definition for diagnosing CSA-AKI complicates the research and comparability between the different studies. Conlon et al. (4) defined CSA-AKI as an increase in baseline serum creatinine of more than 1 mg/dl. In this case, an incidence of 7.9% for CSA-AKI was observed. A CSA-AKI with the need for renal replacement therapy occurred in 0.7% (4). Other studies that used the AKIN or RIFLE criteria observed incidences between 12% and 49% (6,7,33). Chertow et al. (11) analyzed over 42,000 patients who underwent cardiopulmonary bypass surgery and observed an incidence of CSA-AKI with the need for renal replacement therapy of 1.1%. Furthermore, the incidence of CSA-AKI depends on the type of surgery being performed. Coronary artery bypass grafting (CABG) operations seem to have the lowest incidence of CSA-AKI and the lowest incidence of acute renal replacement therapy during hospitalization, followed by valvular surgery (34). The highest incidence of CSA-AKI seems to appear in patients who underwent a combination of CABG and valvular surgery (34). A recent study conducted by Machado et al. (15) using the KDIGO criteria to diagnose CSA-AKI in patients undergoing CABG and valvular surgery observed an incidence of 42% during the first 7 postoperative days. 2% of the study population needed acute renal replacement therapy during hospitalization (15). The development of CSA-AKI was thereby associated with a higher 30-day mortality compared to patients without CSA-AKI (15). In patients who require dialysis during hospitalization, the 30-day mortality is even higher compared to the other severity levels of CSA-AKI and averages between 40% and 60% (15,35). Interestingly, even small rises in serum creatinine are associated with worse patient survival (36). Lassnigg et al. (36) were able to demonstrate that minimal rises in baseline serum creatinine within 48 hours after cardiac surgery are associated with a significantly higher 30-day mortality compared to patients without a postoperative increase in baseline serum creatinine. In 2016, Hu et al. (37) published a meta-analysis consisting of 91 different studies examining the incidence of CSA-AKI using AKIN, RIFLE or KDIGO criteria. The pooled incidence of CSA-AKI in this study was 22.3%.

CSA-AKI is not only associated with a higher short-term mortality, but also with a prolonged hospital stay, more postoperative complications such as stroke or congestive heart failure and increased costs for the health care system (6,14,30,38). In addition, the development of CSA-

AKI is associated with a higher long-term mortality as identified by Loef et al. (39), who observed that a 25% increase in baseline serum creatinine after cardiac surgery is associated with a higher long-term mortality compared to patients without postoperative increase in serum creatinine. The observed increase in long-term mortality was thereby independent of renal recovery at the point of hospital discharge (39). Long-term mortality in patients with CSA-AKI seems to be increased for up to 10 years after the intervention (6). The link between CSA-AKI and higher mortality most likely involves various different factors. Postoperative AKI may lead to a higher risk of serious infection, including sepsis in severe cases. This is particularly true for patients who become dialysis dependent during hospitalization (40,41). Important long-term causes of death in this population include myocardial infarction, stroke and heart failure (42). Other long-term complications include the risk of chronic kidney disease and permanent dialysis dependency (9,26,43). The long-term development of chronic kidney disease is correlated with the duration and severity of CSA-AKI. In fact, the 12-month prevalence of chronic kidney disease was 25% in the CSA-AKI group compared to 9% in patients without CSA-AKI (43). Patients who develop CSA-AKI with the need for renal replacement therapy during hospitalization often remain dialysis dependent. Among these patients, 64% require permanent dialysis and their 1-year survival is lowered to only 10% (26).

Table 1 Literature overview of publications studying the incidence of CSA-AKI

Study	**N**	**Criteria of CSA-AKI**	**Incidence of CSA-AKI**	**Inclusion criteria**
Abel et al. *(1976)* (3)	500	rise in postoperative serum creatinine to >5 mg/dl	7%	CABG surgery
Andersson et al. *(1993)* (35)	2,009	>50% rise in postoperative serum creatinine	16%	CABG surgery
Conlon et al. *(1999)* (4)	2,843	rise in postoperative serum creatinine of 1 mg/dl	7.9%	CABG surgery
Yehia et al. *(2005)*	106	>50% rise in postoperative serum	41.3%	CABG surgery and patients with

(25)		creatinine		preexisting renal dysfunction
Hobson et al. *(2009)* (6)	2,973	RIFLE	43%	any kind of cardio-thoracic surgery and patients without preexisting renal dysfunction
Englberger et al. *(2011)* (24)	4,836	RIFLE and AKIN	18.9% (RIFLE) 26.3% (AKIN)	cardiac surgery with cardiopulmonary bypass
Gallagher et al. *(2013)* (7)	4,694	RIFLE	12%	first time CABG surgery
Machado et al. *(2014)* (15)	2,804	KDIGO creatinine-based definition criteria	42%	any kind of cardio-thoracic surgery
Petäjä et al. *(2017)* (19)	638	complete KDIGO criteria	28.7%	CABG and Valve-surgery
Ferreiro et al. *(2017)* (17)	7,075	KDIGO creatinine-based definition criteria	36.1%	any kind of cardio-thoracic surgery
Howitt et al. *(2018)* (20)	2,267	complete KDIGO criteria	36.1%	any kind of cardio-thoracic surgery

1.3 Risk factors associated with CSA-AKI

1.3.1 Preoperative risk factors

The preoperative risk factors that are associated with the development of CSA-AKI are well investigated and validated. Important preoperative risk factors are older age, reduced left ventricular function, diabetes mellitus, peripheral vascular disease, chronic lung disease, arterial hypertension, the need for emergent operation and preoperatively elevated serum creatinine (44–46). In particular, a preoperatively impaired kidney function has a high

predictive value for the development of CSA-AKI during the first 7 days after surgery (47). A meta-analysis with over 1 million study patients showed that in particular an estimated glomerular filtration rate (eGFR) lower than 45 ml/min/1.73m^2 is an independent risk factor for the development of postoperative AKI (48). Older age and sex seem to play a minor role in this context (48). Importantly, almost all of the aforementioned preoperative risk factors are associated with either decreased renal reserve or impaired renal perfusion. Most of these preoperative and patient-related risk factors are non-modifiable, which means that they play a secondary role in the prevention of CSA-AKI.

1.3.2 Perioperative risk factors

Significant perioperative risk factors are the type of operation performed, the cardiopulmonary bypass time, the use of an intra-aortic balloon pump and the use of red blood cell transfusions (44–46,49). In the last two decades, minimally invasive cardiac surgery has become more and more important in terms of reducing postoperative pain and recovery time, especially in high-risk patients. Results from the PARTNER study showed that there are no significant differences in the incidence of CSA-AKI between minimally invasive transcatheter aortic valve implantation (TAVI) and conventional open aortic valve surgery (50). Moreover, minimally invasive mitral valve surgery is a common alternative to conventional, openly performed mitral valve surgery. The observed incidence of CSA-AKI after minimally invasive mitral valve surgery was 4% in a study with a small study population conducted by Murzi et al. (51). There is inconsistent data on which type of operation has the highest risk of CSA-AKI. A meta-analysis consisting of 14 case-control studies found no differences in the incidence of CSA-AKI between the different types of surgery (46). On the other hand, other studies showed that single valve surgery and especially a combination of CABG operations and valve surgery are independent risk factors for the development of CSA-AKI (34,45,52). In this context, Bove et al. (53) postulates that mitral valve surgery in particular seems to be an independent risk factor of CSA-AKI. Nevertheless, single CABG operations tend to have the lowest risk of developing CSA-AKI compared to the other types of cardiac surgery (44,45). In particular, the use and the length of the cardiopulmonary bypass system as well as the use of red blood cell transfusions are potentially modifiable risk factors in the development of CSA-AKI. It is said that the use of a cardiopulmonary bypass system could be a risk factor for CSA-AKI due to the contact of patients' blood with unphysiological material (54). The CORONARY study was a big randomized-controlled trial to evaluate the differences between off-pump and on-pump cardiac surgery (55). The authors observed a

lower incidence of CSA-AKI when off-pump surgery was performed. However, there was no significant difference between on-pump and off-pump surgery with respect to 30-day mortality, myocardial infarction, stroke and AKI with the need for renal replacement therapy (55). Chawla et al. (56) retrospectively studied the data of 742,909 patients who underwent CABG surgery and observed that patients with preexisting chronic kidney disease show better survival and a lower rate of postoperative need for renal replacement therapy when off-pump operation was performed. Other reported procedure-related risk factors like prolonged cardiopulmonary bypass time, longer aortic cross-clamp time, non-pulsatile flow of the cardiopulmonary bypass system, haemolysis and haemodilution are possibly associated with a higher risk of developing CSA-AKI (57). In conclusion, these observations suggest that the influence of the cardiopulmonary bypass is limited per se.

There is evidence that the duration of cardiopulmonary bypass may be an important perioperative and modifiable risk factor of developing postoperative CSA-AKI (58). A meta-analysis conducted by Kumar et al. (59) strengthens this hypothesis. The mean differences in cardiopulmonary bypass time were thereby 25 minutes between patients with and patients without CSA-AKI. Additionally, the duration of the cardiopulmonary bypass seems to correlate with the severity of CSA-AKI (54). A possible safe time frame could be a cardiopulmonary bypass time of less than 70 minutes (33). However, further studies need to be conducted to determine a safe cut-off for the cardiopulmonary bypass time. Even though the use of red blood cell transfusions should improve organ function through higher oxygen supply and oxygenation, there is evidence that red blood cell transfusions may lead to notable organ damage in patients undergoing cardiac surgery (60). Studies showed that the use of red blood cell transfusions in patients undergoing cardiac surgery can increase the risk of developing CSA-AKI (58), especially in patients with preexisting chronic lung disease (58). An observational study conducted by Haase et al. (49) demonstrated that the given volume of red blood cell transfusions was independently associated with a higher risk of developing CSA-AKI. That observation applied especially to patients with an intraoperative hemoglobin level of 8 g/dl or higher. Therefore, the Society of Thoracic Surgeons and Society of Cardiovascular Anesthesiologists recommends the use of techniques that increase the intraoperative blood volume (e.g. the preoperative use of erythropoietin) and techniques that decrease blood loss during surgery (e.g. intraoperative use of cell salvage techniques) (61). The updated guidelines also recommend that red blood transfusions should only be used if the patient's hemoglobin level is lower than 6 g/dl (62).

1.3.3 Postoperative risk factors

Given that the kidney is most likely damaged during the performed operation and that the rise in serum creatinine is a delayed signal of renal injury, it can be said that postoperative factors can worsen the damage in an already vulnerable kidney gravely. Those postoperative factors are the use of vasopressors, hemodynamic instability including cardiogenic shock, the use of nephrotoxic agents, volume depletion, mechanical ventilation and systemic inflammation including sepsis (2). Another important postoperative risk factor is the need for surgical reexploration after cardiac surgery (63). Surgical reexploration is independently associated with a wide range of adverse outcomes, including AKI and increased operative mortality (63). Although the exact mechanisms of surgical reexploration leading to AKI are not fully understood, it can be safely assumed that the pathogenesis involves almost all of the risk factors mentioned above. Furthermore, surgical reexploration is most likely linked to the use of red blood cell transfusions which, as previously discussed, can also lead to renal injury and failure. Among the risk factors discussed above, perioperative and postoperative risk factors tend to be more modifiable than preoperative risk factors. Therefore, adjusting perioperative and postoperative risk factors may result in a lower incidence of CSA-AKI.

1.4 Pathophysiology of cardiac surgery-associated acute kidney injury

The pathophysiology of CSA-AKI is a complex and multifactorial process. The various factors that are involved in the pathogenesis of CSA-AKI may lead to renal injury in many different ways and most likely differ from patient to patient. It is assumed that the underlying cause of CSA-AKI is a cardiorenal syndrome type 1 (64). A cardiorenal syndrome type 1 is defined as a pathological interaction between heart and kidneys. In this context, an abrupt decrease in cardiac function (e.g. cardiogenic shock or decompensated congestive heart failure) can lead to acute or chronic renal injury (64). Important influencing factors include renal hypoperfusion, ischemia-reperfusion injury, the use of a cardiopulmonary bypass system, neuro-humoral activation, inflammation, oxidative stress and nephrotoxic agents. All of the mentioned pathophysiological factors can occur preoperatively, perioperatively and postoperatively or at all of these times (65). Despite the abundance of different hypotheses of the pathogenesis of CSA-AKI, it remains incompletely understood.

1.4.1 Preoperative events

1.4.1.1 General factors

Patients undergoing cardiac surgery often already suffer from various comorbidities and a certain degree of renal impairment before entering the operating theater. They are more likely

to have previous myocardial infarctions, extracardiac arteriopathy, reduced left ventricular ejection fraction and reduced renal perfusion. Some of these patients may have severe complications like cardiogenic shock and require inotropic support or an intra-aortic balloon pump. In fact, these preexisting medical conditions can be worsened by the use of typical medication in this population. This includes the use of diuretics, non-steroidal anti-inflammatory drugs, angiotensin-enzyme inhibitors and angiotensin-receptor blockers that can cause functional renal damage by impairing the autoregulation of renal blood flow (66). In addition, recurring episodes of renal hypoperfusion can lead to endothelial injury, causing further tubular ischemia and damage (67). The mentioned changes in preoperative hemodynamics can then lead to higher renal vulnerability and to further insults in the peri- as well as postoperative setting.

1.4.1.2 Genetic polymorphisms

Various studies were able to demonstrate that different genetic polymorphisms may have an important impact on the development of CSA-AKI. Most of the studied genes are associated with the body´s inflammatory system, the response to oxidative stress and the regulation of renal blood flow. But then again, it has to be said that the results of the different studies are inconsistent and partly conflicting (68).

1.4.1.3 Proinflammatory polymorphisms

Cardiac surgery is associated with a strong and powerful systemic proinflammatory activation of a patient´s immune system (69). Thus, patients experience a postoperative increase in proinflammatory mediators, which may be associated with a higher incidence of CSA-AKI (70). Therefore, patients with a genetic predisposition for an exaggerated immune response may have a greater risk of developing CSA-AKI. In this context, Brull et al. (71) were able to identify different Interleukin-6 (IL-6) alleles that are associated with an increased expression of IL-6 after cardiac surgery. Shortly after, several studies observed that higher blood concentrations of IL-6 after cardiac surgery may lead to a higher incidence of CSA-AKI in these patients (72,73). Other genetic polymorphisms that may be associated with a higher rate of complications following cardiac surgery, including CSA-AKI, are polymorphisms of Interleukin-10 (IL-10) and tumor necrosis factor alpha (TNF-α) (74,75). However, further studies concerning this topic were not able to confirm a correlation between TNF-α polymorphisms and AKI in patients undergoing cardiac surgery (76).

1.4.1.4 Further genetic polymorphisms

In order to identify genetic polymorphisms associated with the regulation of the renal vascular tone, several studies examined the genes of angiotensin-converting enzyme, angiotensinogen, angiotensin receptor 1 and endothelial NO synthase (73,77). However, only one study was able to identify a positive correlation between polymorphisms of the angiotensin-converting enzyme gene and a higher incidence of CSA-AKI (77). Polymorphisms of the other regulating genes, on the other hand, seem to play a minor role in the development of CSA-AKI. The apolipoprotein E (APOE) is an important part of lipoprotein metabolism and also plays an essential role in modulating the immune system. Therefore, it is substantially involved in the pathogenesis of diseases such as coronary heart disease, arteriosclerosis and Alzheimer´s disease (78,79). Studies showed that a polymorphism in one of the 3 APOE alleles is associated with small postoperative rises in serum creatinine after cardiac surgery (77,80). These findings suggest that this polymorphism could lead to a greater renal injury in cardiosurgical patients. Nevertheless, the reported results could not be confirmed by other studies (76).

