From the Department of Medicine Solna
Karolinska Institutet, Stockholm, Sweden

PERIOPERATIVE ACUTE KIDNEY INJURY - RISK FACTORS AND OUTCOMES

Daniel Hertzberg

Karolinska Institutet

Stockholm 2016

Published by Karolinska Institutet
Printed by E-print AB, Stockholm, Sweden

ISBN 978-91-7676-399-5

Karolinska Institutet

Institutionen för Medicin Solna

PERIOPERATIVE ACUTE KIDNEY INJURY - RISK FACTORS AND OUTCOMES

AKADEMISK AVHANDLING som för avläggande av medicine doktorsexamen vid Karolinska Institutet offentligen försvaras i Welandersalen B2, plan 00, Karolinska Universitetssjukhuset, Solna.

Fredagen den 25 november 2016, kl 09.00.

av

Daniel Hertzberg (né Olsson)

MD

Principal Supervisor:
Martin J. Holzmann, Associate Professor
Karolinska Institutet
Department of Medicine Solna

Co-supervisor:
Ulrik Sartipy, Associate Professor
Karolinska Institutet
Department of Molecular Medicine and Surgery

External mentor:
Johan Holmdahl, MD, PhD
University of Gothenburg
Sahlgrenska Academy
Department of Nephrology

Opponent:
Sven-Erik Ricksten, Professor
University of Gothenburg
Department of Anesthesiology and Intensive Care

Examination Board:
Jonas Spaak, Associate Professor
Karolinska Institutet
Department of Clinical Sciences,
Danderyd Hospital

Juan-Jesus Carrero-Roig, Associate Professor
Karolinska Institutet
Department of Clinical Science, Intervention and Technology (CLINTEC)

Gunnar Sterner, Associate Professor
Lund University
Internal Medicine Research Unit

Stockholm 2016

Dedicated to those undergoing cardiac surgery

POPULÄRVETENSKAPLIG SAMMANFATTNING

Njurarna har flera livsviktiga funktioner. Från blodet till urinen filtrerar njurarna bort nedbrytnings- och restprodukter, gifter och läkemedel. De reglerar vätske-, salt-, och syra-bas-balansen i blodet och producerar även aktiva hormoner som är involverade i nybildningen av röda blodkroppar, kalcium-omsättningen, och regleringen av blodtrycket (1). Njurarna är två bönformade organ som vilar i bukens bakre del bakom bukhinnan, på var sin sida om kotpelaren. De omges av var sin kapsel med en öppning vid mitten av njuren där nerver, lymfkärl, njurartär, njurven, och urinledare ansluter. Trots sin ringa storlek, är njurarna normalt väl genomblödda och de erhåller cirka 20% av det totala blodflödet från hjärtat. Dock bjuder kärlen i njurarna på ett gott flödesmotstånd vilket bygger upp ett tryck i de kärl som skall filtrera blod till urin. I vardera njure finns cirka 1 miljon urinproducerande enheter som kallas nefron. Nefronet börjar med ett läckande mikroskopiskt blodkärlnystan med specifik filterstorlek och negativ laddning och släpper igenom små och företrädelsevis positivt laddade molekyler. Detta kärlnystan är omgivet av en kapsel där primärurin samlas upp och strömmar till ett anslutande rör (tubuli) som är nästa del av nefronet. Primärurinen passerar genom tubuli och koncentreras genom att vatten och många molekyler återabsorberas ut till blodet. Utan återresorptionen från primärurinen skulle motsvarande hela blodvolymen utsöndras på cirka 30 minuter. En molekyl som knappt återresorberas alls är nedbrytningsprodukten kreatinin. Kreatininets koncentration i blodet speglar därför njurens filtrationsförmåga väl, utan att störas av variation i återresorptionen. Den lämpar sig därmed väl som en markör för njurens filtrationsförmåga, framförallt på kort sikt (1).

Akut njurskada, tidigare kallat akut njursvikt, är en plötslig försämring av njurfunktionen. Diagnosen akut njurskada ställs genom att mäta koncentrationen av kreatinin i blodet alternativt genom att mäta urinproduktionen. En ökning av kreatinin-koncentrationen på >26 µmol/L inom två dygn eller en urinproduktion som sjunker till <0,5 ml/kg kroppsvikt/timme under ≥6 timmar definieras som akut njurskada. I vissa fall kan orsaken till akut njurskada ställas genom vidare provtagning men i många fall saknas specifika diagnostiska test. Istället fastställs orsaken genom en sammanvägd klinisk bedömning. Möjliga skademekanismer är många och akut njurskada beskriver endast att en skada har skett men säger inget om orsaken. Akut njurskada drabbar ofta patienter som är kritiskt sjuka, exempelvis vid blodförgiftning samt vid stor kirurgi. Särskilt vanligt är akut njurskada vid hjärtkirurgi. Riskfaktorer för akut njurskada är bland annat hög ålder, hjärtsvikt, kronisk njursjukdom och diabetes. Orsakerna kan vara syrebrist till följd av lågt blodtryck, inflammation, och förekomst av molekyler eller gifter som skadar nefronerna. Vid svår akut njurskada kan filtrationsförmågan påverkas till den grad att dialys är nödvändig. Under det senaste decenniet har dock allt mer uppmärksamhet riktats åt mildare akuta njurskador och dess betydelse. Vid mildare akut njurskada normaliseras ofta kreatinin-koncentrationen och urinproduktionen inom några dagar från att skadan har inträffat. Traditionellt sett har man därmed menat att njurarna är bra på att återhämta sig. Flertalet nya studier har dock visat att det finns ett samband mellan mildare grader av akut njurskada och ökad sjukdomsbörda och försämrad prognos på längre

sikt även om njurfunktionen återhämtar sig. Frågan är om akut njurskada i sig skadar kroppen och leder till sjukdom eller om akut njurskada är ett sekundärt tecken på sjukdom och ökad sårbarhet i andra organ än i njuren, som till exempel i hjärtat. Forskare inom området är väsentligen överens om att akut njurskada orsakar sjukdom och skada, vilket har negativa konsekvenser även om kreatininkoncentrationen och njurfiltrationen normaliseras efter skadan.