Another genetic polymorphism that may lead to a higher risk of developing CSA-AKI could be a variation of the gene of the membrane-associated enzyme NADPH oxidase which produces reactive oxygen species in endothelial cells and neutrophils (81). The discovered polymorphism leads to an overproduction of superoxide and could therefore be associated with adverse clinical outcome including postoperative AKI (82).

1.4.2 Intraoperative events

1.4.2.1 Renal hypoperfusion and ischemia-reperfusion injury

Due to low blood flow, low blood pressure, non-pulsatile perfusion with hemodilution and changes in patients' body temperature, the use of a cardiopulmonary bypass system in cardiac surgery is often associated with renal hypoperfusion (83). In addition to hemodynamic changes caused by the use of the cardiopulmonary bypass system, a reduced left ventricular ejection fraction in the early postoperative stage may be a common trigger for developing CSA-AKI (38). These intra- and postoperatively occurring hemodynamic changes lead to a neuro-humoral adaption of the body, with an activation of the renin-angiotensin-aldosterone system (RAAS). It is understood that the activation of RAAS stimulates the generation of vasopressin and endothelin-1, which leads to systemic vasoconstriction and subsequently to renal hypoperfusion (84). The resulting hypoperfusion especially affects the outer area of the

renal medulla because the majority of the renal oxygen supply is used in this part of the kidney (85). If a low left ventricular ejection fraction or a general hypotensive state persists after cardiac surgery, acute renal damage will occur, causing a decline of patients' glomerular filtration rate (GFR). The prolonged ischemic state of the kidney may cause structural tubular injury leading to acute tubular dysfunction (86). Furthermore, it was demonstrated that patients with AKI need 2.4 times as much oxygen to reabsorb the same amount of sodium in the renal tubules than patients without AKI. This means that the reinstatement of the relation between GFR and oxygen consumption is accompanied by a severe impairment of the relation between oxygen supply and oxygen demand in ischemic AKI (87). Regarding this point, one can only speculate about the underlaying mechanisms. A possible explanation may be the loss of epithelial cell-polarization and the dissolution of intercellular tight junctions, which could lead to acute inefficacy of tubular sodium reabsorption (88,89). After terminating the use of the cardiopulmonary bypass system, blood flow and subsequently renal perfusion may improve. However, during this period of time the kidney may be vulnerable to ischemia-reperfusion injury. If ischemia-reperfusion injury occurs, it may contribute to CSA-AKI. Statistics state that ischemia-reperfusion injury affects between 5% and 20% of all ICU patients and increases in-hospital mortality to up to 50% (90,91). An MRI-study conducted by Oostendorp et al. (92) was able to demonstrate that an ischemic-reperfusion injury of the kidney leads to a decline in renal perfusion and subsequently to an impairment of renal oxygenation. This phenomenon occurs particularly in the renal medulla due to vasoconstriction, endothelial blockage, formation of edema and capillary obstruction (93). Finally, this leads to an opening of mitochondrial permeability transition pores causing acute cell damage and necrosis (94). Furthermore, the rapid reperfusion of renal tissue is associated with the generation of reactive oxygen species. This leads to the activation of a systemic inflammatory response by induction of proinflammatory transcription factors like nuclear factor-κB (95,96). Moreover, the activation of this systemic inflammatory cascade results in the deubiquitination of receptor-interacting protein kinase 1, causing programmed cell death of renal tubular cells (97,98). In addition, the induction of proinflammatory transcription factors leads to the formation of different cytokines and chemokines that activate neutrophils, macrophages and lymphocytes which damage renal parenchymal cells by infiltrating the parenchyma of the kidney (70).

Beyond that, the use of a cardiopulmonary bypass system is associated with intravascular hemolysis, which is characterized by an increase in hemoglobin in patients' blood. The rise in

free hemoglobin leads to an increased nitric oxide consumption. This may result in damage of tubular cells through renal hypoperfusion by limiting NO bioavailability (99). Another important consequence of renal hypoperfusion and ischemia-reperfusion injury is the development of an intestinal fibrosis leading to a decline of renal oxygen supply (100). In conclusion, all mentioned factors result in structural and functional impairment of renal function leading to further hypoxia, which over time may support the development of chronic kidney disease (101).

1.4.2.2 Inflammation and oxidative stress

The surgical tissue injury itself and the contact of the blood with the cardiopulmonary bypass pump are associated with a significant increase of proinflammatory cytokines and chemokines via the activation of various inflammatory pathways, when compared to patients undergoing off-pump procedures (102). Furthermore, the use of a cardiopulmonary bypass system leads to the activation of alternate complement pathways which may contribute to the development of CSA-AKI (102). This theory is supported by findings of Zhang et al. (103), who observed a higher blood concentration of proinflammatory cytokines in patients with CSA-AKI as well as increased mortality. Moreover, the use of a cardiopulmonary bypass system is associated with the production of free radicals and oxidative stress. The cardiopulmonary bypass circuit exposes patients' blood to an unphysiological surface causing a mechanical destruction of red blood cells and a subsequent release of free hemoglobin as well as free iron radicals (104). These free iron radicals, generated through hemolysis, promote the production of reactive oxygen species via Fenton-Haber-Weiss reaction, which leads to an increase in oxidative stress (105). The generation of free radicals and the release of catalytic iron results in myocardial injury and the development of AKI as proven in experimental animal studies (106). The freely circulating iron can induce pathological alterations in renal tubular epithelial cells, such as impaired proliferative cell function and the induction of lipid peroxidation (107). Billings et al. (108) showed in a case-control study that patients who develop CSA-AKI after surgery present a concentration of free hemoglobin that is 2 times higher compared to patients without CSA-AKI with a similar cardiopulmonary bypass time. It can be assumed that a simultaneously existing ischemic-reperfusion syndrome could exacerbate the oxido-inflammatory injury via the release of even more free radicals.

1.4.2.3 Other intraoperative events

The use of an aortic clamp during cardiac operation can provoke the disengagement of cholesterol emboli due to mechanical forces (109). This especially affects patients with

preexisting severe arteriosclerosis. Cholesterol emboli may lead to an increase in serum creatinine and the development of CSA-AKI (110). Septic emboli, on the other hand, affect 30% of patients with active endocarditis. Furthermore, they can cause renal infarction and an immune-complex glomerulonephritis (111).

1.4.3 Postoperative events

Most postoperative events that affect renal function in cardiac surgery are similar to those in the general intensive care setting. That includes the usage of vasopressors, exposure to nephrotoxic medication such as aminoglycoside antibiotics, hemodynamic instability and sepsis (2). One of the most critical factors may be the patient´s postoperative cardiac performance including the need for inotropic medication or mechanical support. Regarding this point, it is widely assumed that arterial hypotension plays the leading role in the pathophysiology of CSA-AKI. A study conducted by Palomba et al. (45) to identify risk factors and to develop a predictive scoring system for CSA-AKI showed that not only a reduced cardiac output, but also an increased central venous pressure are independent risk factors for CSA-AKI. A recent review concerning this topic points out that systemic venous hypertension as “congestive kidney failure” could play an important role in the postoperative development of CSA-AKI (112). These findings suggest that acute increases in central venous pressure should be carefully handled to avoid the development of postoperative CSA-AKI in an intensive care setting.

1.5 Biomarkers and subclinical cardiac surgery-associated acute kidney injury

A CSA-AKI is characterized as an acute deterioration in renal function after cardiac surgery. Indeed, a rise in serum creatinine of 0.1 mg/dl to 0.2 mg/dl after the intervention can be interpreted as a physiological adjustment reaction of the patient’s organism. However, only an increase of more than 0.3 mg/dl can be diagnosed as a clinical AKI as defined by the KDIGO guidelines (27). Despite this, the rise in serum creatinine occurs typically after 48 hours following the triggering event for AKI (113). Therefore, it is possible that the renal tubular system is already irreversibly damaged at the time of clinical diagnosis of CSA-AKI when serum creatinine is being used as a diagnostic tool. As a response to ischemic and nephrotoxic events during hospitalization, the renal tubular cells release certain proteins into blood and urine (113). These proteins can be measured in blood or urine and may be used as novel biomarkers for the early detection of subclinical CSA-AKI, which could massively improve patient outcome in a cardiac surgical setting and in the ICU. The most studied and most

promising renal biomarkers for the diagnosis of subclinical CSA-AKI are neutrophil gelatinase-associated lipocalin (NGAL) and Interleukin-18 (IL-18) (113,114).

1.5.1 Neutrophil gelatinase-associated lipocalin

NGAL is a protein and renal biomarker that is physiologically produced in small amounts by the epithelial cells of the kidney (115). In case of an ischemic injury of the kidney, the proximal tubular cells release an increased amount of NGAL in urine and blood. Therefore, the rise of NGAL in urine and blood is associated with the dose and duration of renal ischemia (115). The rise in urinary NGAL typically takes place 3 hours after the triggering event. After the use of a cardiopulmonary bypass system, urinary NGAL increases up to 25 times and decreases to baseline level 6 hours after surgery (113). Mishra et al. (113) conducted the first study which was able to demonstrate that NGAL is a sensitive and specific predictor of CSA-AKI. This observation applies especially for patients with a preoperatively normal kidney function (116). A pooled analysis by Haase et al. (117) showed that a pathological increase in urinary NGAL, in the absence of an increase in serum creatinine, is a powerful predictor of AKI and other adverse outcomes. In addition to the measurement of urinary NGAL, it is possible to measure NGAL in patients' plasma (118). In fact, the increase in plasma NGAL after renal injury correlates with the severity, the duration of AKI and the length of ICU stay (119).

1.5.2 Interleukin-18

IL-18 is an essential cytokine that plays an important role in the innate immune system. It is a relevant mediator of ischemic tissue injury of any kind and general inflammation (120). Experimental animal studies were able to demonstrate that the production of IL-18 is associated with acute ischemic injury of the kidney (121). The urinary concentration of IL-18 in mice with acute ischemic injury of the kidney was twice as high as in mice without ischemic AKI. Consequently, IL-18 is increasingly produced by the damaged tubular epithelial cells of the kidney (121). To prove that IL-18 plays an important role in the pathogenesis of ischemic AKI, mice were injected with an IL-18-neutralizing serum before triggering the ischemic insult. The incidence of ischemic AKI was significantly lower in mice with IL-18-neutralizing serum compared to mice without the preischemic use of IL-18-neutralizing serum (122). Not only mice but also critically ill ICU patients with ischemic AKI show increased urinary concentrations of IL-18. Furthermore, IL-18 concentrations were increased in these patients even before an AKI was clinically apparent and diagnosed by using changes in baseline serum creatinine (123). Thus, IL-18 may be used as a predictive

biomarker for diagnosing subclinical AKI. Parikh et al. (114) studied the predictive use of IL-18 in patients undergoing cardiac surgery. It was observed that urinary IL-18 is an early predictive biomarker of CSA-AKI. Additionally, they showed that the concentration of IL-18 correlates with the severity of CSA-AKI.

In summary, it can be said that proinflammatory cytokine IL-18 is both a mediator and predictive biomarker of CSA-AKI.

1.5.3 Cystatin C

Cystatin C is a post-gamma protein that was discovered in 1961 by Butler and Flynn using gel electrophoresis (124). This protein is freely filtered by the glomeruli, completely reabsorbed in the proximal tubular system and does not underlie any renal secretion mechanisms (125). Therefore, it does not depend on patients' muscular mass, diet, sex or tubular secretion like serum creatinine does. Uzun et al. (126) compared the concentrations of serum cystatin C of healthy patients with the serum concentration of patients with GFR lower than 60 ml/min/1.73m^2 along with other validated methods to determine renal function. All in all, the results demonstrate that the serum cystatin C level may be used as marker for renal injury. Furthermore, it was observed that serum cystatin C increases 1 to 2 days before serum creatinine in critically ill patients with AKI (127). Based on these findings, it can be assumed that cystatin C may be a useful biomarker to diagnose subclinical AKI. A study conducted by Koyner et al. (128) to evaluate the predictive value of cystatin C in a cardiosurgical setting showed that urinary cystatin C is superior to serum cystatin C. Additionally, it further demonstrated that the concentration of urinary cystatin C within the first 6 hours after ICU admission correlates with the incidence of CSA-AKI.

1.5.4 Tissue inhibitor of metalloproteinases-2 and insulin-like growth factor-binding protein 7

An observational study conducted in 2013 to validate the predictive value of biomarkers for AKI in critically ill patients was able to identify two new and promising urinary biomarkers for the prediction of AKI (129). The newly discovered urinary proteins were Tissue inhibitor of metalloproteinases-2 (TIMP-2) and insulin-like growth factor-binding protein 7 (IGFBP7). TIMP-2 and IGFBP7 are of vital importance in the induction of G1 cell cycle arrests. For instance, a G1 cell cycle arrest can be induced when renal tubular epithelial cells are exposed to an ischemic insult to protect the cell against further injuries (130). Meersch et al. (131) analyzed 50 patients undergoing cardiac surgery and showed that the product of TIMP-2 and IGFBP7 is an early predictor for CSA-AKI. In addition, the product of TIMP-2 and IGFBP7

correlates with the probability of complete renal recovery (131). This theory was confirmed in a randomized clinical trial by Zarbock et al. (132). In this study, patients received either remote ischemic preconditioning (RIPC) or sham RIPC in the control group before undergoing cardiac surgery. The RIPC group showed a preoperatively higher product of TIMP-2 and IGFBP7 and showed a lower incidence of CSA-AKI within the first 72 hours after surgery. Patients with a postoperatively increased product of TIMP-2 and IGFBP7, on the other hand, showed a higher incidence of CSA-AKI. In conclusion, it can be assumed that the G1 cell cycle arrest proteins TIMP-2 and IGFBP7 have a renoprotective effect and that they may be used as a clinical tool for diagnosing subclinical CSA-AKI.

1.6 Prevention of cardiac surgery-associated acute kidney injury

1.6.1 Statins

Several observational studies in patients undergoing cardiac surgery showed that the preoperative use of statins is associated with decreased concentrations of the C-reactive protein, decreased incidence of postoperative atrial fibrillation, reduced risk of perioperative myocardial infarction and a shorter length of hospitalization compared to patients without the preoperative administration of statins (133–135). Moreover, statins improve the functional capability of endothelial cells, inhibit the production of free radicals and consequently reduce oxidative stress, improve the bioavailability of free NO, reduce the general systemic inflammatory response and have a variety of pleiotropic effects (136–141). Due to the mentioned pharmacological characteristics of statins, it can be assumed that HMG-CoA reductase inhibitors may have a protective effect in patients undergoing cardiac surgery (142). Therefore, a retrospective study examined the association between the preoperative use of statins and the incidence of CSA-AKI in CABG patients (143). In this study, the admission of statins immediately before the CABG operation reduced the risk of CSA-AKI, especially in younger patients. Another retrospective analysis examining the association between the early postoperative use of statins and the risk of CSA-AKI showed similar results (144). Despite those promising results in several retrospective analyses, the protective effect of statins regarding a decreased risk for CSA-AKI and decreased mortality could not be confirmed in randomized controlled trials (145–147).

1.6.2 Remote ischemic preconditioning

RIPC is a clinical procedure to strengthen the endogenous protection of the patient´s tissue against ischemic injury by inducing short periods of ischemia and subsequent reperfusion in distal parts of the body (148). Experimental animal studies demonstrated that brief periods of

regional ischemia shortly before the onset of complete ischemia may reduce the amount of myocardial injury caused by complete ischemia (149). It is widely assumed that the underlying mechanism consists in the activation of intracellular kinases that lead to a modification of mitochondria with a subsequent opening of ATP-dependent potassium channels and the closing of mitochondrial permeability transition pores (150,151). Other experimental studies indicate that particularly the period of reperfusion is associated with the activation of these prosurvival intracellular kinases (152). This protective phenomenon is not only limited to the myocardium. It can also occur in the kidney or any other kind of human tissue. Therefore, it was concluded that RIPC might reduce the incidence of CSA-AKI. Zimmerman et al. (153) demonstrated that RIPC does prevent AKI in patients undergoing cardiac surgery. Nevertheless, data concerning the renoprotective effect of RIPC is inconsistent. Other randomized-controlled studies were not able to reproduce the risk reduction of AKI after RIPC in cardiosurgical patients (154,155). To summarize the results of the association between RIPC and CSA-AKI a Cochrane review examined 28 randomized-controlled trials and determined that there is no significant difference in the incidence of CSA-AKI or the need for renal replacement therapy between patients who received RIPC preoperatively and patients who did not (156).

1.6.3 Fenoldopam

Fenoldopam is a synthetic benzazepine derivate, which acts as selective dopamine D1 receptor agonist. The selective agonism of Fenoldopam results in renal vasodilation and inhibition of the tubular sodium reabsorption of the kidney. The intravenous admission of Fenoldopam in healthy patients and patients with arterial hypertension leads to an increase in renal blood flow and a decrease in vascular resistance due to its selective renal vasodilation (157). A small prospective, randomized double-blind and placebo-controlled trial with 80 patients observed that patients in the Fenoldopam group showed a decreased incidence of CSA-AKI compared to patients in the placebo group (158). But these findings could not be confirmed in a bigger randomized double-blind and placebo-controlled study with 667 patients conducted by Bove et al. (159). Furthermore, the study had to be cancelled due to an increased incidence of hypotension in the Fenoldopam group.

1.6.4 Mannitol

Mannitol is an osmotically active substance that is used in the priming liquid of the cardiopulmonary bypass system to reduce the probability of postoperative renal dysfunctions. Two randomized-controlled studies tried to show a renoprotective effect of Mannitol in the

priming fluid by comparing it to Hartman´s solution in the pump prime (160,161). One of the studies was conducted by Smith et al. (160) and compared the effect of Mannitol and Hartman´s solution in patients with preoperatively impaired kidney function. The other clinical trial conducted by Yallop et al. (161) examined the renoprotective effect of Mannitol in patients with normal kidney function. Ultimately, both studies were not able to show any differences in renal function, urine output or microalbuminuria between the two study populations. Another prospective trial analyzed the effect of the postoperative use of mannitol in high-risk patients with clinically manifest CSA-AKI (162). The treatment with mannitol induced renal vasodilation and increased renal blood flow in the study population. Despite that, mannitol did not affect the filtration fraction of the kidney or renal oxygenation compared to previous control measurements (162). Based on the available data, the use of mannitol in the priming fluid of cardiosurgical patients cannot be currently recommended.

1.6.5 KDIGO-based approach to high-risk patients

A recent randomized-controlled trial conducted by Meersch et al. (163) examined the effect of implementing the KDIGO guidelines to reduce the incidence of CSA-AKI in high-risk patients undergoing cardiac surgery. High-risk patients were identified by postoperative measurement of the product of urinary TIMP-2 and IGFBP7. The implemented "KDIGO bundle of care" consists of close monitoring of postoperative serum creatinine and urine output, optimization of volume status and hemodynamics, avoidance of nephrotoxic drugs, discontinuation of ACE inhibitors and strict normalization of blood glucose levels (27). High-risk patients who were treated by the "KDIGO bundle of care" showed a significant decrease in postoperative CSA-AKI compared to high-risk patients receiving the standard postoperative care of the respective center (163). Furthermore, implementation of KDIGO guidelines reduced the severity of CSA-AKI in high-risk patients. No differences could be shown between the two study populations for the postoperative need for renal replacement therapy and length of hospitalization (163). The underlying mechanisms of the reduction in frequency and severity of CSA-AKI may include a decrease in oxidative stress and inflammation as well as an improvement of renal blood flow and oxygenation. Given these promising results, further studies need to be conducted to evaluate the impact of the implementation of KDIGO guidelines on long-term morbidity and mortality.

2 Materials and methods

2.1 Study design

This was a single-center prospective observational study with an enrollment spanning over two periods: from September 2014 to October 2014, and from April 2015 to July 2015. The study was conducted at the department of cardiac surgery at Charité university medicine Berlin, Campus Mitte. Ethical approval was obtained from the Charité Ethics Commission, and all patients provided written informed consent prior to any data collection. The study aimed at identifying risk factors for AKI and long-term outcome after planned cardiac surgery when the KDIGO criteria are being used. The primary endpoint of this study was all-cause mortality after completed surgery. At the day of admission to hospital, patients were screened for in- and exclusion criteria. If patients met all inclusion criteria and no exclusion criterion, the trial physician explained the procedure and possible risks of the study. Preoperative serum creatinine was determined through venous blood collection. Postoperatively, we evaluated if patients developed a CSA-AKI within 7 days. After 3 years post-intervention we then reviewed the survival status of all study patients.

2.2 Inclusion criteria

Inclusion criteria were:

- 18 years or older
- elective operation
- no need for permanent renal replacement therapy
- informed written consent

2.3 Exclusion criteria

Exclusion criteria were:

- not at least 18 years old
- emergency operation
- need for permanent renal replacement therapy
- denied consent
- operation on aorta

2.4 Patients

During the two enrollment periods 146 patients were operated on in the department of cardiac surgery at Charité University Medicine Berlin, Campus Mitte. 120 of these patients met all inclusion criteria and no exclusion criteria, and were included in our study. One patient was excluded as surgery was cancelled. The most frequent types of surgery performed were CABG operations, operations on heart valves, and combinations of CABG operations and operations on heart valves. Furthermore, all patients were categorized into 4 subgroups according to their preoperative estimated glomerular filtration rate (eGFR):

1. eGFR > 90 ml/min
2. eGFR 60 - 90 ml/min
3. eGFR 59 - 30 ml/min
4. eGFR < 30 ml/min

Postoperatively, patients were screened for CSA-AKI and categorized according to the severity level of AKI.

2.5 Data collection

Patients were screened and interviewed at time of admission to the hospital. The collected information included age, sex, prior medical history, cardiac risk factors, operative details and symptom status, including the NYHA functional class and the European system for cardiac operative risk evaluation II (EuroSCORE II) (164), which was calculated for each patient in accordance with published guidelines using a dedicated calculator. Data for this calculator was collected from previous physician´s letters and the electronic SAP file system of the Charité University Medicine Berlin. Serum creatinine levels were determined preoperatively by venous blood collection, and the Chronic Kidney Disease Epidemiology Collaboration (CKDepi) formula served for calculation of the individual eGFR (165). Perioperative data such as cardiopulmonary bypass (CPB) time and aortic clamp time were collected from operation and anesthesia reports. Missing data was retrieved from perfusionists' documentation reports. In the first 24 h after admission to the ICU the worst Acute Physiology and Chronic Health Evaluation II (APACHE II) (166), Simplified Acute Physiology Score II (SAPS II) (167) and Sepsis-related Organ Failure Assessment (SOFA) (168) were calculated and recorded. During the patient´s ICU and hospital stay, serum creatinine levels were determined at least once per day. Patient urine output was measured

hourly. Additionally, length of ICU stay, time on mechanical ventilation and, if applicable, the need for renal replacement therapy were recorded.

2.6 EuroSCORE II

EuroSCORE II is a commonly used tool for preoperative risk stratification in patients undergoing cardiac surgery. It estimates the in-hospital mortality and the probability to die within the first 30 and 90 days following cardiac surgery. EuroSCORE II is a further development of the EuroSCORE (169) established in 1999, which turned out to overestimate mortality. We opted for the EuroSCORE II official calculator which is freely accessible on the Internet (170).

The following variables were entered into the stated calculator:

- age (years)
- gender
- preoperative eGFR
- extracardiac arteriopathy
- poor mobility
- previous cardiac surgery
- chronic lung disease
- active endocarditis
- critical preoperative state
- diabetes on insulin
- NYHA symptom classification
- CCS class angina pectoris
- function of left ventricle
- recent myocardial infarction (within the last 90 days)
- pulmonary hypertension
- urgency of the operation
- weight of the intervention
- surgery on thoracic aorta

2.7 Calculation of eGFR using the CKD-epi formula

For the calculation of the eGFR the CKD-epi formula was used:

$$eGFR = 141 \cdot \min\left(S_{Cr/\kappa}, 1\right)^{\alpha} \cdot \max\left(S_{Cr/\kappa}, 1\right)^{1.209} \cdot 0.993^{age} \cdot 1.018\ [\text{if female}] \cdot 1.159\ [\text{if black}]$$

Symbols:

- S_{Cr} (standardized serum creatinine) = mg/dl
- κ = 0.7 (females) or 0.9 (males)
- α = -0.329 (females) or -0.411 (males)
- min = indicates the minimum of S_{Cr}/κ or 1
- max = indicates the maximum of S_{Cr}/κ or 1
- age = years

2.8 Definition of AKI

For the definition of AKI, we used the Kidney Disease: Improving Global Outcome (KDIGO) guidelines that were published in 2012 (27). The KDIGO guidelines are the international standard for diagnosing AKI and may be regarded as a further development of the RIFLE criteria and the AKIN criteria (22,23). The KDIGO criteria use changes in baseline serum creatinine and reduction in urine output over a certain period of time to diagnose and categorize AKI. An AKI is defined by an increase in serum creatinine of at least 0.3 mg/dl within 48 hours, or an increase of at least 50% compared to baseline creatinine within 7 days, or an urine output of less than 0.5 ml/kg/h over a period of at least 6 hours. In addition, AKI can be divided into 3 different severity levels according to the increase in baseline serum creatinine and the amount of reduction in urine output (Table 2).

Table 2 KDIGO criteria for diagnosing and categorizing AKI

Stage	Serum creatinine	Urine output
1	increase of more than or equal to 150% to 200% in baseline serum creatinine within 7 days OR increase in baseline serum creatinine of at least 0.3 mg/dl within 48 hours	less than 0.5 ml/kg/h in urine output for at least 6 to 12 hours
2	increase in baseline serum creatinine of more than 200% to 300% within 7 days	less than 0.5 ml/kg/h in urine output for more than 12 hours
3	increase in baseline serum creatinine to more than 300% within 7 days OR	less than 0.3 ml/kg/h in urine output for at least 24 hours OR

	increase in serum creatinine to at least 4.0 mg/dl OR need for renal replacement therapy	anuria for more than 12 hours

Seven days after the intervention we divided patients into non-AKI (AKIN 0) and three AKI classes according to the KDIGO criteria (AKIN 1-3). AKI class was determined by changes in serum creatinine from baseline and urine output measurements recorded every hour during the patient´s stay. For the calculation of the AKI class we used elevations relative to the baseline serum creatinine level. We compared the lowest serum creatinine during hospitalization with the highest serum creatinine rise and calculated the creatinine δ accordingly. If oliguria lasted for more than 6, 12, or 24 hours during the stay, the corresponding severity level of AKI was recorded for each patient. Furthermore, we analyzed if there was a need for renal replacement therapy during hospitalization. The most severe AKI class was recorded for each patient.

AKIN 0 = no AKI

AKIN 1 = stage 1 AKI

AKIN 2 = stage 2 AKI

AKIN 3 = stage 3 AKI

2.9 Patient survival

In this study every patient was classified according to their survival status. Patients who died during their stay in the hospital were identified through research of the electronic SAP file system of the Charité University Medicine Berlin. Survival of all other patients was assessed via telephone survey by reaching out to patients, family members and primary attending physicians, as appropriate. The primary outcome of this analysis was all-cause mortality within three years after completed surgery. Patients who died were classified “dead” and the exact date of death was recorded. Patients who were alive at the time of the telephone survey were classified “alive” at the date of the telephone survey. Patients who did not meet the criteria for primary outcome were censored on the date of last contact with family members or attending physicians.

2.10 Statistical analysis

For the statistical analysis we used SPSS 25.0 software (IBM Corp, Armonk, NY, USA).

A double-sided p-value (probability value) less than 0.05 was considered statistically significant for all tests. All p-values were rounded to three decimal places.

The Shapiro-Wilk test and distribution plots were used to test continuous variables for normality of distribution. For continuous data that met criteria for normality of distribution, results are shown as mean with standard deviation (SD). Additionally, the student's t-test was used for group comparisons. For continuous data that did not meet criteria for normal assumption, results are shown as median with interquartile range (IQR). The Mann-Whitney U test was used to evaluate the independence of group levels. The Pearson chi-squared test or Fisher´s exact test were applied as appropriate for categorical variables.

Survival probabilities were estimated with the product-limit method (Kaplan-Meier algorithm). Differences in survival between groups were analyzed using the log-rank test. Also, Kaplan-Meier survival curves were plotted for the survival analysis of all patients, non-AKI vs. AKI, stratified by KDIGO classification and stratified by preoperative eGFR. The appropriate mortality rates were calculated for 30 days as well as for 1, 2 and 3 years of follow-up. Furthermore, survival models were initiated from the time of admission to the ICU until the event of death or last follow-up. AKIN 2 and AKIN 3 were combined for a clearer overview.

We first selected potential predictors through univariate analysis. Hazard ratios were generated by using logistic regression for risk of developing AKI and the Cox proportional hazards model for patient survival. The following multivariate analysis was used to adjust for factors independently associated with risk of developing AKI and patients' survival. This included backward elimination, forward selection and the enter method. For each approach, the same variables were used. The number of covariates was restricted to 1 per 8 dependent endpoints (171).

The multivariate logistic regression analysis was adjusted for:

- age
- diabetes mellitus
- eGFR at admission
- NYHA III/IV
- preoperative use of diuretics

The multivariate Cox regression analysis included:

- AKI

- EuroSCORE II

The mentioned factors were chosen a priori, based on literature on patients undergoing cardiac surgery, our clinical experience with AKI in these patients and the results of the univariate analysis.