I denna avhandling studeras patienter som genomgår hjärtkirurgi där akut njurskada är vanligt förekommande. Akut njurskada drabbar mellan 5 till 30% av patienterna beroende på typ av kirurgisk intervention och definition på akut njurskada. Studierna berör njurskadlig läkemedelsbehandling, riskfaktorer för akut njurskada och vilka konsekvenserna för de som drabbas av akut njurskada kan bli.

I första studien undersökte vi om patienter som fick ett tillägg av antibiotikan teicoplanin till ordinarie förebyggande antibiotikabehandling i samband med hjärtkirurgi hade en ökad risk för akut njurskada. Resultaten visade att patienter som behandlats med teicoplanin hade en 40% ökad risk att utveckla akut njurskada jämfört med de som inte fick teicoplanin.

I den andra studien undersökte vi om det fanns ett samband mellan typ 1 eller typ 2 diabetes och en ökad risk för att utveckla akut njurskada i samband med kranskärlskirurgi (ibland kallad bypass eller kranskärl-bypass). Resultaten visade att typ 1 diabetes var förenat med en nästan femdubbelt ökad risk för att utveckla akut njurskada, och typ 2 diabetes var förenat med 25% ökad risk.

I den tredje studien undersökte vi om patienter som drabbats av akut njurskada efter kranskärlskirurgi hade en ökad risk att utveckla hjärtsvikt på lång sikt. Med en uppföljningstid på cirka 4 år i snitt kunde vi visa på att patienter som drabbades av akut njurskada hade nästan fördubblad risk att drabbas av hjärtsvikt.

I den fjärde studien undersökte vi om minimala förändringar i njurfunktionen efter kranskärlskirurgi var förenade med ökad risk för död på kort och lång sikt. Vi undersökte även om man löpte större risk att dö, eller drabbas av antingen hjärtsvikt, hjärtinfarkt, eller stroke som ett kombinerat utfall. Resultaten visade att även minimala förändringar i njurfunktionen var förenade med ökad dödlighet på lång sikt, men ej på kort sikt, samt en ökad risk för det kombinerade utfallet död, hjärtsvikt, hjärtinfarkt eller stroke.

Sammanfattningsvis har avhandlingens studier bidragit med en ökad förståelse kring riskfaktorer och konsekvenser av akut njurskada i samband med hjärtkirurgi. Resultaten kan i framtiden användas för att förbättra hälsovinsten av hjärtkirurgi ytterligare.

På framsidan ses en retuscherad version av illustrationen av den Vitruvianske mannen tecknad av Leonardo da Vinci. Bilden är ett exempel på hur konst och vetenskap förenades under Renässansen. Njurar är tillagda och på bröstet finns ett snitt som illustrerar ärret efter en hjärtoperation. Den blottande positionen liknar i ett liggande läge patientens utsatta position på operationsbordet.

ABSTRACT

Background: Acute kidney injury (AKI) is defined as a sudden decrease in renal filtration function. It is common among critically ill patients and patients undergoing major surgery, especially cardiac surgery. AKI is defined by either an elevated serum creatinine (SCr) concentration or a decrease in urine production. Because AKI often presents secondary to many other critical diseases and conditions, it has historically received little attention. During the last decade, however, AKI has received greater attention, and even minor AKIs has been clinically recognized. Recent studies have shown that patients who develop AKI have a worse prognosis. The aim of this thesis was to further investigate the risk factors for and outcomes of AKI in patients undergoing cardiac surgery.

Patients and methods: Patients undergoing cardiac surgery were studied. The cohorts were identified using the *SWEDEHEART* register. The first study was performed to investigate whether prophylactic use of the antibiotic teicoplanin is associated with an increased risk of AKI (n = 2809 patients). The second study was performed to investigate whether type 1 diabetes mellitus (T1DM) and type 2 diabetes mellitus (T2DM) are risk factors for the development of AKI after coronary artery bypass grafting (CABG) (n = 36,106 patients). The third study was carried out to determine whether patients who developed AKI after CABG had an increased long-term risk for developing heart failure (n = 24,018 patients). Finally, the fourth study was performed to investigate whether even minimal increases in the SCr concentration after CABG are associated with long- and short-term mortality and the composite outcome of long-term mortality, heart failure, myocardial infarction, and stroke (n = 25,686 patients).

Results: Antibiotic prophylaxis with teicoplanin was associated with an increased risk of AKI after cardiac surgery. Additionally, a dose-dependent relationship was identified where a 600-mg dose had a higher odds ratio (OR) than a 400-mg dose of teicoplanin. Both patients with T1DM and T2DM had a significantly higher risk of developing AKI after CABG than patients without diabetes; patients with T1DM had a higher risk than those with T2DM. Patients who developed AKI after CABG had an increased long-term risk of developing heart failure. AKI was also associated with increased long- and short-term mortality and an increased risk of the combined outcome of long-term mortality, heart failure, myocardial infarction, or stroke. Even minimal increases in the SCr concentration of 0 to 26 μmol/L was associated with increased long-term mortality, and the combined outcome, but was not associated with short-term mortality.

Conclusion: Patients treated with teicoplanin and patients with T1DM or T2DM are at an increased risk of developing AKI in cardiac surgery. Patients developing AKI after CABG have an increased long-term risk of developing heart failure. Minimal increases in serum creatinine is associated with an increased long-term risk of death and cardiovascular events. AKI but not minimal increases in SCr was associated with increased 30-day mortality.

LIST OF PUBLICATIONS

This thesis is based on the following studies, which are referred to in the text by roman numerals (I to IV). The studies are found at the end of the thesis.