3 Results

3.1 Total study population

3.1.1 Preoperative data

During the two study enrollment periods, from September 2014 to October 2014 and from April 2015 to July 2015, a total of 119 patients was included in this study. The median age of the study population was 69.4 years (61.9 – 75.5) and 72.3 % (n=86) of patients were male. Preoperative comorbidities included arterial hypertension (81.5 %), diabetes mellitus (26.1 %), coronary artery disease (72.8 %), extracardiac arteriopathy (22.7 %), previous myocardial infarction (MI) (23.5 %) and NYHA symptom classification III/IV (26.1 %). Chronic medication included ACE inhibitors (79.8 %), beta blockers (81.5 %) and diuretics (43.7 %). The median serum creatinine at admission was 0.99 mg/dl (0.82 – 1.24) and the mean eGFR was 71.04 ml/min/1.73m^2 (±22.34). The majority of patients (74 %) had an eGFR higher than 60 ml/min/1.73m^2. Only 8 patients (6.7 %) had a preoperative eGFR lower than 30 ml/min/1.73m^2. Furthermore, 36.1 % (n=43) were active smokers at the time of intervention and the median EuroSCORE II was 1.81 (1.02 – 3.31).

Table 3 Preoperative data

Characteristics	**Patients (n=119)**
Age – y, median (IQR)	69.4 (61.9 – 75.5)
Male – n. (%)	86 (72.3 %)
Hypertension – n. (%)	97 (81.5 %)
Diabetes mellitus – n. (%)	31 (26.1 %)
Coronary artery disease – n. (%)	86 (72,3 %)
Extracardiac arteriopathy – n. (%)	27 (22.7 %)
Previous MI – n. (%)	28 (23.5 %)
NYHA III/IV – n. (%)	31 (26.1 %)
ACE inhibitors – n. (%)	95 (79.8 %)
Beta blockers – n. (%)	97 (81.5 %)
Diuretics – n. (%)	52 (43.7 %)
Current smoker – n. (%)	43 (36.1 %)

eGFR at admission – ml/min, mean (SD)	71.04 (±22.34)
eGFR > 90 ml/min – n. (%)	22 (18.5 %)
eGFR 60-90 ml/min – n. (%)	66 (55.5 %)
eGFR 30-59 ml/min – n. (%)	23 (19.3 %)
eGFR < 30 ml/min – n. (%)	8 (6.7 %)
Creatinine at admission – mg/dl, median (IQR)	0.99 (0.82 - 1.24)
EuroSCORE II, median (IQR)	1.81 (1.02 - 3.31)

3.1.2 Surgical data

CABG surgery was the most frequent intervention in this study, with 65 (54.6 %) performed with a cardiopulmonary bypass system (on-pump) and 7 (5.9 %) without (off-pump). Heart valve surgery was performed 35 (29.4 %) times. 8.4 % (n=10) were operations combining CABG and heart valve surgery (CABG + Valve). The median cardiopulmonary bypass time was 79 minutes (60 – 104) and the median aortic clamp time was 52 minutes (32 – 73).

Table 4 Surgical data

Characteristics	**Patients (n=119)**
Type of surgery – n. (%)	
On-pump CABG	65 (54.6 %)
Off-pump CABG	7 (5.9 %)
Valve	35 (29.4 %)
CABG + Valve	10 (8.4 %)
Other	2 (1.7 %)
Coronary artery bypass time – min, median (IQR)	79.0 (60.0 – 104.0)
Aortic clamp time – min, median (IQR)	52.0 (32.0 – 73.0)

3.1.3 Postoperative data

The median mechanical ventilation time of patients was 9 hours (6 – 13). Patients stayed in the ICU for a median of 2 days (1 – 4). The mean ICU risk scores were 19.87 (±7.04) for APACHE II, 42.35 (±15.21) for SAPS II and 6.51 (±2.93) for SOFA score.

Table 5 Postoperative data

Characteristics	Patients (n=119)
Mechanical ventilation – h, median (IQR)	9 (6 – 13)
Length of stay in ICU – d, median (IQR)	2 (1 – 4)
APACHE II, mean (SD)	19.87 (±7.04)
SAPS II, mean (SD)	42.35 (±15.21)
SOFA, mean (SD)	6.51 (±2.93)

3.2 Study population and CSA-AKI

During their hospital stay, 63.9 % (n=76) did not meet the AKI definition, whereas the remaining 36.1 % (n=43) developed CSA-AKI as defined by the KDIGO criteria. AKI subgroups were as follows: 72.1 % (n=31) developed AKIN 1, 7.0 % (n=3) developed AKIN 2 and 20.9% (n=9) developed AKIN-3. Additionally, 5.9 % (n=7) of patients required renal replacement therapy during their stay in the ICU.

Table 6 CSA-AKI groups as defined by KDIGO

	Patients (n=119)	Patients with CSA-AKI (n=43)
all AKI groups – n (%)	43 (36.1 %)	43 (100 %)
AKIN 1	31 (26.1 %)	31 (72.1 %)
AKIN 2	3 (2.5 %)	3 (7.0 %)
AKIN 3	9 (7.6 %)	9 (20.9 %)
Dialysis	*7 (5.9 %)*	*7 (16.3 %)*

3.2.1 Preoperative data and CSA-AKI

Patients with CSA-AKI were significantly older than patients without CSA-AKI (72.9 years (64.5 – 77.8) vs. 68.2 years (60.2 – 73.5); p=0.023). Furthermore, patients who developed a CSA-AKI were more likely to suffer from comorbidities such as diabetes mellitus (39.5 % vs. 19.4 %; p=0.017), NYHA III/IV (39.5 % vs. 18.4 %; p=0.017) and a previous myocardial infarction (37.2 % vs. 15.8 %; p=0.013). No differences between the two groups were found for arterial hypertension, coronary artery disease and extracardiac arteriopathy. The preoperative use of diuretics was more frequent in the CSA-AKI group (67.4 % vs. 30.3 %; p<0.001). Concerning the preoperative use of ACE inhibitors and beta blockers, we could not find a significant difference between the two study populations. In addition, patients with

CSA-AKI were more likely to have a higher serum creatinine at admission (1.09 mg/dl (0.90 – 1.62) vs. 0.91 mg/dl (0.77 – 1.09); p<0.001) as well as a lower preoperative eGFR (59.63 ml/min/1.73m^2 (±24,73) vs. 77.40 ml/min/1.73m^2 (±18.06); p<0.001).

Furthermore, the median EuroSCORE II occurred as significantly higher in the CSA-AKI group than in patients without CSA-AKI (2.95 (1.68 – 6.21) vs. 1.34 (0.90 – 2.14); p<0.001). We did not observe a difference regarding the number of active smokers between the two study groups.

Table 7 Preoperative data of patients without and with CSA-AKI

Characteristics	**Patients without CSA-AKI**	**Patients with CSA-AKI**	**p**
n. (%)	76 (63.9 %)	43 (36.1 %)	
Age – y, median (IQR)	68.2 (60.2 – 73.5)	72.9 (64.5 – 77.8)	0.023
Male – n. (%)	54 (71.1 %)	32 (74.4 %)	0.832
Hypertension – n. (%)	59 (77.6 %)	38 (88.4 %)	0.219
Diabetes mellitus – n. (%)	14 (18.4 %)	17 (39.5 %)	0.017
Coronary artery disease – n. (%)	52 (68.4 %)	34 (79.1 %)	0.287
Extracardiac arteriopathy – n. (%)	13 (17.1 %)	14 (32.6 %)	0.069
Previous MI – n. (%)	12 (15.8 %)	16 (37.2 %)	0.013
NYHA III/IV – n. (%)	14 (18.4 %)	17 (39.5 %)	0.017
ACE inhibitors – n. (%)	63 (82.9 %)	32 (74.4 %)	0.342
Beta blockers – n. (%)	60 (78.9 %)	37 (86.0 %)	0.462
Diuretics – n. (%)	23 (30.3 %)	29 (67.4 %)	<0.001
Smoking – n. (%)	24 (31.6 %)	19 (44.2 %)	0.233
eGFR at admission – ml/min, mean (SD)	77.40 (±18.06)	59.63 (±24.73)	<0.001
eGFR > 90 ml/min – n. (%)	18 (23.7 %)	4 (9.3 %)	
eGFR 60-90 ml/min – n. (%)	46 (60.5 %)	20 (46.5 %)	
eGFR 30-59 ml/min – n. (%)	11 (14.5 %)	12 (27.9 %)	
eGFR < 30 ml/min – n. (%)	1 (1.3 %)	7 (16.8 %)	
Creatinine at admission – mg/dl, median (IQR)	0.91 (0.77 – 1.09)	1.09 (0.90 – 1.62)	<0.001
EuroSCORE II, median (IQR)	1.34 (0.90 – 2.14)	2.95 (1.68 – 6.21)	<0.001

3.2.2 Surgical data and CSA-AKI

Patients with CSA-AKI and without CSA-AKI had no statistically significant difference in either the type of surgery, the cardiopulmonary bypass time (85 minutes (60 – 120) vs. 76 minutes (59.75 – 99.75); p=0.164), or the aortic clamp time (51 minutes (30 – 91) vs. 52 minutes (35.5 – 67.75); p=0.535).

Table 8 Surgical data of patients without and with CSA-AKI

Characteristics	Patients without CSA-AKI (n=76)	Patients with CSA-AKI (n=43)	p
Type of surgery – n. (%)			
On-pump CABG	44 (57.9 %)	21 (48.8 %)	0.444
Off-pump CABG	4 (5.3 %)	3 (7.0 %)	0.702
Valve	23 (30.3 %)	12 (27.9 %)	0.837
CABG + Valve	4 (5.3 %)	6 (14.0 %)	0.166
Other	1 (1.3 %)	1 (2.3 %)	0.681
Coronary artery bypass time – min, median (IQR)	76.0 (59.75 – 99.75)	85.0 (60.0 – 120.0)	0.164
Aortic clamp time – min, median (IQR)	52.0 (35.5 – 67.75)	51.0 (30.0 – 91.0)	0.535

3.2.3 Postoperative data and CSA-AKI

We observed statistically significant differences regarding the time of mechanical ventilation and the length of stay in the ICU between the two study groups. Patients with CSA-AKI were more likely to be mechanically ventilated for a longer period of time (13 hours (9 – 24) vs. 9 hours (6 – 11); p<0.001) and were more likely to have a longer stay in the ICU than patients without CSA-AKI (4 days (2 – 7) vs. 1 day (1 – 2); p<0.001). Regarding ICU risk scores, statistically significant differences were found for the APACHE II score (21.88 (±7.32) vs. 18.74 (±6.72); p=0.019) and the SOFA score (7.33 (±3.23) vs. 6.05 (±2.60); p=0.022). We did not observe a difference in the level of the SAPS II score between the two study groups.

Table 9 Postoperative data in patients without and with CSA-AKI

Characteristics	Patients without CSA-AKI (n=76)	Patients with CSA-AKI (n=43)	p
Mechanical ventilation – h, median (IQR)	7 (6 – 11)	13 (9 – 24)	<0.001
Length of stay in ICU – d, median (IQR)	1 (1 – 2)	4 (2 – 7)	<0.001
APACHE II, mean (SD)	18.74 (±6.72)	21.88 (±7.32)	0.019

SAPS II, mean (SD)	40.39 (±15.18)	45.81 (±14.82)	0.062
SOFA, mean (SD)	6.05 (±2.60)	7.33 (±3.23)	0.022

3.3 Predictors for developing CSA-AKI

3.3.1 Predictors in univariate logistic regression analysis

In the univariate logistic regression analysis, older age was a predictor for the development of CSA-AKI (HR: 1.58; 95% CI: 1.03 – 2.40; p=0.035). Conversely, gender was no predictor for CSA-AKI. Comorbidities predictive of CSA-AKI were diabetes mellitus (HR: 2.90; 95% CI: 1.25 – 6.73; p=0.013), a previous MI (HR: 3.61; 95% CI: 1.32 – 7.57; p=0.010) and NYHA III/IV (HR: 2.90; 95% CI: 1.25 – 6.73; p=0.013). Arterial hypertension, coronary artery disease, extracardiac arteriopathy and smoking did not increase the relative risk for developing CSA-AKI. In terms of chronic medication, the preoperative use of diuretics is a predictor for CSA-AKI in the univariate analysis (HR: 4.77; 95% CI: 2.14 – 10.67; p<0.001), whereas the preoperative use of ACE inhibitors and beta blockers did not increase the relative risk for CSA-AKI. Statistically significant predictive scoring systems for the development of CSA-AKI were the EuroSCORE II (HR: 1.63; 95% CI: 1.28 – 2.07; p<0.001), the APACHE II score (HR: 1.39; 95% CI: 1.05 – 1.84; p=0.021) and the SOFA score (HR: 1.17; 95% CI: 1.02 – 1.34; p=0.025). In contrast, a higher eGFR at admission was associated with a lower relative risk of developing CSA-AKI (HR: 0.68; 95% CI: 0.55 – 0.82; p<0.001). Surgical parameters like aortic clamp time and cardiopulmonary bypass time did not reach statistical significance in our study. Postoperative predictors for CSA-AKI were the mechanical ventilation time (HR: 1.20; 95% CI: 1.10 – 1.30; p<0.001) and the length of ICU stay (HR: 1.29; 95% CI: 1.11 – 1.51; p=0.001).

Table 10 Predictors for CSA-AKI in univariate logistic regression analysis

Predictor	**Univariate analysis**	
	HR (95% CI)	**p**
Age per 10 years	1.58 (1.03 – 2.40)	0.035
Male sex	1.19 (0.51 – 2.76)	0.694
Coexisting medical conditions		
Hypertension	2.19 (0.75 – 6.43)	0.154
Diabetes mellitus	2.90 (1.25 – 6.73)	0.013
Coronary artery disease	1.74 (0.72 – 4.20)	0.215
Extracardiac arteriopathy	2.34 (0.98 – 5.61)	0.057

Previous MI	3.61 (1.32 – 7.57)	0.010
NYHA III/IV	2.90 (1.25 – 6.73)	0.013
Medication		
ACE inhibitors	0.60 (0.24 – 1.49)	0.271
Beta blockers	1.64 (0.59 – 4.58)	0.341
Diuretics	4.77 (2.14 – 10.67)	<0.001
Smoking	1.72 (0.79 – 3.71)	0.171
eGFR at admission per 10 ml/min	0.68 (0.55 – 0.82)	<0.001
EuroSCORE II per 1 point	1.63 (1.28 – 2.07)	<0.001
Surgical data		
Coronary artery bypass time per h	1.66 (0.98 – 2.82)	0.059
Aortic clamp time per h	1.46 (0.76 – 2.80)	0.254
Postoperative data		
Mechanical ventilation per h	1.20 (1.10 – 1.30)	<0.001
Length of ICU stay per d	1.29 (1.11 – 1.51)	0.001
APACHE II per 5 points	1.39 (1.05 – 1.84)	0.021
SAPS II per 10 points	1.27 (0.99 – 1.63)	0.063
SOFA per 1 point	1.17 (1.02 – 1.34)	0.025

3.3.2 Predictors in multivariate logistic regression analysis

After adjustment for age, diabetes mellitus, eGFR at admission, the preoperative use of diuretics and NYHA III/IV, the multivariate analysis suggested that the eGFR at admission (HR: 0.77; 95% CI: 0.61 – 0.95; p=0.016), diabetes mellitus (HR: 2.74; 95% CI: 1.01 – 7.46; p=0.048) and the preoperative use of diuretics (HR: 3.71; 95% CI: 1.50 – 9.20; p=0.005) were independently associated with the development of CSA-AKI. Age and NYHA III/IV, on the other hand, were not independently associated with the development of CSA-AKI.