I. **Antibiotic prophylaxis by teicoplanin and risk of acute kidney injury in cardiac surgery**
Daniel Olsson, Martin J. Holzmann, Ulrik Sartipy
Journal of Cardiothoracic and Vascular Anesthesia 2015; 29: 626-631

II. **Type 1 and type 2 diabetes mellitus and risk of acute kidney injury after coronary artery bypass grafting**
Daniel Hertzberg, Ulrik Sartipy, Martin J. Holzmann
American Heart Journal 2015; 170: 895-902

III. **Acute kidney injury following coronary artery bypass surgery and long-term risk of heart failure**
Daniel Olsson, Ulrik Sartipy, Frieder Braunschweig, Martin J. Holzmann
Circulation: Heart Failure 2013; 6:83-90

IV. **Minimal changes in postoperative creatinine values and early and late mortality and cardiovascular events after coronary artery bypass grafting**
Marcus Liotta[a], **Daniel Olsson**[a], Ulrik Sartipy, Martin J. Holzmann
American Journal of Cardiology 2014; 113: 70-75

[a] The authors contributed equally

TABLE OF CONTENTS

ABBREVIATIONS

AKI	Acute kidney injury
AKIN	Acute Kidney Injury Network
CABG	Coronary artery bypass grafting
CI	Confidence interval
CKD	Chronic kidney disease
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CRS	Cardiorenal syndrome
EuroSCORE	European System for Cardiac Operative Risk Evaluation
GFR	Glomerular filtration rate
ICD	International Classification of Diseases
KDIGO	Kidney Disease: Improving Global Outcomes
LVEF	Left ventricular ejection fraction
MDRD	Modification of Diet in Renal Disease
OR	Odds ratio
PIN	Personal identity number
RIFLE	Risk, Injury, Failure, Loss of kidney function, and End-stage renal disease
SCr	Serum creatinine
SWEDEHEART	Swedish Web-system for Enhancement and Development of Evidence-based care in Heart disease Evaluated According to Recommended Therapies

INTRODUCTION

Acute kidney injury (AKI) is defined as a sudden decrease in glomerular filtration rate (GFR) that results in decreased urine production and increased blood concentrations of solutes normally filtered from blood to urine. The definition of AKI covers the whole spectrum of renal dysfunction from a minor decline in GFR to renal failure requiring dialysis. Studies have shown that AKI is associated with higher mortality, a longer hospital stay, and the development of chronic kidney disease (CKD) in a variety of settings (2–4). Historically, most research has focused on severe reductions in GFR, in some instances requiring dialysis. Minor kidney injuries have received less attention. One explanation for this is the kidneys' high capacity to clinically recover their GFR; it has been thought that the kidneys readily heal after an insult. However, studies have suggested that even a transient decline in renal function is associated with an increased risk of developing CKD (5,6).

Cardiac surgery includes cardiac revascularization, valve surgery, and surgery involving the chamber walls and large adjacent blood vessels. AKI is a frequent complication after cardiac surgery, with an incidence of approximately 10% to 30% depending on the type of cardiac procedure performed (4,7). Etiological risk factors for AKI specific to cardiac surgery are factors mostly related to the use of cardiopulmonary bypass (7). Risk factors for AKI in both cardiac surgery and non-cardiac surgery include blood transfusion, hypotension, systemic inflammation, anemia, and the use of certain drugs such as antibiotics (8). Based on results from earlier studies, the development of AKI after cardiac surgery is important and needs further exploration. It will also be helpful to study AKI as a phenomenon in the cardiac surgery setting, not only because AKI is common but also because cardiac procedures are well standardized in many cases and the patients form a quite homogenous group. This is in contrast to for example the intensive care setting, in which AKI is common but the reasons for admission are much more heterogeneous.

The aim of this thesis was to further investigate the risk factors for and outcomes of AKI in patients undergoing cardiac surgery.

BACKGROUND

HISTORICAL PERSPECTIVE OF ACUTE KIDNEY INJURY

Acute renal failure has long been known as a devastating disorder. During World War I, many wounded soldiers developed "war nephritis" after traumatic injuries likely associated with rhabdomyolysis, shock, and sepsis (3). One of the earliest reports of acute renal failure in the 20th century was on war nephritis, published in *The Lancet* 1917 (9). Later, during World War II in 1941, a male leather worker became trapped beneath the debris of a demolished hostel and was hospitalized for a severe crush injury on his left leg. However, his urine production stopped and he died 6 days later. Autopsy showed swollen kidneys, and histological specimens showed tubular pigment casts. This case was described by Beall et al. and is one of the earliest published articles on acute renal failure with a pathophysiologic description (10). In 1945, Dr. Willem Kolff described the first survivor of dialysis. Later, in 1947, Bywaters began using hemodialysis to treat renal failure. In 1951, the term "acute renal failure" was introduced in the chapter entitled "Acute renal failure related to traumatic injuries" in the textbook *The Kidney: Structure and Function in Health and Disease.* In 1967, Silverstein developed hemofiltration, which increased the range of AKI treatments, and in 1979, Kramer developed continuous arteriovenous hemofiltration (3).

DEFINITION OF ACUTE KIDNEY INJURY

In 1994, a meta-analysis on risk factors for acute renal failure after surgery was published. The analysis included 28 studies, but none of them used the same definition of acute renal failure (11). This study highlighted the lack of uniform diagnostic criteria for acute renal failure, which made comparisons among studies very difficult (12). In an attempt to unify the diagnostic criteria for acute renal failure, the Acute Dialysis Quality Initiative published a consensus definition of acute renal failure called the Risk, Injury, Failure, Loss of kidney function, and End-stage renal disease (RIFLE) criteria in 2004 (13). Acute renal failure was also renamed AKI. Traditionally, the term "acute renal failure" was closely associated with the need for dialysis; therefore, the new term "acute kidney injury" was established to emphasize that even minor changes in renal function require further attention. The AKI era was thus started. The RIFLE criteria classify AKI according to a relative increase in the SCr concentration, or decrease in GFR, or a decrease in urine output. Five stages of severity were defined (Table 1). Since the RIFLE criteria were introduced, there was an increased interest in the clinical effects of AKI. The RIFLE criteria have been evaluated in different clinical settings, including critical care and cardiac surgery (14–17). Studies using the RIFLE criteria have shown a stepwise association with the stage of AKI and worse clinical outcomes such as increased mortality, longer intensive care unit stay, and reduced renal recovery (14–17). Even a transient decrease in renal function is associated with increased mortality (18).

Since the RIFLE criteria was introduced further effort has been put to find an optimal definition of AKI that could both serve as a sensitive and specific definition and also be easy to use in both research and clinical practice. In 2007, the Acute Kidney Injury Network (AKIN) revised the RIFLE criteria by adding an absolute change in the SCr concentration of 26 μmol/L within 48 hours to AKI stage 1 and excluding the GFR criteria (19). The additional criterion of an absolute change in the SCr concentration increased the sensitivity for AKI stage 1 (20). Renal replacement therapy was excluded from the AKIN criteria because this therapy was regarded as an outcome of AKI rather than an AKI stage (19). The RIFLE and AKIN criteria were later unified with the 2012 Kidney Disease: Improving Global Outcomes (KDIGO) criteria (Table 1) (21). The KDIGO criteria include both a short (24-hour) and extended (48-hour) time frame for the diagnosis of AKI. KDIGO also reintroduced a GFR criterion for stage 3 AKI, but the criterion was limited to patients <18 years of age.

Since 2004, many studies have used the RIFLE, AKIN, and KDIGO consensus criteria. However, a lot of them have not included urine output criteria because such data are often unavailable in observational cohort studies. Therefore, evidence for changes in urine output is relatively weak (17). Additionally, the widespread use of diuretics in belief to improve the outcome in AKI or to improve the patient's fluid balance, further complicates the use of urine output criteria. It has been argued that the KDIGO stage 1 criterion of a urine output of <0.5 mL/kg/h for 6 hours is too liberal and not as closely associated with mortality and dialysis as is the SCr criterion for AKI stage 1 (22). A cutoff value of 0.3 instead of 0.5 mL/kg/h has been found to be a better predictor (22).

A weakness of the SCr criteria is that AKI and an elevated SCr concentration might already be present when the patient is admitted to the hospital (23). A further increase in the SCr concentration after admission might underestimate the true severity of AKI. There have earlier been attempts to back-calculate the baseline SCr concentration from algorithms originally aimed at estimating the GFR. These algorithms often include age, sex, and weight. However, these calculations have been shown to be imprecise and to have a low specificity for the diagnosis of AKI than using the true baseline SCr concentration (24). Several investigators are currently focusing on serial measurements of the SCr concentration within a short time period and estimation of AKI according to SCr kinetics and variability (25).

Table 1. Definition of AKI according to the RIFLE (13), AKIN (19) and KDIGO (21) criteria.

AKI stage	Increase in serum creatinine concentration	Urinary output criteria
RIFLE		
Risk	≥1.5- to 2-fold increase, *or* decrease in GFR >25%	<0.5 ml/kg/h for ≥6h to <12 hours
Injury	≥2.0- to 3.0-fold increase, *or* decrease in GFR >50%	<0.5 ml/kg/h for ≥12h
Failure	≥3.0-fold, *or* 44 μmol/l absolute increase if baseline SCr ≥354 μmol/l *or* decrease in GFR ≥75%	<0.3 ml/kg/h for ≥24h *or* anuria for ≥12 h
Loss of Kidney Function	Complete loss of renal function for >4 weeks	
End-stage Renal Disease	End-stage renal disease >3 months	
AKIN		
Stage 1	≥1.5- to 2-fold increase, *or* ≥26.4 μmol/l absolute increase within 48 h	<0.5 ml/kg/h for >6h to 12 hours
Stage 2	>2.0- to 3.0-fold increase	<0.5 ml/kg/h for >12h
Stage 3	>3.0-fold increase, *or* ≥44 μmol/l absolute if baseline ≥354 μmol/l	<0.3 ml/kg/h for ≥24h *or* anuria for ≥12 h
KDIGO		
Stage 1	≥1.5- to 1.9-fold increase within 7 days, *or* >26.5 μmol/l within 48 hours	<0.5 ml/kg/h for 6 to 12 h
Stage 2	≥2.0- to 2.9-fold increase within 7 days	<0.5 ml/kg/h for ≥12 hours
Stage 3	≥3.0-fold increase, *or* >354 μmol/l increase within 7 days, or initiation of renal replacement therapy, *or* a decrease of GFR to <35 ml/min/1.73m^2 in patients <18 years of age	<0.3 ml/kg/h for ≥24h *or* anuria for ≥12 h

AKI = acute kidney injury, AKIN = Acute Kidney Injury Network, KDIGO = Kidney Disease: Improving Global Outcomes, RIFLE = Risk, Injury, Failure, Loss of kidney function, and End-stage renal disease.

CHRONIC KIDNEY DISEASE AND ACUTE KIDNEY DISEASE

Chronic kidney disease

Aiming to devise a uniform nomenclature and definition of chronic renal dysfunction, the National Kidney Foundation Kidney Disease Outcomes Quality Initiative established a consensus classification of renal dysfunction in 2002 using the term "chronic kidney disease" (26). The definition of CKD has been refined and updated by the KDIGO CKD Work Group, which defines CKD as "abnormalities of kidney structure or function, present for >3 months, with implications for health" (27). The KDIGO criterion for CKD is either a GFR of <60 mL/min/1.73 m^2 for >3 months or signs of kidney damage for >3 months. Kidney damage is defined as the presence of one or more of the following: albuminuria, urine sediment abnormalities, electrolyte and other abnormalities due to tubular disorders, abnormalities detected by histology, structural abnormalities detected by imaging, or a history of kidney transplantation (27). CKD is staged according to cause of CKD, GFR category, and degree of albuminuria (Table 2) (27). The prognosis of CKD has been well studied and there has been found a strong association between CKD stages and increased risk of cardiovascular disease, and death (28). Both CKD and cardiovascular disease share several risk factors such as diabetes mellitus and obesity (29).

Table 2. Staging of chronic kidney disease according to KDIGO (27)

GFR category	Description of function	GFR (mL/min/1.73m^2)
G1	Normal	≥90
G2	Mildly decreased	60-89
G3a	Mildly to moderately decreased	45-59
G3b	Moderately to severely decreased	30-44
G4	Severely decreased	15-29
G5	Kidney failure	<15
Albuminuria category	**Description of albuminuria**	**Albumin (mg)/creatinine (mmol)**
A1	Normal	<3
A2	Moderately increased	3-30
A3	Severely increased	>30

GFR = Glomerular filtration rate, KDIGO = Kidney Disease: Improving Global Outcomes.