Table 11 Predictors for CSA-AKI in multivariate logistic regression analysis

Predictor	Multivariate analysis	
	HR (95% CI)	p
Age per 10 years	1.17 (0.70 – 1.95)	0.552
Diabetes mellitus	2.74 (1.01 – 7.46)	0.048
NYHA III/IV	1.34 (0.49 – 3.68)	0.574
eGFR at admission per 10 ml/min	0.77 (0.61 – 0.95)	0.016
Diuretics	3.71 (1.50 – 9.20)	0.005

3.4 Predictors for patient mortality

3.4.1 Predictors in univariate Cox proportional hazards model

The univariate Cox proportional hazards model showed that older age is a predictor for patient all-cause mortality (HR: 1.66; 95% CI: 1.01 – 2.73; p=0.045). Comorbidities predictive of patient all-cause mortality were diabetes mellitus (HR: 2.35; 95% CI: 1.07 – 5.19); p=0.034), extracardiac arteriopathy (HR: 2.95; 95% CI: 1.34 – 6.50; p=0.007), a previous MI (HR: 2.82; 95% CI: 1.28 – 6.21; p=0.010) and NYHA III/IV (HR: 3.47; 95% CI: 1.58 – 7.60; p=0.002). Other preoperative factors like gender, arterial hypertension, coronary artery disease and smoking did not predict all-cause mortality in this study. Neither did the preoperative use of ACE inhibitors, beta blockers or diuretics. Another statistically significant predictor for patient mortality was the preoperatively assessed EuroSCORE II (HR: 1.22; 95% CI: 1.13 – 1.31; p<0.001). A higher eGFR at admission, on the other hand, was associated with a lower relative risk of dying (HR: 0.70; 95% CI: 0.59 – 0.83; p<0.001). Surgical predictors like aortic clamp time and cardiopulmonary bypass time did not reach statistical significance in this study. Overall, postoperative predictors for patients' death were a longer mechanical ventilation time (HR: 1.01; 95% CI: 1.00 – 1.02; p<0.001), length of ICU stay (HR: 1.04; 95% CI: 1.04 – 1.06; p=0.001), a higher APACHE II score (HR: 1.50; 95% CI: 1.12 – 2.03; p=0.007) and a higher SAPS II score (HR: 1.31; 95% CI: 1.01 – 1.69; p=0.039). Most importantly, the development of CSA-AKI was a strong predictor for patients' all-cause mortality in the univariate Cox regression analysis (HR: 17.99; 95% CI: 5.37 – 60.28; p=0.001) as well as the postoperative need for renal replacement therapy (HR: 4.19; 95% CI: 1.43 – 12.27; p=0.009). The generated hazard ratios for the different severity levels of AKI according to the KDIGO criteria were as follows: 17.30 (95% CI: 5.03 – 59.52; p<0.001) for AKIN 1, 10.93 (95% CI: 1.14 – 105.16; p<0.038) for AKIN 2 and 24.50 (95% CI: 5.81 – 103.25; p<0.001) for AKIN 3.

Table 12 Predictors for patient mortality in univariate Cox proportional hazards model

Predictor	Univariate analysis	
	HR (95% CI)	**p**
Age per 10 years	1.66 (1.01 – 2.73)	0.045
Male sex	1.26 (0.51 – 3.17)	0.617
Coexisting medical conditions		
Hypertension	0.79 (0.30 – 2.10)	0.632
Diabetes mellitus	2.35 (1.07 – 5.19)	0.034
Coronary artery disease	1.20 (0.48 – 3.00)	0.697
Extracardiac arteriopathy	2.95 (1.34 – 6.50)	0.007
Previous MI	2.82 (1.28 – 6.21)	0.010
NYHA III/IV	3.47 (1.58 – 7.60)	0.002
Medication		
ACE inhibitors	0.70 (0.28 – 1.76)	0.449
Beta blockers	0.64 (0.26 – 1.61)	0.343
Diuretics	2.20 (0.99 – 4.90)	0.054
Smoking	1.20 (0.54 – 2.68)	0.653
eGFR at admission per 10 ml/min	0.70 (0.59 – 0.83)	<0.001
EuroSCORE II per 1 point	1.22 (1.13 – 1.31)	<0.001
Surgical data		
Coronary artery bypass time per h	1.54 (0.97 – 2.44)	0.065
Aortic clamp time per h	1.08 (0.53 – 2.20)	0.844
Postoperative data		
Mechanical ventilation per h	1.01 (1.00 – 1.02)	0.010
Length of ICU stay per d	1.04 (1.02 – 1.06)	<0.001
APACHE II per 5 points	1.50 (1.12 – 2.03)	0.007
SAPS II per 10 points	1.31 (1.01 – 1.69)	0.039
SOFA per 1 point	1.14 (1.00 – 1.29)	0.054
AKI (AKIN 1-3)	17.99 (5.37 – 60.28)	0.001
AKIN 1	17.30 (5.03 – 59.52)	<0.001
AKIN 2	10.93 (1.14 – 105.16)	0.038
AKIN 3	24.50 (5.81 – 103.25)	<0.001
Dialysis	*4.19 (1.43 – 12.27)*	*0.009*

3.4.2 Predictors in multivariate Cox proportional hazards model

After adjustment for EuroSCORE II and AKI (AKIN 1 to AKIN 3) the multivariate Cox-Regression analysis indicated that EuroSCORE II (HR: 1.11; 95% CI: 1.01 – 1.21; p=0.024) as well as AKI (HR: 13.58; 95% CI: 3.89 – 47.41; p<0.001) remain independent predictors for patients' risk of death during the first 3 years after the intervention.

Table 13 Predictors for patient mortality in multivariate Cox proportional hazards model

Predictor	Multivariate analysis	
	HR (95% CI)	p
EuroSCORE II	1.11 (1.01 – 1.21)	0.024
AKI (AKIN 1-3)	13.58 (3.89 – 47.41)	<0.001

3.5 Survival analysis

24 patients in the study population died and 3 patients (2.5%) were censored due to loss of follow-up during the observational period. The median follow-up was 3.27 years (3.13 – 3.37). 30-day mortality of the whole study population was 2.5% (n=3). Overall 1-year mortality, 2-year mortality and 3-year mortality of our study population were 10.2% (n=12), 17% (n=20) and 20.5% (n=24), respectively. Figure 1 shows the Kaplan-Meier survival curve for the whole study population.

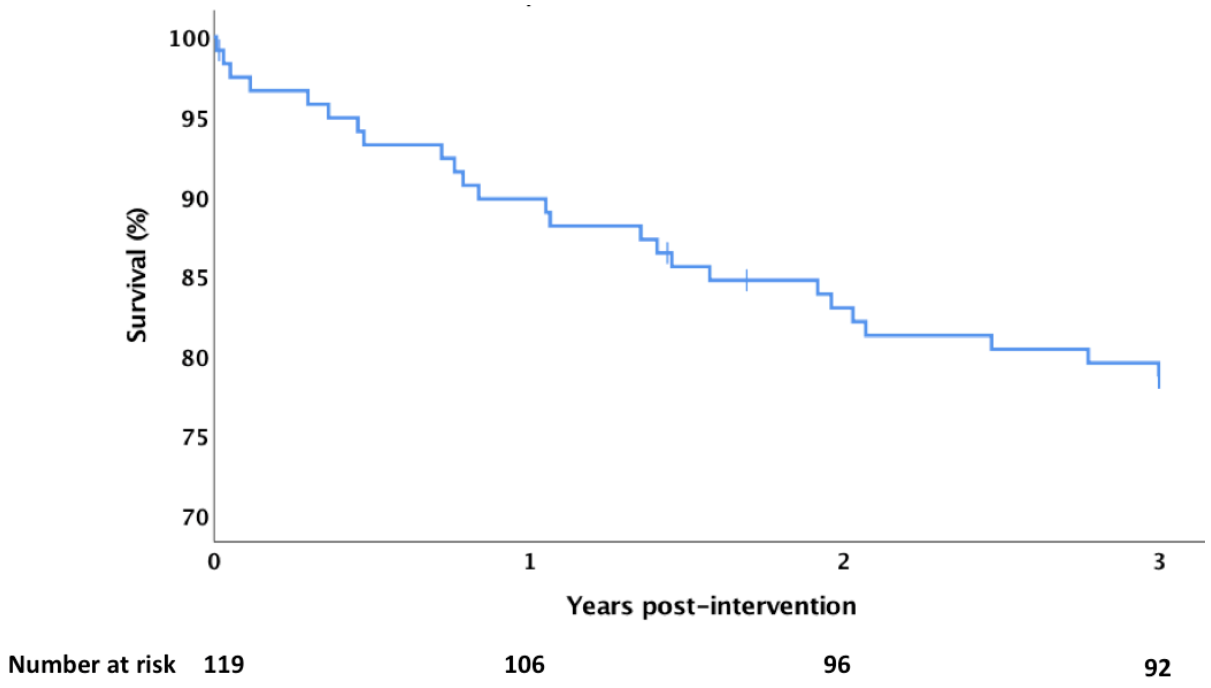


Figure 1. Estimated survival for all patients using a Kaplan-Meier algorithm.

30-day mortality was 0% for patients without CSA-AKI and 7% for patients with CSA-AKI. The Kaplan-Meier plots indicated that patients with CSA-AKI have a worse long-term outcome over the follow-up period (p<0.001). The proportion of survivors among patients with CSA-AKI was 72.1% at 1 year and 50.6% at 3 years, whereas the proportion of survivors among patients without CSA-AKI was 100% at 1 year and 96% at 3 years (Figure 2).

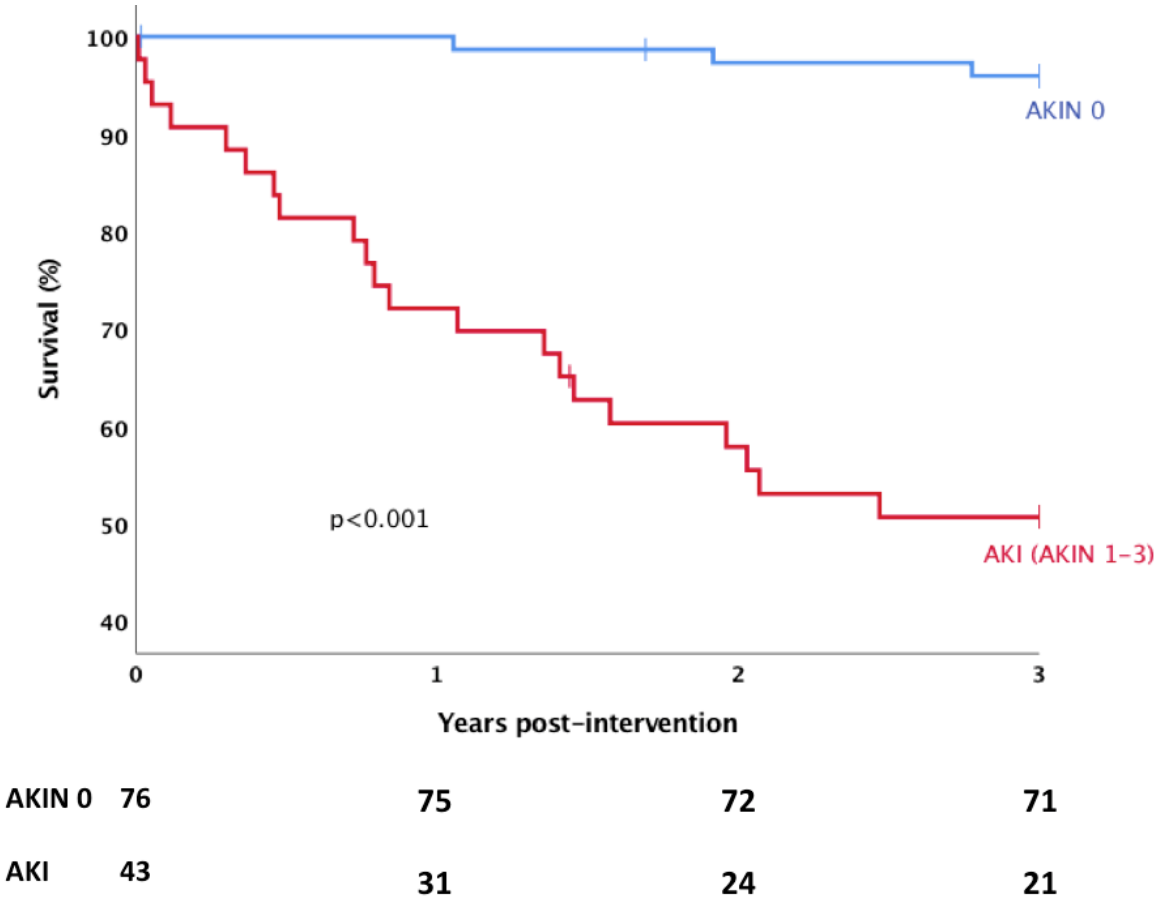
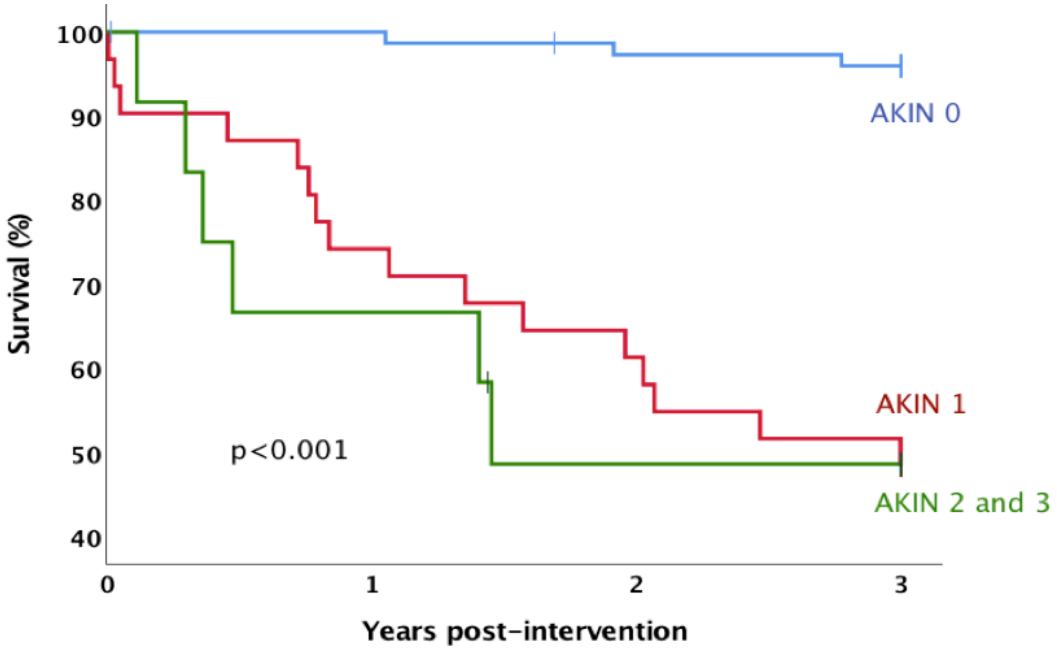


Figure 2. Estimated survival for AKIN 0 and AKI (AKIN 1-3) using a Kaplan-Meier algorithm**.**

30-day mortality for patients stratified by KDIGO classification was as follows: 6.5% (n=2) for AKIN 1, and 8.3% (n=1) for AKIN 2 and 3. 1-year mortality among patients with CSA-AKI according to KDIGO classification was 25.8% (n=8) for AKIN 1, and 33.3% (n=4) for AKIN 2 and 3. Furthermore, 2- and 3-year mortality were 39.7% (n=12) and 48.4% (n=15) in the AKIN 1 group as well as 51.4% (n=6) and 51.4% (n=6) in the AKIN 2 and 3 group, respectively. The log-rank test indicated that there was a statistically significant difference in survival between those groups (p<0.001).