Acute kidney disease

To further develop a uniform nomenclature of acute, subacute, and chronic renal dysfunction, the KDIGO AKI Work Group proposed the concept of "acute kidney disease" (30). The concept of acute kidney disease emphasizes the potentially vulnerable period after AKI during which some patients recover their renal function better than others. Further awareness, research, and focus of the period following AKI might enhance renal recovery and prevent patients from progressing to CKD. Acute kidney disease is defined as having or developing one or more of the following within the past 3 months: AKI, a GFR of <60 mL/min/1.73 m^2, a ≥35% decrease in the GFR, a ≥50% increase in the SCr concentration, or signs of kidney damage.

RENAL PHYSIOLOGY

The kidneys perform three vital functions; excretion of waste products, homeostasis, and hormone production. They filter water-soluble metabolites, toxins, and drugs from blood to be excreted in the urine. They control the fluid-, salt- and acid-base balance in the blood. The kidneys also produce hormones involved in erythropoiesis, calcium-turnover, and regulation of fluid balance and blood pressure (1).

Even though the weight of the kidneys is only 0.5% of total body weight, nearly 20% of cardiac output goes to the kidneys. The blood enters the kidneys via renal arteries that divide into progressively smaller branches until they become afferent arterioles located proximally to the glomerulus (Figure 1). After the glomerulus blood drains to efferent arterioles. The glomerulus is the first part of the nephron - an independent urine-producing unit of which there are roughly two million in the kidneys - and constitutes a cluster of blood vessels. The glomerulus has a greater permeability than other capillaries and filters molecules depending on their size and charge. The glomerular filtration barrier between the capillary lumen and bowman's capsule is comprised of several layers with different filter sizes. One such layer is also negatively charged and is thought to prevent negative proteins from passing through. The filtered primary urine is collected in bowman's capsule and

drained into the tubule. Approximately 180 L of primary urine is filtered daily through the glomerulus, however the majority is reabsorbed by the renal tubules leading to a urine output of approximately 1 ml/kg bodyweight/hr. The filtration over the glomerulus is a passive process driven by the blood pressure that is higher than both the hydrostatic pressure within bowman's capsule, and the oncotic pressure exerted by the blood. The primary urine resembles plasma except that it contains very small amounts of proteins and thus has almost no oncotic pressure.

The afferent arteriole and efferent arteriole regulates the blood pressure in the glomerulus and their tone is regulated by sympathetic innervation and chemical mediators (1). The efferent arteriole divides into peritubular capillaries that surround the tubule. The nephrons located in the juxtamedullary region form the vasa recta that pass down to the renal medulla. To maintain an adequate blood filtration capacity, the glomeruli need a high renal blood flow. The opposite is needed in the renal medulla where a low blood flow is necessary to maintain a high osmotic gradient. This enables fluid reabsorption from the part of the renal tubule that descends to the medulla to concentrate the primary urine. The renal blood flow is thereby unevenly distributed and only a minor portion is going to the renal medulla (1). The sodium resorption is energy consuming and is thought to be a large part of the renal oxygen consumption (31). Due to the relative low blood flow, but also a high metabolic activity, the renal medulla is exquisitely sensitive to decreased oxygen delivery.

The renal autoregulation consists of two mechanisms that maintain renal blood flow and glomerular filtration; The first is a baroreceptor-mechanism in afferent arterioles. If the blood pressure drops it will lead to a decrease in wall tension/diameter in the arteriole. This will lead to a subsequent stimulation of neighboring granular cells to release renin into the circulation. Activating the renin-angiotensin-aldosterone-system lead to water retention and increased mean arterial pressure (32). The second mechanism is the tubuloglomerular feedback where the macula densa in the tubule reacts to decreased volume and sodium chloride concentration, signaling the afferent arteriole to dilate. The renal autoregulation has been studied in dogs and has been found to maintain renal blood flow down to a mean arterial pressure of 65 mmHg. However, after sympathetic stimulation this threshold increases to around 95 mmHg (33).