All mortality rates for the different patient populations are shown in Table 14.

The median survival in the AKIN 2 and 3 group was 1.45 years. The median survival for the other groups could not be calculated because more than 50% of the patients were still alive at the end of the follow-up period. 1- and 3-year mortality for patients with need for renal replacement therapy during their ICU stay were 28.6% (n=2) and 57.1% (n=4), respectively.



AKIN 0	**76**	**75**	**72**	**71**
AKIN 1	**31**	**23**	**19**	**16**
AKIN 2 and 3	**12**	**8**	**5**	**5**

Figure 3. Estimated survival for AKIN 0, AKIN 1, AKIN 2 and 3 using a Kaplan-Meier algorithm**.**

Table 14 Estimated mortality for all patients, and for patients with and without CSA-AKI

Mortality	All patients	AKIN 0	AKI	AKIN 1	AKIN 2 and 3
30 days – % (n.)	2.5 % (3)	0 % (0)	7 % (3)	6.5 % (2)	8.3 % (1)
1 year – % (n.)	10.2 % (12)	0 % (0)	27.9 % (12)	25.8 % (8)	33.3 % (4)
2 years – % (n.)	17 % (20)	2.7 % (2)	42.1 % (18)	39.7 % (12)	51.4 % (6)
3 years – % (n.)	20.5 % (24)	4 % (3)	49.4 % (21)	48.4 % (15)	51.4 % (6)

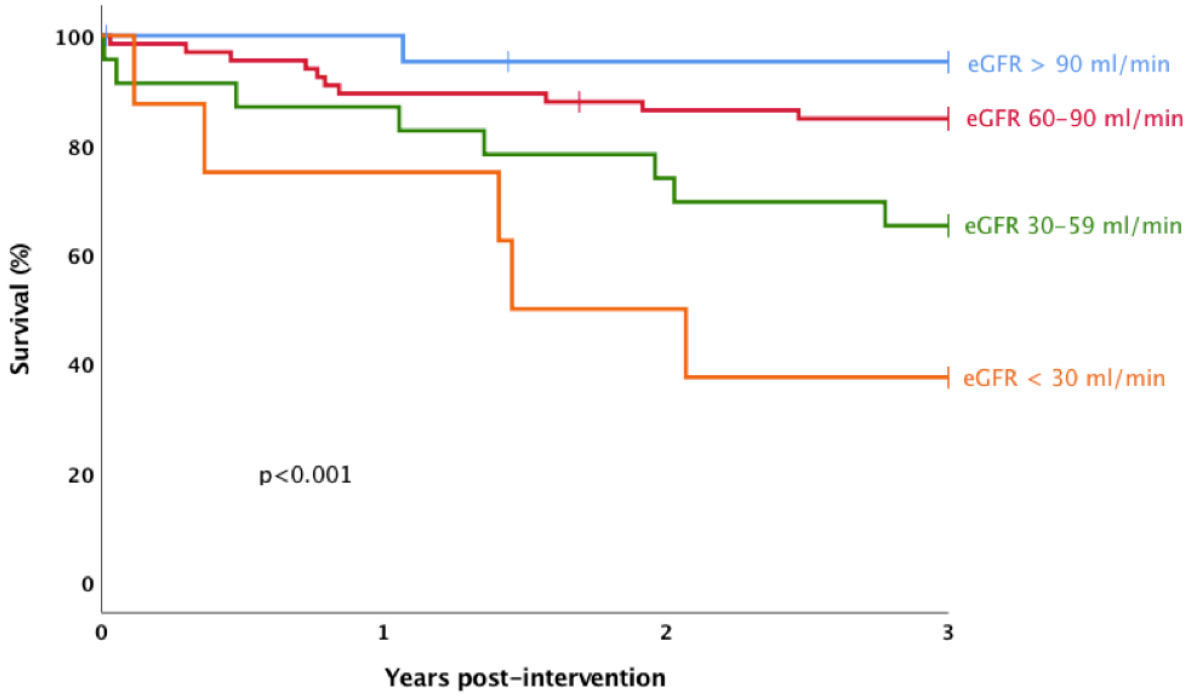


Figure 4. Estimated survival stratified by preoperative eGFR using a Kaplan-Meier algorithm**.**

Figure 4 shows patient survival stratified by preoperative kidney function. The Kaplan-Meier plot indicates that patients with a lower preoperative eGFR have a worse long-term outcome ($p<0.001$).

4 Discussion

4.1 Necessity of this study

Previous observational studies showed that CSA-AKI is an independent risk factor for increased morbidity and short-term as well as long-term mortality (3,6,7,9,11,12). Despite this knowledge, the incidence of CSA-AKI remained relatively high over the last few decades (3,6,33). Thus, it can be assumed that the identification of risk factors and the development of appropriate preventive measures do not show a sufficient effect. Therefore, the aim of this study was to reevaluate important risk factors for CSA-AKI and patient mortality. In addition, we wanted to identify patients at risk who require closer short-term and long-term follow-up, to reduce morbidity and mortality in these patients.

To date, only two long-term studies have made use of the complete KDIGO criteria to diagnose CSA-AKI (19,20).

4.2 Materials and methods

This study is a prospective single-center observational study. The fact that we gathered all our data prospectively is a major advantage of this study. There is no missing data since collection of data was not dependent on the documentation of people who were not involved in the study process. Therefore, all data can be trusted and the risk of bias is relatively low. However, only randomized-controlled clinical trials are able to prove causal connections between the appearances of different events during the study period. Therefore, our study can only suggest that there is an association between CSA-AKI and increased long-term mortality.

Prospective trials studying long-term mortality in patients with CSA-AKI normally include a small number of patients due to the long study period and the heavy workload compared to retrospective studies. Petäjä et al. (19), for example, conducted a small prospective study with 638 patients over a period of 2.5 years to identify risk factors for CSA-AKI and to evaluate the association between CSA-AKI and long-term mortality. A retrospective study conducted by Hobson et al. (6) was able to include almost 3,000 patients to study patient survival over a 10-year period. Due to the bigger study population, this retrospective study has a higher significance compared to our study. In contrast, due to the possibility of missing data, the risk of bias is significantly increased in retrospective observational studies.

With only 119 patients, our study population is quite small compared to other studies. In larger retrospective studies, the number of patients included can reach up to 33,000 (44). Due to our small study population, it is difficult to apply our findings to the general population. Nevertheless, our study population represents a good sample of patients undergoing cardiac surgery in our center because the majority of patients participated in this trial during the two study enrollment periods. Furthermore, patients with chronic kidney disease were included in this study, which could have led to a higher postoperative incidence of CSA-AKI due to the preoperatively impaired kidney function.

AKI was diagnosed using the complete KDIGO criteria, including rise in baseline serum creatinine and decrease in urine output over a certain period of time. Other studies using the KDIGO criteria for diagnosing CSA-AKI only used the rise in baseline serum creatinine, which could lead to underestimation of CSA-AKI (15). Before the KDIGO criteria were established in 2012, studies used RIFLE, AKIN or self-made criteria to diagnose CSA-AKI. The mentioned criteria are similar, but only the use of the complete KDIGO criteria allows the identification of all patients with clinically manifest CSA-AKI. This is why the comparison of the different results may be difficult.

4.3 Patients

Our patient collective was markedly older and more morbid than the average patient in other studies (19,20,58,172). The median age of the whole study population was 69 years and the median age of the CSA-AKI group was even 73 years. Our findings suggest an association between older age and the development of CSA-AKI. This finding is consistent with the results of many other observational trials studying patients undergoing cardiac surgery (4,5,44,45). 82% of all patients suffered from arterial hypertension and 72% from coronary artery disease. In addition, our study population has a higher proportion of patients with preoperative use of ACE inhibitors and Beta blockers (19,58,172). This observation can be explained by the higher percentage of patients with severe comorbidities. Our study population included only a small proportion of women. More than two thirds (72.3%) of the study population was male. Interestingly, other recent studies also pointed out that the majority of patients undergoing cardiac surgery are men (19). Our study suggests that there is no significant association between gender and CSA-AKI. Nonetheless, the data concerning this topic is controversial. Thakar et al. (44) developed the Cleveland Clinical Foundation scoring system to estimate the probability of CSA-AKI. This scoring system includes female gender as a risk factor for postoperative AKI. Another clinical predictive scoring system

developed by Palomba et al. (45), on the other hand, does not include female gender as an independent risk factor for CSA-AKI.

Furthermore, our findings would suggest that there is a statistically significant association between the development of CSA-AKI and diabetes mellitus, a previous MI, NYHA III/IV, the preoperative eGFR and the preoperative EuroSCORE II. The EuroSCORE II in this study was 1.34 in the AKIN 0 group and 2.95 in the AKI group. This risk stratification score was notably higher in other previous studies (27,166,168). A possible explanation could be that emergency operations and operations on the aorta were exclusion criteria in this study. The mentioned criteria lead to a significant increase in the final EuroSCORE II. Our study suggests that patients with CSA-AKI have a significantly higher EuroSCORE II than patients without CSA-AKI. The EuroSCORE II includes several comorbidities such as diabetes mellitus, extracardiac arteriopathy and NYHA classification as well as the preoperative eGFR. This strengthens the possible influence of the aforementioned comorbidities. According to the EuroSCORE II, the in-hospital mortality increases with the existence of those comorbidities and a lower preoperative eGFR. It can be assumed that patients with a higher EuroSCORE II are sicker and may have a worse preoperative kidney function. Therefore, those patients are more likely to develop CSA-AKI than patients with a lower EuroSCORE II. Recent studies observed a similar association between a higher EuroSCORE II and the development of CSA-AKI (27,166,168). Machado et al. (15) even suggest that a higher preoperative EuroSCORE II is associated with a more severe CSA-AKI.

There was no association between the different types of surgery and the development of CSA-AKI in our study. One reason might be the small study population; only 7 patients underwent off-pump operations and only 10 patients underwent an operation combining CABG and valve surgery. Therefore, it might be difficult to show differences between those groups and to reach statistical significance. A meta-analysis by Yi et al. (46) confirms our findings. The meta-analysis, consisting of 14 case-control studies, did not find an absolute association between the type of surgery and CSA-AKI. In contrast, Sirvinskas et al. (52) postulate that especially valve surgery and a combination of CABG and valve surgery are associated with CSA-AKI.

Cardiopulmonary bypass time was 9 minutes longer in the CSA-AKI group compared to the AKIN 0 group, but there was no statistically significant difference between our two study populations. Other studies suggest that a prolonged cardiopulmonary bypass time might be associated with a higher incidence of CSA-AKI (45,83,173). Boldt et al. (174) found that

patients with a cardiopulmonary bypass time greater than 90 minutes suffered more pronounced kidney damage than patients with a cardiopulmonary bypass time of less than 70 minutes. This finding could explain why there is no significance difference in cardiopulmonary bypass time between the AKIN 0 group and AKI group. Both groups have a median cardiopulmonary bypass time of less than 90 minutes and greater than 70 minutes.

Postoperative factors associated with CSA-AKI are the duration of mechanical ventilation, the length of ICU stay, APACHE II score and SOFA score. A study conducted by Ryckwaert et al. (175) also showed that a postoperative increase in serum creatinine is associated with a longer duration of mechanical ventilation and a longer ICU stay. It can be assumed that the duration of mechanical ventilation and the length of ICU stay can be complications of postoperative AKI as well as independent risk factors.

4.4 CSA-AKI

In this study, 36.1% of patients undergoing cardiac surgery developed CSA-AKI according to the complete KDIGO criteria. The current data demonstrates that AKI is a common problem in patients undergoing cardiac surgery. Our data complements previous findings on the incidence of AKI following cardiac surgery when the KDIGO criteria are being used. In a very recent study Howitt et al. (20) also found that 36.1% of cardiosurgical patients developed CSA-AKI when the KDIGO criteria are being used. Petäjä et al. (19) showed an incidence of 28.7% in their prospective observational study which had a similar study design compared to our study. However, there is some evidence that urine output is not a reliable indicator of AKI following cardiac surgery and may lead to overdiagnosis of CSA-AKI (33,176). Other observational studies using AKIN or RIFLE criteria to diagnose AKI found incidences that vary between 12% and 49% (6,7,10,12,33,172). One reason could be the use of different definitions to diagnose CSA-AKI. Englberger et al. (24) showed that the use of AKIN classification leads to a significantly higher incidence of CSA-AKI if serum creatinine is not corrected for fluid balance, when compared to the use of RIFLE classification. Another study conducted by Bastin et al. (18), on the other hand, could not show a significant difference in the incidence of CSA-AKI when AKIN, RIFLE or KDIGO criteria are being used.

Nevertheless, such big discrepancies cannot entirely be explained by the use of different definitions of CSA-AKI. Therefore, another reason may lie within the inhomogeneous study populations. Patient-related factors that increase the incidence of CSA-AKI in different studies may be the older age of the study population, more severe comorbidities, the inclusion

of patients with preoperatively impaired kidney function and the preoperative use of diuretics or ACE inhibitors. Several studies examining the incidence of CSA-AKI included only patients undergoing CABG surgery (7,12,38). Therefore, the observed incidences of CSA-AKI might be lower compared to studies including other types of cardiac surgery due to the lower risk of CSA-AKI in CABG patients (44,45). Incidences of CSA-AKI might be higher in studies including patients undergoing valve surgery, combined operations and operations on aorta (6,30,159). Other surgical factors that could lead to differing incidences may be the proportion of off-pump operations, the complexity of the performed operation, the inclusion of emergency operations and the cardiopulmonary bypass time (57,58). Furthermore, postoperative factors seem to play an important role as well, including the use of vasopressors, nephrotoxic agents and the occurrence of postoperative complications like hemodynamic instability or sepsis (2). In conclusion, incidences of CSA-AKI may differ greatly from hospital to hospital due to different definitions of CSA-AKI, different patient collectives, the performed procedure and differences in postoperative handling of cardiosurgical patients in the ICU.