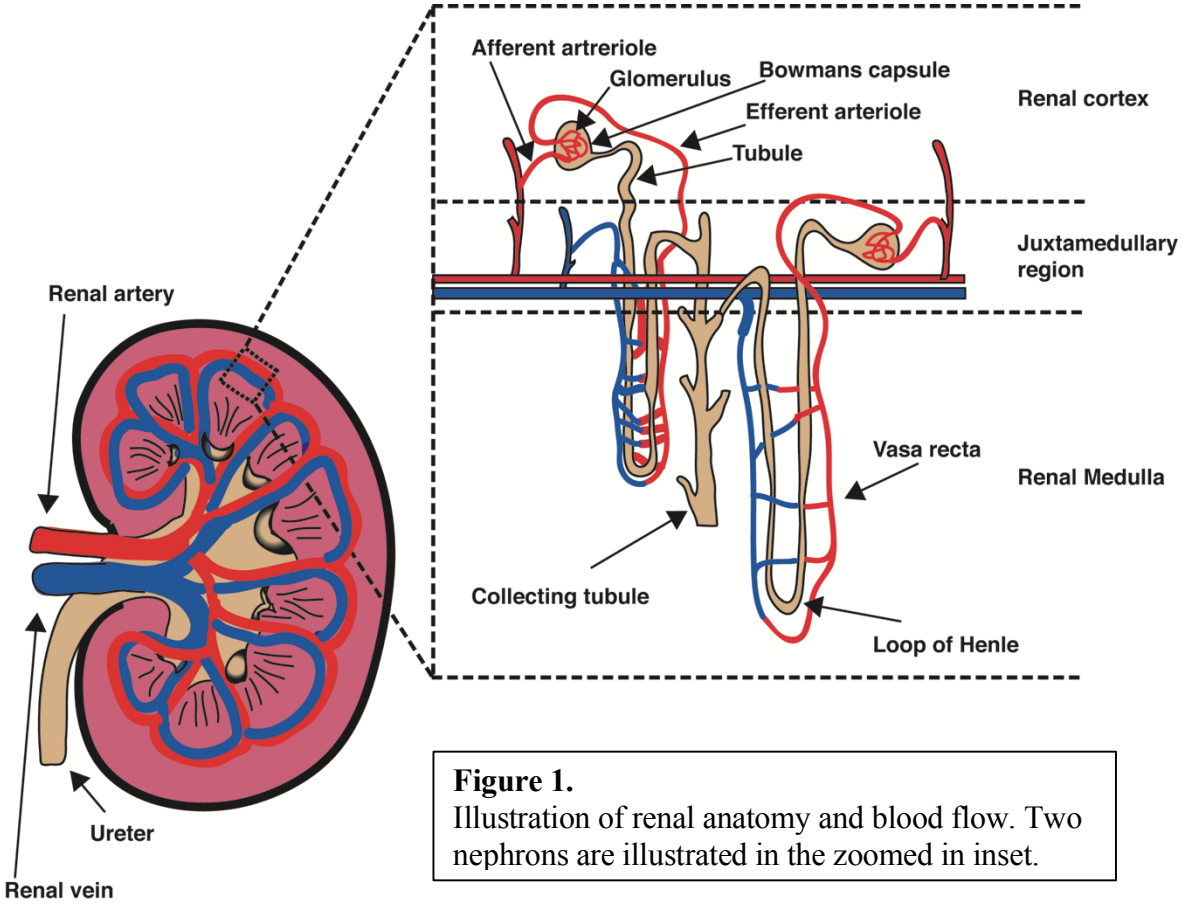

Figure 1.
Illustration of renal anatomy and blood flow. Two nephrons are illustrated in the zoomed in inset.

ACUTE KIDNEY INJURY BIOMARKERS

Serum creatinine

Creatinine is generated from breakdown of creatine. Creatine is a protein based on the amino acids glycine and arginine. The last step in the biosynthesis of endogenous creatine mainly occurs in the liver, but the precursor guanidinoacetate is mainly synthesized in the kidneys. Creatine is also ingested through the diet, mainly from meat, but is also a common supplement in sports nutrition to enhance athletic performance. It is transported to many organs via the blood and serves as a high-energy phosphate transporter for adenosine triphosphate production (34). The highest concentrations of creatine are found in skeletal muscle. In skeletal muscle, creatine acts as an adenosine triphosphate buffer and constitutes >90% of the body's total pool of creatine and phosphorylcreatine (34). Creatine and phosphorylcreatine are spontaneously and irreversibly broken down to creatinine at an almost constant rate (34). A 70-kg man contains around 120 g of creatine and phosphorylcreatine, and around 1.7% (2 g) is converted to creatinine per day (34). Raw meat contains around 4 g/kg of creatine. Creatinine is membrane-permeable and diffuses freely into the blood. It is freely excreted into the urine by glomerular filtration, and around 15% is also actively secreted into the urine by tubular cells (35). A minor proportion is metabolized or excreted in the feces (34).

Because creatinine is produced at a constant rate, is almost metabolically inert, and is almost solely excreted by glomerular filtration, it can serve as a marker for the GFR. Urine stasis or an injury occurring between the glomerulus and collecting duct will inhibit excretion of creatinine via the urine, leading to a subsequent increase in the SCr concentration. An acute increase in the SCr concentration can be caused by AKI, but may also be caused by dietary intake, rhabdomyolysis, muscle trauma, and reduced tubular secretion secondary to certain medications such as trimethoprim and cephalosporins (36). Chronic causes of an increased SCr concentration are CKD, large muscle mass, and high intake of creatine (sports nutrition) (36). Among individuals with stable renal function, the SCr concentration varies by about 8% during the day (35).

The SCr concentration has been criticized for being a late and unspecific marker for AKI (24). After a sudden decline in GFR it can take 24 to 48 hours before the SCr concentration is reaching a new steady state (37). Additionally, almost half of the nephrons can be lost without a change in the steady-state SCr concentration because of compensatory hyperfiltration (38). However, the author argues that the SCr concentration is not a poor marker in general; in fact, it is an adequate biomarker of GFR (38). The SCr concentration is a global marker for glomerular filtration, and an increase in the SCr concentration reveals effects of AKI from the glomerulus to the collecting duct. Few factors other than a change in GFR will cause a significant and acute change in the SCr concentration. The usefulness of the SCr concentration depends on the purpose for its use, in what setting it is being used, and how often it is measured. For example, is it being used for early detection in interventional studies? Or is it being used to study prognosis and risk factors?

New biomarkers

An ideal AKI biomarker would allow for instantaneous diagnosis of AKI, identification of the injury location and etiology, and prediction of the patient's outcome. During the past decade, many new biomarkers for AKI have been identified, providing hope for further improvements in AKI diagnostics (39). These molecules are analyzed in blood or urine and serve as markers for estimated renal filtration function, structural injury or indirect signs of structural injury, and even cellular stress. The biomarkers are of various quality. Many are still undergoing validation, and very few have been introduced in clinical practice. There are still uncertainties regarding their cut-off values, sex- and age-related differences, and interpretation in different settings such as sepsis, cardiac surgery, and CKD (40,41).

Currently, one of the most popular tests for AKI is the NephroCheck Test (Astute Medical Inc., San Diego, CA), which is the first point-of-care device to detect early AKI (42). The NephroCheck Test analyzes both tissue inhibitor of metalloproteinase-2 (TIMP-2) and insulin-like growth factor binding protein 7 (IGFBP7) and is an example of a combined test with higher sensitivity than if these two parameters were analyzed separately. These molecules are markers for cellular arrest and are thought to serve as very early indicators of AKI. In the context of sepsis, the NephroCheck Test predicted KDIGO stage 2 or 3 AKI within 12 hours following testing (43,44).

GLOMERULAR FILTRATION RATE

GFR is the total amount of blood that is filtered through all glomeruli in the kidneys per minute. The GFR is dependent on the filtration surface area, permeability of the glomeruli, and net filtration pressure. GFR can be measured using substances that are metabolically inert, freely filtered, and not reabsorbed or secreted in the tubules. No such endogenous substance has been identified; instead, exogenous substances (e.g., inulin) are the gold standard for GFR measurement. Calculation of GFR is based on the blood and urine concentration of the substance after administration (35). However, the use of exogenous substances is expensive and time-consuming and carries a risk of complications. Of the many important renal functions, GFR can be used to assess overall renal function and determine the stage of CKD. It is also used for dose adjustment of medications with renal elimination (45). GFR is usually expressed in milliliters per minute per 1.73 m^2. The area of 1.73 m^2 is the average surface area of an adult. An individual's true GFR can thereby be overestimated or underestimated in a very small or large individual, respectively. The GFR varies according to age, sex, body size, and ethnicity. A normal resting GFR is around 120 to 130 mL/min/1.73m^2 in young adults and declines from this age around 9 mL/min/1.73m^2 per decade (46–48).

The SCr concentration is in balance with GFR, and the properties of creatinine make it suitable for estimation of GFR. However, it is not possible to directly transform the SCr concentration into GFR because of individual differences in creatinine turnover, which is mainly dependent on total muscle mass. To overcome this problem, mathematical equations have been developed using both the SCr concentration and body composition parameters (Table 3). Estimated GFR is calculated from its inverse relationship with the SCr concentration adjusted for non-renal variables that influence the SCr concentration, such as age, sex, and ethnicity. New formulas also include other biomarkers such as cystatin C. Cystatin C has properties similar to those of creatinine, and GFR estimations using both SCr and cystatin C are reportedly more accurate than the use of either one alone (45).

Many consider that measured GFR is more clinically important than the estimated GFR because it provides the "true" value of the GFR. This is thought to be especially important in the long-term monitoring of renal function because among other parameters, the muscle mass of patients with CKD can vary substantially. However, this has been questioned because parameters used in GFR measurement also vary (e.g., inulin vs. iothalamate), and the measured GFR does not consistently improve prediction of renal-related outcomes (49). Estimated GFR is considered suitable to monitor changes in renal function in many cases (35).

Table 3. Overview of some of the most frequently used equations for estimation of GFR in adults.

Name	Year introduced	Variables included	Comments
Cockcroft-Gault formula (50)	1976	SCr, age, sex, weight	Generally overestimates GFR around 10 to 20 % since it estimates creatinine clearance. Overestimates GFR in obese, and underestimates in elderly (51,52). Accurate in individuals <65 years with GFR 20 to 60.
MDRD Study Equation (53)	1999	SCr, age, sex, urea, albumin, ethnicity	Have been updated/modified several times. Underestimates GFR among patients with GFR >60. More precis than equation above. The study material did not include individuals >70 years of age.
Lund-Malmö-1 equation (54)	2007	SCr, age	Mostly validated in Swedish Caucasians. The Lund-Malmö-2 equation includes lean body mass which removes bias in obese and underweight men (45).
CKD-EPI formula (55)	2009	Age, sex, SCr, ethnicity	Comparable with MDRD among individuals with GFR<60. More precise among individuals with GFR >60.

CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration, GFR = glomerular filtration rate, MDRD = Modification of Diet in Renal Disease, SCr = serum creatinine.

INCIDENCE AND OUTCOMES

The reported worldwide incidence of AKI has increased during the last few decades (2). In some parts of the world, this increased incidence may be explained by the aging population and increased number of individuals with multiple diseases. The increased use of radiological examinations with iodinated contrast agents and the use of nephrotoxic drugs might also partly explain the increasing incidence of AKI. Variations in the incidence of AKI and complications associated with AKI might also be explained by the plentiful definitions of AKI that are in use worldwide. It is also possible that increased awareness and reporting of AKI among clinical practitioners have led to increased incidences in studies using diagnostic codes.

AKI is common in the hospital setting. Approximately 20% of hospitalized adults and 30% of hospitalized children develop AKI (2). The frequency of AKI varies depending on the clinical setting and is most common in patients who are critically ill, have undergone cardiac surgery, or have been hospitalized for heart failure, with a pooled incidence of around 32%, 32%, and 24% respectively (2).

The mortality associated with AKI is high but depends on the clinical context. A large meta-analysis by Susantitaphong et al. has investigated the pooled AKI-associated mortality in several clinical contexts (2). In 91 of the 106 included studies the duration of follow-up was <3 months. The highest AKI-associated mortality was among patients with trauma, critical illness, and hematologic or oncologic disease, in whom the mortality is around 25% to 30% (2). The AKI-associated mortality among patients who have undergone cardiac surgery was around 8% (2). AKI is also associated with the development of CKD, longer intensive care unit and hospital stays, and increased health care costs (3). Approximately 5% to 20% of critically ill patients who require dialysis due to AKI remain dialysis-dependent at hospital discharge (3,56). Around 5% of patients who develop stage 2 to 3 AKI after isolated CABG progress to end-stage renal disease requiring dialysis within a period of 5 years after surgery (4).

CAUSES OF ACUTE KIDNEY INJURY

Traditionally, the etiologies of AKI have been divided into three categories: prerenal, renal, and postrenal AKI (Figure 2). This categorization is used to help the clinician identify the cause of AKI. Depending on the extent of the insult, any of these three categories of AKI can cause loss of renal functional mass and CKD. The combination of prerenal and renal AKI is common and may occur, for example, in patients with sepsis or those undergoing cardiac surgery. AKI is seldom symptomatic; clinical signs and symptoms are related to the underlying cause. The most common etiologies of AKI are presented in Figure 2. (57)