Regarding our 43 patients with CSA-AKI, 72.1% developed AKIN 1, 7% developed AKIN 2 and 20.9% developed AKIN 3. The proportion of patients developing AKIN 1 corresponds with the findings of other studies using the KDIGO criteria to diagnose CSA-AKI (15,19,20). Petäjä et al. (19), in a prospective study using the complete KDIGO criteria to diagnose CSA-AKI, found that 65.6% of patients with AKI developed AKIN 1. Almost all studies, regardless of the system to diagnose CSA-AKI, show that more than 50% of patients with CSA-AKI develop a stage 1 AKI (6–8,15,19,20,33). A possible explanation is that patients easily meet the criteria for stage 1 AKI. The criteria for stage 2 and stage 3 may be met with more difficulty, so that these stages are therefore diagnosed less frequently. In this study, we identified a higher proportion of patients developing AKIN 3 than patients developing AKIN 2. One reason for this finding could be the small size of our study population. In our study, only 3 patients developed AKIN 2 and 9 patients developed AKIN 3. As a result, the real distribution of AKIN 2 and AKIN 3 could not be shown due to a lack of patients in those groups. These findings are inconsistent with the data of other observational studies. These studies suggest that the number of patients is smallest in the most severe AKI group, regardless of the classification system being used (6,10,17,19,20). Hobson et al. (6), in one of the first retrospective observational studies excluding patients with preexisting chronic kidney disease, showed that 22% of the patients had AKI stage 1, 13% had AKI stage 2 and 8% had

AKI stage 3. In our study, 26.1% of all patients developed AKIN 1. The higher incidence of AKIN 1 in our study might be explained by the inclusion of patients with preexisting chronic kidney disease. Dialysis-dependent renal failure normally occurs infrequently in patients undergoing cardiac surgery. Our findings suggest that 5.9% of all patients need acute renal replacement therapy after cardiac surgery. The need for acute renal replacement was more frequent in our study than was reported elsewhere. This might be due to the variable criteria for the initiation of dialysis and the more morbid study population (4,15,38,176,177).

4.5 Predictors for CSA-AKI

In 1976, Abel et al. (3) conducted one of the first studies that identified risk factors for CSA-AKI. It was shown that older age, preoperatively increased serum creatinine, cardiopulmonary bypass time, NYHA III/IV and the preoperative use of diuretics were predictors for AKI following cardiac surgery. Throughout the last few decades, several observational studies have been conducted to identify and categorize predictors for CSA-AKI (30,31,38,173,178). Parolari et al. (31) used a logistic regression analysis to identify predictors of CSA-AKI and divided them into preoperative, intraoperative and postoperative predictors. Preoperative predictors were age, diabetes mellitus, smoking and preoperative serum creatinine. Intraoperative predictors were use of inotropes, red blood cell transfusions, aortic cross-clamp time and furosemide administration during cardiopulmonary bypass. Postoperative predictors were red blood cell transfusions, administration of vasoconstrictors, inotropes, diuretics and antiarrhythmics. Karkouti et al. (58) chose another approach to classify predictors of CSA-AKI and divided predictors into modifiable and non-modifiable predictors. In particular, 3 potentially modifiable predictors were independently and strongly associated with CSA-AKI: preoperative anemia, perioperative red blood transfusions and surgical reexploration.

The univariate logistic regression analysis of our study identified age, diabetes mellitus, previous MI, NYHA III/IV, preoperative administration of diuretics, preoperative eGFR, EuroSCORE II, mechanical ventilation, length of ICU stay, APACHE II and SOFA score as predictors of CSA-AKI. The subsequent multivariate logistic regression analysis showed that the eGFR at admission, the preoperative use of diuretics and diabetes mellitus are independently associated with CSA-AKI. These findings support the results of previous studies that aimed to identify predictors of CSA-AKI (38,173,178). In contrast to other studies, we were not able to show an independent association between the development of CSA-AKI and age as well as NYHA III/IV (31,38,173,178). The aforementioned comorbidities as well as the general pathological pathway of CSA-AKI are oftenly

exacerbated by the frequent use of diuretics and ACE inhibitors, which also contribute to impair renal hemodynamics and glomerular function. Nevertheless, it remains unclear why especially diurectics have such a powerful impact in this study.

Due to the small number of patients developing CSA-AKI, we could only enter a limited number of factors in the multivariate analysis. Therefore, not all factors that were statistically significant in the univariate analysis could be entered in the multivariate analysis. This may have led to a distortion of our findings because the independent association between all given factors and CSA-AKI could not be shown. The effect of our small sample size is also shown in our relatively wide 95% confidence intervals. Our findings suggest that the relative risk of CSA-AKI decreases with a better preoperative eGFR by 32% per 10 ml/min/1.73m^2. These results confirm the direct influence of a preoperatively impaired kidney function on subsequent kidney injury and renal complications following cardiac surgery. In particular, an eGFR below 60 ml/min/1.73m^2 seems to be a significant, independent predictor of CSA-AKI (173). These at-risk patients may benefit from prehydration and closer surveillance during hospitalization (163). Furthermore, Ho et al. (179) demonstrated that a reduction of more than 10% in baseline serum creatinine may predict a lower risk of CSA-AKI, whereas a rise of more than 10% may predict a higher risk of CSA-AKI.

The available data regarding diabetes mellitus as a predictor of CSA-AKI is inconsistent. In our study, diabetes mellitus narrowly reached statistical significance in the multivariate analysis. A study conducted by Moschopoulou et al. (180) showed that diabetes mellitus is not an independent predictor of AKI following cardiac surgery. Hertzberg et al. (181), on the other hand, found that type 1 and type 2 diabetes mellitus are linked to an increased risk of CSA-AKI. Interestingly, the relative risk of CSA-AKI was markedly higher in patients with type 1 diabetes mellitus compared to patients with type 2 diabetes mellitus. Diabetes mellitus is an important risk factor of arteriosclerosis and endothelial injury of the microvascular system (182). Therefore, diabetes mellitus is a crucial risk factor for vascular disease in general and subsequently for critical ischemia, in particular in the lower extremities (183). In addition, vascular disease caused by diabetes mellitus extends into the renal microvascular system leading to diabetic nephropathy. Diabetic nephropathy is associated with glomerular hypertrophy, thickening of glomerular basement membrane, and accumulation of extracellular matrix resulting in tubulointerstitial and glomerular sclerosis and fibrosis (182). These alterations affect renal perfusion and filtration, making the kidney more vulnerable to insults occurring in the peri- and postoperative period. Other important preoperative predictors for

CSA-AKI that were not assessed in our study are the body mass index (BMI), atrial fibrillation, endocarditis and cardiac catherization within a 5-day period before surgery (173,178). Cardiac catherization before cardiac surgery can be an essential predictor for CSA-AKI due to the increased risk of contrast-induced nephropathy after coronary angiography.

We were able to demonstrate that in addition to its normal usage in short-term mortality prediction, increasing points on the EuroSCORE II are predictive of CSA-AKI. The EuroSCORE II includes several important independent preoperative predictors of CSA-AKI such as eGFR, previous myocardial infarction, diabetes mellitus, endocarditis and complexity of surgery, which were assessed in large observational studies. Therefore, it might be used as an additive tool to predict the risk of CSA-AKI and identify high-risk patients, as shown by Duthie et al. (184).

One of the most studied intraoperative predictors of CSA-AKI is the duration of cardiopulmonary bypass. However, our results do not confirm that the duration of cardiopulmonary bypass is a predictor of AKI following cardiac surgery. As already indicated above, bypass times of greater 90 minutes seem to significantly increase the risk of CSA-AKI (174). The cardiopulmonary bypass time was 79 (60 – 104) minutes in this study. Compared to other studies, the cardiopulmonary bypass time was relatively short in our study population possibly due to the smaller number of complex and combined operations (31,173,174). The cardiopulmonary bypass is associated with the use of unphysiological material, non-pulsatile flow during bypass, activation of inflammatory cascades and an increase in the oxidative stress level leading to alterations in kidney function. In addition, during bypass, renal oxygenation and perfusion pressures are reduced. Therefore, longer on-pump times might cause increased functional and structural damage of the kidney (57).

Our data demonstrates that the duration of mechanical ventilation and the length of ICU stay are postoperative risk factors in the development of AKI. Van den Akker et al. (185) reports that mechanical ventilation exceeding 24 hours is associated with a 3-times increased risk of developing AKI in critically ill patients. The underlaying mechanisms may include hemodynamic factors and selective renal vasoconstriction due to sympathetic stimulation induced by mechanical ventilation.

In conclusion, the pathogenesis of CSA-AKI is a multifactorial process in which the amount and the temporal occurrence of systemic and renal insults play an important role. Therefore, the identified crucial predictors have to be seen and prevented as a whole if possible.

Unfortunately, however, the preoperative risk factors for CSA-AKI in particular haven´t changed over the last few decades and only a handful of risk factors seem to be modifiable per se.

4.6 Predictors for patient mortality

The results of our study show that CSA-AKI is an independent predictor of patient mortality. After adjustment for EuroSCORE II, which includes several predictors that were statistically significant in the univariate Cox regression analysis, CSA-AKI remained an important and independent risk factor for increased mortality. Our study suggests that the development of CSA-AKI during hospitalization is associated with a 14-times increased risk of all-cause death within the first 3 years after the intervention. Furthermore, we identified a hazard ratio of 17.3 for AKIN 1 and a hazard ratio of 24.5 for AKIN 3 in the univariate Cox regression analysis. That means that a more severe level of AKI seems to be associated with a higher relative risk of all-cause death in cardiosurgical patients. However, hazard ratios for all-cause mortality in the AKIN 2 group were lower when compared to AKIN 3 group, possibly due to the very small number of patients in this group. There were only 3 patients in the AKIN 2 group and 9 patients in the AKIN 3 group. Therefore, those groups may have been significantly underpowered, as mentioned before. Consequently, the risk of bias in these two groups is very high compared to the AKIN 1 group. This assumption is also represented in the very wide 95% confidence intervals of the AKIN 2 and AKIN 3 group. Several previous studies were able to demonstrate that AKI is independently associated with increased short-term and long-term mortality in patients undergoing cardiac surgery, and in critically ill patients in general (1,6,7,11,30). Machado et al. (15) demonstrated that CSA-AKI based on the KDIGO criteria is an independent predictor of 30-day mortality and that a more severe level of AKI is associated with a higher relative risk of short-term all-cause mortality. An observational trial studying independent predictors of long-term mortality in cardiac surgery using the KDIGO criteria also discovered that a more severe level of AKI is independently associated with a higher relative risk of long-term mortality (19). In conclusion, our study confirms previous findings that the severity of AKI defined by the rise in baseline serum creatinine, the degree of oliguria and the need for renal replacement therapy after cardiac surgery is a strong and independent predictor of patients' all-cause mortality (6). However, all of these parameters only measure the decline in renal function, ignoring the dimension of time of CSA-AKI, which can also lead to structural damage and subsequently to adverse outcome. A study conducted by Brown et al. (186) found that the duration of CSA-AKI is also an

independent predictor of patient mortality. It was shown that an AKI-duration of more than 7 days in particular increases the relative risk of mortality drastically. They also suggest that especially high-risk groups of patients are those discharged with persistent CSA-AKI or elevated serum creatinine. These results were confirmed by Engoren et al. (16) who reported on the one hand that the severity of CSA-AKI is important in late outcome, but on the other that the amount of residual GFR at time of discharge seems to be the factor associated with better patient survival. Further studies need to be conducted to evaluate the impact of the combination of duration and severity of CSA-AKI on patient survival.

The univariate Cox regression analysis of our study showed that age, diabetes mellitus, extracardiac arteriopathy, previous myocardial infarction, NYHA III/IV, eGFR at admission and EuroSCORE II were statistically significant predictors of patient mortality. These results complement the findings of previous studies examining independent risk factors for patient survival after cardiac surgery (6,7,9,17). It can be assumed that diabetes mellitus and extracardiac arteriopathy, including peripheral vascular disease, lead to endothelial dysfunction which is associated with impaired renal function and contributes to an increase in cardiovascular mortality (187). We hypothesize that the higher influence of arteriosclerosis and diabetes mellitus in our study population is associated with vascular damage in renal vessels, which predisposes to CSA-AKI and subsequently to increased mortality. In any case, the risk of mortality seems to be higher at a lower level of baseline eGFR. Similar findings were published by Thakar et al. (177), who were also able to demonstrate that the risk of death associated with renal impairment is offset by a higher baseline eGFR before surgery. Additionally, our study suggests that the relative risk of all-cause mortality decreases by 30% per 10 ml/min/1.73m^2 of preoperative eGFR. But we assume that the implication of a similar increase in eGFR will be much greater in patients with worse kidney function.

The EuroSCORE II was primarily designed as an estimator of 30-day mortality (164). Nevertheless, our study demonstrates that it can also be used as an independent predictor of long-term all-cause mortality. The multivariate analysis indicates that the relative risk of death within 3 years increases by 11% per 1 point. Our results are supported by findings of Barili et al. (188), who demonstrated that the EuroSCORE II is nonlinearly associated with long-term mortality in cardiosurgical patients since most of its variables are themselves independent predictors of long-term mortality after surgery.

Our study did not analyze the association between the different types of surgery and patient survival. Hobson et al. (6) showed that patients undergoing valve, aortic and thoracic surgery

had an increased risk of long-term mortality compared to patients undergoing single CABG surgery. Interestingly, a subgroup analysis revealed that CSA-AKI was associated with decreased survival in patients receiving all kinds of cardiac operations except for valve surgery. A possible explanation could be that the patients undergoing valve surgery tend to be younger and are less likely to suffer from severe arteriosclerosis compared to patients undergoing CABG surgery. Xu et al. (9) suggest that the duration of cardiopulmonary bypass could also be an intraoperative predictor of long-term mortality in cardiosurgical patients. Unfortunately, we were not able to reproduce these findings in our study due to the reasons given. Nonetheless, we assume that it could have been an independent predictor of mortality if entered in the multivariate analysis with other factors since it had almost reached statistical significance in the univariate Cox regression analysis.

Postoperative predictors of patient mortality in our study were the duration of mechanical ventilation, length of ICU stay, and APACHE II and SAPS II scores. Hassan et al. (189) showed that cardiosurgical patients with a prolonged ICU length of stay have greater in-hospital mortality and worse long-term survival. In fact, patients with an ICU stay of greater than 7 days seem to have the worst outcome. Previous studies also stated that a higher APACHE II and SAPS II score are independently associated with long-term mortality (190,191). The APACHE II and SAPS II score were primarily developed to predict short-term, particularly in-hospital mortality. Furthermore, there is an ongoing debate as to whether they are also able to predict long-term survival. Concerning the APACHE II score, studies suggest that an APACHE II score greater than 20 may result in increased long-term mortality, whereas a score of less than 10 does not have a negative effect on patient survival (190). In this study, the mean APACHE II score was 21.88 in the CSA-AKI group and 18.74 in patients without CSA-AKI. The SOFA score did not reach statistical significance in the univariate regression analysis. A possible explanation may be that it predominately reflects the patient´s acute condition. In contrast to the APACHE II and SAPS II score, variables like age and preexisting comorbidities do not enter the risk calculation. Therefore, it seems more suitable for predicting a short-term outcome. Nevertheless, since the development of the EuroScore, all the mentioned risk stratification scores have played a more minor role in predicting short-term survival in cardiosurgical patients.

4.7 Survival analysis

Previous studies suggested an association between worse outcome and CSA-AKI, defined by the KDIGO criteria, compared to patients without CSA-AKI (15,16,19,20). Our study

confirms that similarly to 30-day mortality, long-term mortality was progressively worse with the rising severity of CSA-AKI. By 3 years, the absolute difference in mortality after cardiac surgery was 45.4% between patients with and without CSA-AKI. The survival rates after 3 years were 96%, 51.6% and 48.6% for AKIN 0, AKIN 1, and AKIN 2 and 3, respectively. Our study population shows a significantly better long-term survival in patients without CSA-AKI and a worse long-term outcome in patients with CSA-AKI compared to other studies (6,7,16,17,19). Gallagher et al. (7), for example, observed an absolute difference in mortality of 13.6% after 5 years between patients with and without CSA-AKI. The observed 3-year mortality rate of almost 50% in the AKI group is usually reached after 6 to 10 years in other long-term observational studies (6,17). These findings suggest that AKI following cardiac surgery could be an even more important risk factor for long-term mortality than already assumed. Furthermore, there is evidence that the different severity levels of CSA-AKI lead to a similar 3-year mortality. However, AKIN 2 and 3 might be underpowered due to the small number of patients, which may lead to biased results in this group. Nevertheless, KDIGO stage 1 CSA-AKI in particular has a crucial impact on long-term mortality. The observed effect of AKIN 1 on long-term outcome is inconsistent with previous studies. In previous studies, the 3-year mortality rate for stage 1 CSA-AKI varies between 10% and 20% (6,17,19). Unfortunately, we were not able to assess the further development in the AKIN 1 group due to the end of the observational period after 3 years. It would have been interesting to evaluate if the mortality in the AKIN 1 group continues at the same rate or if it progressively decreases and vanishes at some point. Hobson et al. (6) suggest that even after 10 years, all-cause mortality remains increased for all AKI severity levels. Furthermore, they were able to demonstrate that even patients with complete renal recovery at hospital discharge show a significantly increased 10-year mortality. In contrast, Ferreiro et al. (17) found in an observational study over a 15-year period that the association between CSA-AKI and long-term mortality vanishes after 5 years, regardless of the severity level. Despite these facts, patients with the need for renal replacement therapy during hospitalization seem to have the worst short-term and long-term outcome (6,30).

We can only speculate over the kidneys' exact role in long-term survival. Renal dysfunction is associated with diseases like arterial hypertension and diabetes mellitus. These diseases are important factors of poorer prognosis themselves. In addition, renal deterioration in association with these determinants worsens patients' outcome significantly. A study conducted by Hansen et al. (42) suggests that CSA-AKI is associated with an increased 5-year

risk of MI, congestive heart failure and stroke. Therefore, we assume that renal injury may increase cardiovascular risk in many ways. Previous experimental studies showed that AKI permanently damages the microvascular system of the kidney. This leads to changes in renal structure and deterioration of the kidney function (101,192). Subsequently, this results in various physiological changes including proteinuria, high levels of homocysteine, anemia and uremia, which as independent cardiovascular risk factors can increase cardiac risk and affect cardiovascular outcome. Thus, the injured kidney seems to interact with other vital organs due to increased inflammation, oxidative stress and accelerated cardiovascular disease, leading to a higher mortality in patients at risk (192–194). It appears that even small changes in baseline serum creatinine, which do not fulfill RIFLE, AKIN or KDIGO criteria, are associated with higher short and long-term mortality among patients undergoing cardiac surgery (8,16,36). It was also shown that patients with postoperative decreases in baseline serum creatinine between 0.1 and 0.3 mg/dl within the first 48 hours after surgery had the lowest mortality rate (36). Additionally, Liotta et al. (8) reported that tiny elevations in baseline serum creatinine lower than 0.3 mg/dl are associated with increased 6-year mortality, but not with 30-day mortality, demonstrating the long-term influence of minimal kidney damage. Indeed, Engoren et al. (16) indicate that the risk of dying associated with tiny elevations in baseline serum creatinine is lower than for KDIGO stages 2 and 3. Conversely, compared to the more severe stages of CSA-AKI, there are far more cardiosurgical patients with minimal rises in baseline serum creatinine, which may lead to a higher number of late deaths in this group. In conclusion, this means that the impact of even small rises in baseline serum creatinine on long-term outcome should not be underestimated.

At this point, there only are few studies using the complete KDIGO criteria to examine the association between CSA-AKI and mortality (19,20). Howitt et al. (20) analyzed the differences in outcomes of patients developing CSA-AKI when KDIGO serum creatinine criteria or urine output criteria are being used to diagnose AKI. They demonstrated that mortality in patients with CSA-AKI diagnosed by urine output alone is lower compared to patients diagnosed by rises in serum creatinine. It is commonly understood that oliguria is an adequate physiological response to the stress of such complex operations and therefore does not necessarily lead to irreversible kidney damage. Previous studies that examined the association between postoperative eGFR and mortality reported that patients with a postoperative eGFR of less than 60 ml/min/1.73^2 have worse long-term survival compared to patients with a preoperative eGFR greater than 75 ml/min/1.73m^2 (195). In addition, our study

shows that there is also an association between preoperative eGFR and long-term mortality. The Kaplan-Meier survival plot indicates that patients with a preoperative eGFR of less than 60 ml/min/1.73m^2 in particular have increased long-term mortality compared to patients with an eGFR greater than 60 ml/min/1.73m^2, possibly due to the greater risk of postoperative serum creatinine elevations and clinically manifest AKI. This finding underlines the crucial impact of preoperative risk stratification and renal dysfunction on adverse long-term outcomes in patients undergoing cardiac surgery.

4.8 Limitations

There are several clear limitations to this study. The most important limitation might be the small study population with only 119 patients, and subsequently the very limited number of patients in the AKIN 2 and AKIN 3 groups. Consequently, AKIN 2 and 3 might be too underpowered to find differences in mortality. This leads to a higher risk of bias and to less validity in the statistical analysis of this subgroup. This is certainly reflected in the wide 95% confidence interval on the more severe levels of CSA-AKI. Further studies need to be conducted to better estimate the effect of different levels of CSA-AKI on long-term survival when the complete KDIGO criteria are being used. Secondly, this is only a single-center observational study, which may lead to different incidences and risk factors of CSA-AKI, due to possible iatrogenic causes of CSA-AKI and different prophylaxis or treatment strategies that may be particular to our center. Therefore, our findings cannot be generalized to other institutions. Like all observational studies, our study was open to residual bias and unknown confounding risk factors, which can be marked as problematic in general. Thirdly, the primary outcome of our observational study was all-cause death. This means that the exact causes of death and possible long-term complications are missing for our study population. Consequently, the observed effect of CSA-AKI on long-term survival may not be directly associated with the renal injury and may be a surrogate for serious damage of other vital organ systems, thereby being a signal for an increase in long-term mortality. Concerning long-term renal complications, Rydén et al. (196) demonstrated that a rise in baseline serum creatinine after cardiac surgery is associated with an almost 3-fold increase in long-term development of end-stage renal disease. Fourthly, reaching statistically significant results in the univariate regression analyses is difficult given the relatively small number of events of CSA-AKI (n=43) and all-cause death (n=24) during our study period. Furthermore, due to the small number of events, only a limited number of predictors could be entered into the multivariate analysis to assure clean statistical results. For this reason, we were only able to

identify a limited number of independent predictors of CSA-AKI as well as patient mortality following cardiac surgery. That might have led to misinterpretation of the results, as not every statistically significant and important predictor that was identified in the univariate analysis could enter the multivariate analysis. Fifthly, it was difficult to assess the influence of the cardiopulmonary bypass time due to the small number of off-pump operations. This could bias the incidence of CSA-AKI and could have led to shorter bypass times in general. Therefore, we were not able to show a beneficial effect of off-pump CABG operations or shorter bypass times on CSA-AKI as the CORONARY study demonstrated (55). Also, all examined patients underwent elective cardiac surgery, which limits the extension of our findings to emergency operations and critically ill patients in general. Finally, we lack information on the postoperative medication during patients' ICU stay. Therefore, we were not able to identify and analyze important postoperative and possibly modifiable risk factors that may be associated with the development of CSA-AKI and mortality.

4.9 Conclusion and outlook on further research

In this single-center cohort of patients undergoing cardiac surgery who survived the primary operation, the development of CSA-AKI was associated with a significant increase in all-cause mortality during our follow-up period. In particular, we showed that even a KDIGO stage 1 AKI affects patients' outcome gravely and perhaps even more significantly than has been previously assumed. Furthermore, the complete KDIGO classification using changes in baseline serum creatinine and urine output provides a useful tool for identifying patients with CSA-AKI and as a consequence those at risk of short-term and long-term death. Additionally, we confirmed that AKI is still a common problem in patients undergoing cardiac surgery and that patients at risk need to be identified at an early stage to prevent this complication. In addition, we determined several risk factors of CSA-AKI. Our study suggests that the baseline renal function before cardiac surgery in particular is an independent risk factor of CSA-AKI and postoperative mortality. A preoperative eGFR of less than 60 ml/min/1.73m^2 seems to be a reasonable criterion to select patients for closer monitoring during hospitalization. Unfortunately, it remains incompletely understood why CSA-AKI is associated with increased long-term mortality. However, the knowledge of this important dynamic is essential so as to better plan individual health care and allocate resources. At present, there are several predictive scoring systems as well as biomarkers and pharmacological measures to prevent CSA-AKI. Unfortunately, the majority of the scoring systems for anticipating AKI only estimate the individual patient´s risk for the postoperative need for renal replacement therapy

(44,197) . The postoperative need for renal replacement is clearly one of the most important risk factors of in-hospital and long-term mortality (26). However, as shown in our study, even less severe levels of AKI should be prevented by any means to improve patients' short-term and long-term outcome. The AKICS score to predict clinical CSA-AKI without the need for renal replacement therapy developed by Palomba et al. (45) uses its own criteria to diagnose AKI in a small study population and is therefore not recommendable for the general population. To date, we lack a predictive scoring system that uses modern and validated criteria, like those used in the KDIGO guidelines, to anticipate and treat early stages of CSA-AKI. Biomarkers in urine and blood to predict postoperative AKI have shown promising results during the last couple of years. However, these biomarkers have only been tested and validated in small study populations, which complicates the transfer of the findings onto the broad population. Additionally, the measurements of those biomarkers are expensive and not available in every hospital. Consequently, this restricts their general application heavily. Further studies with larger cohorts need to be conducted to find less expensive biomarkers and a more sensitive combination of biomarkers, which would be available to the general population. A successful preventive measure would seem to be the strict use of the KDIGO guidelines to prevent AKI in high-risk patients as shown by the PrevAKI trial (163). The use of the KDIGO guidelines and the given bundles of care is easily practicable and a safe method for reducing the incidence of CSA-AKI that can be applied to any patient. Therefore, this can be highly recommended so as to improve patients' outcome. If these measures fail and an AKI becomes clinically manifested, it seems indispensable that those patients go through closer monitoring during hospitalization and closer follow-up inspections in the ambulant setting. CSA-AKI may result in an increased cardiovascular risk as well as in progressive renal damage, even after the normalization of renal function. This is an important message for cardiac surgeons, critical care specialists, cardiologists, nephrologists and medical physicians performing follow-up inspections in the ambulant setting. At this point, we want to highlight the importance of good collaboration between the different medical specialties so as to provide ideal follow-up care. It is highly problematic that specific follow-up for patients with mild CSA-AKI is almost non-existent. We hope that our study will stimulate closer monitoring of patients at risk during hospitalization and closer post discharge follow-up of patients who develop even mild levels of AKI after cardiac surgery, and particularly because most of our highlighted risk factors for CSA-AKI (e.g. Diabetes mellitus, preoperative kidney function and diuretics in chronic medication) are difficult to modify. Future studies should determine the optimal follow-up period and management of patients with postoperative AKI.

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6 Eidesstattliche Versicherung

„Ich, Richard Kehnscherper, versichere an Eides statt durch meine eigenhändige Unterschrift, dass ich die vorgelegte Dissertation mit dem Thema: „Long-term Survival After Cardiac Surgery-Induced Acute Kidney Injury: A Prospective Observational Study“; „Langzeitüberleben nach Herzchirurgie-induziertem akuten Nierenversagen: eine prospektive Beobachtungsstudie“ selbstständig und ohne nicht offengelegte Hilfe Dritter verfasst und keine anderen als die angegebenen Quellen und Hilfsmittel genutzt habe.

Alle Stellen, die wörtlich oder dem Sinne nach auf Publikationen oder Vorträgen anderer Autoren/innen beruhen, sind als solche in korrekter Zitierung kenntlich gemacht. Die Abschnitte zu Methodik (insbesondere praktische Arbeiten, Laborbestimmungen, statistische Aufarbeitung) und Resultaten (insbesondere Abbildungen, Graphiken und Tabellen) werden von mir verantwortet.

[Für den Fall, dass Sie die Forschung für Ihre Promotion ganz oder teilweise in Gruppenarbeit durchgeführt haben:] Ich versichere ferner, dass ich die in Zusammenarbeit mit anderen Personen generierten Daten, Datenauswertungen und Schlussfolgerungen korrekt gekennzeichnet und meinen eigenen Beitrag sowie die Beiträge anderer Personen korrekt kenntlich gemacht habe (siehe Anteilserklärung). Texte oder Textteile, die gemeinsam mit anderen erstellt oder verwendet wurden, habe ich korrekt kenntlich gemacht.

Meine Anteile an etwaigen Publikationen zu dieser Dissertation entsprechen denen, die in der untenstehenden gemeinsamen Erklärung mit dem/der Erstbetreuer/in, angegeben sind. Für sämtliche im Rahmen der Dissertation entstandenen Publikationen wurden die Richtlinien des ICMJE (International Committee of Medical Journal Editors; www.icmje.og) zur Autorenschaft eingehalten. Ich erkläre ferner, dass ich mich zur Einhaltung der Satzung der Charité – Universitätsmedizin Berlin zur Sicherung Guter Wissenschaftlicher Praxis verpflichte.

Weiterhin versichere ich, dass ich diese Dissertation weder in gleicher noch in ähnlicher Form bereits an einer anderen Fakultät eingereicht habe.

Die Bedeutung dieser eidesstattlichen Versicherung und die strafrechtlichen Folgen einer unwahren eidesstattlichen Versicherung (§§156, 161 des Strafgesetzbuches) sind mir bekannt und bewusst.“

Datum Unterschrift

Anteilserklärung an etwaigen erfolgten Publikationen

[Sollten bereits Teile aus Ihrer Monographie publiziert worden sein, dann müssen Sie dies im Vorwort nach dem Deckblatt erklären und diese Anteilserklärung ausfüllen.

Die Anteile an den etwaigen Publikationen sind so deutlich und detailliert zu erklären, dass es der Promotionskommission und den wissenschaftlichen Gutachtern ohne Probleme möglich ist zu erkennen, was Sie selbst dazu beigetragen haben. Wünschenswert wäre ein konkreter Bezug zur Publikation wie z. B.: „aus meiner statistischen Auswertung sind die Tabellen 1, 4, 47 und 60 entstanden.“]

[Name des Doktoranden/der Doktorandin] hatte folgenden Anteil an den folgenden Publikationen:

Publikation 1: [Autoren], [Titel], [Zeitschrift], [Erscheinungsjahr]

Beitrag im Einzelnen (bitte detailliert ausführen):

Publikation 2: [Autoren], [Titel], [Zeitschrift], [Erscheinungsjahr]

Beitrag im Einzelnen (bitte detailliert ausführen):

Publikation 3: [Autoren], [Titel], [Zeitschrift], [Erscheinungsjahr]

Beitrag im Einzelnen (bitte detailliert ausführen):

_____

Unterschrift, Datum und Stempel des/der erstbetreuenden Hochschullehrers/in

_____

Unterschrift des Doktoranden/der Doktorandin

7 CURRICULUM VITAE

„Mein Lebenslauf wird aus datenschutzrechtlichen Gründen in der elektronischen Version meiner Arbeit nicht veröffentlicht.“

8 Acknowledgements

In Liebe und Dankbarkeit meiner Familie gewidmet.