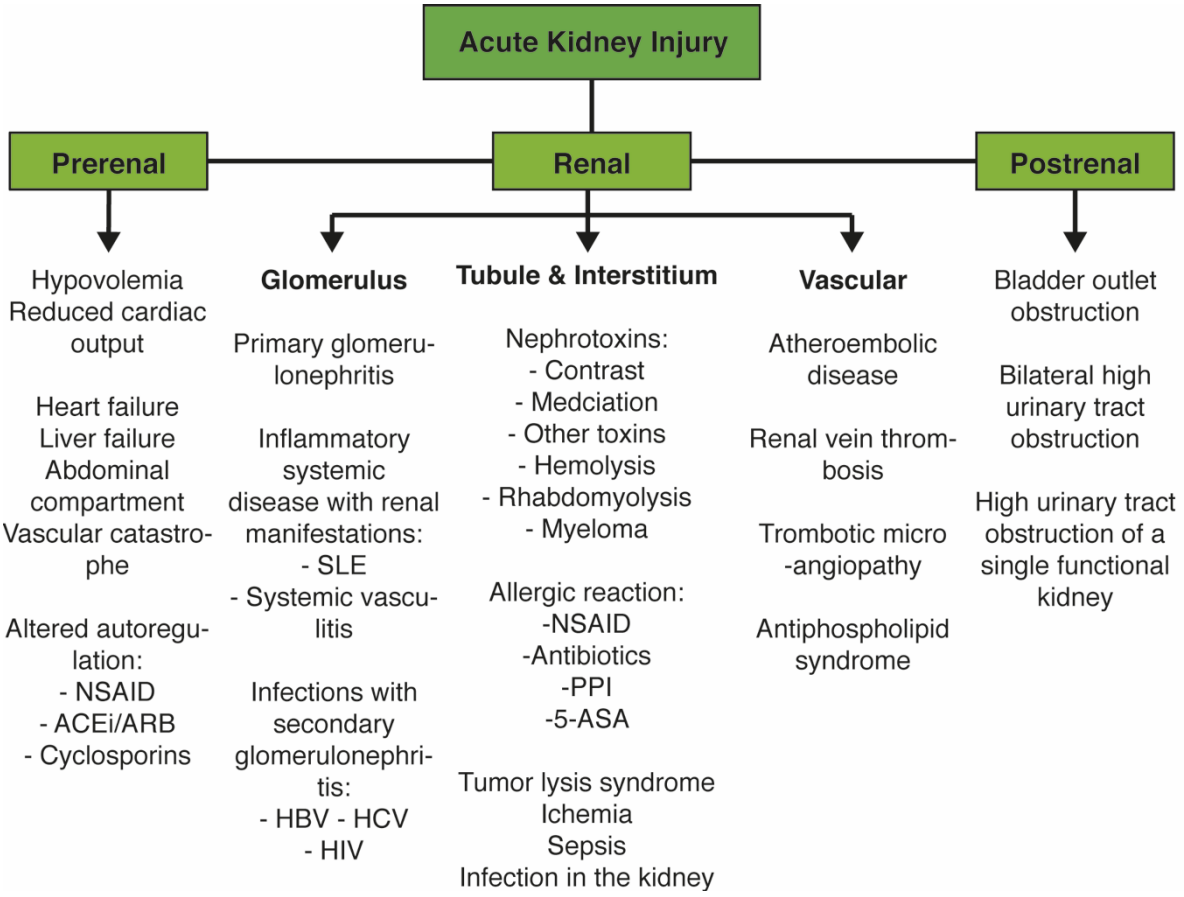

Figure 2.
Schematic overview of the most common etiologies of AKI divided into prerenal, renal, and postrenal causes.
5-ASA = 5-aminosalicylic acid, ACEi = Angiotensin converting enzyme inhibitor, ARB = angiotensin receptor blocker, HBV = hepatitis B virus, HCV = hepatitis C virus, NSAID = nonsteroidal anti-inflammatory drug, PPI = proton pump inhibitor, SLE = systemic lupus erythematosus.
Figure from Hertzberg et al. 2016 (58). Reprinted and modified with permission from

Perioperative AKI

Perioperative AKI is defined as rapid deterioration of renal function during or shortly after surgery. The incidence of perioperative AKI is most common in cardiac, orthopedic, and abdominal surgery with an incidence of around 25%, 22%, and 20%, respectively (59). The

incidence is higher in surgical patients with several risk factors for AKI, such as in patients undergoing gastric bypass surgery or hip fracture surgery (59). The incidence is also dependent on the specific surgical procedure being performed. The mechanisms for perioperative AKI are often multifactorial. Important factors in perioperative AKI are hypoperfusion, venous congestion, nephrotoxin exposure, inflammation, and oxidative stress (Figure 3) (60). Risk factors for perioperative AKI can be divided into three categories: preoperative demographic characteristics and comorbidities, acute preoperative conditions and nephrotoxin exposure, and intraoperative procedures and complications. Patient characteristics and comorbidities associated with AKI include high age, female sex, CKD, diabetes, congestive heart failure, chronic obstructive pulmonary disease, peripheral vascular disease, and high body mass index (21,59,61,62). Preoperative conditions such as dehydration, anemia, and acute decompensated heart failure are also associated with AKI (59). Perioperative risk factors for AKI include hypotension, hypovolemia, blood loss, anemia, blood transfusion, and cardiopulmonary bypass (8).

In cardiac surgery, much attention has been directed toward the cardiopulmonary bypass circuit (63). This circuit is thought to cause ischemia/reperfusion injury, activation of inflammatory pathways due to exposure to artificial surfaces, hemolysis with subsequent release of heme and labile iron, and generation of reactive oxygen species (63). The lack of pulsatile blood flow may be another contributing factor (59). Prolonged durations of cardiopulmonary bypass, aortic cross-clamping, and deep hypothermic circulatory arrest are other risk factors for AKI in cardiac surgery. These factors are also associated with low cardiac output syndrome (59,64). Cardiac surgery without cardiopulmonary bypass (off-pump surgery) has been thought to reduce the risk of AKI. A meta-analysis of randomized controlled trials showed a lower incidence of AKI but no decreased need for renal replacement therapy in patients who underwent off-pump compared to on-pump surgery (65). These results are consistent with other studies showing that off-pump surgery does not reduce the risk of dialysis within 30 days or 1 year (66–68). However, Chawla et al. investigated differences in the benefits of off-pump surgery with respect to preoperative renal function and found that off-pump surgery in patients with CKD undergoing CABG was associated with a lower risk of death and need for renal replacement therapy (69). Blood loss, anemia, and blood transfusions are related to perioperative AKI in patients undergoing cardiac surgery. The age of the red blood cells is not associated with adverse outcomes, including AKI (70). Perioperative administration of iodinated contrast, aminoglycosides, angiotensin-converting enzyme inhibitors, and loop diuretics is also associated with AKI in patients undergoing cardiac surgery (64).

The rate of AKI after cardiac surgery is strongly correlated with the surgical procedure. CABG is associated with the lowest incidence of AKI, while valve replacement, especially with concurrent CABG, is associated with the highest incidence of AKI (59).

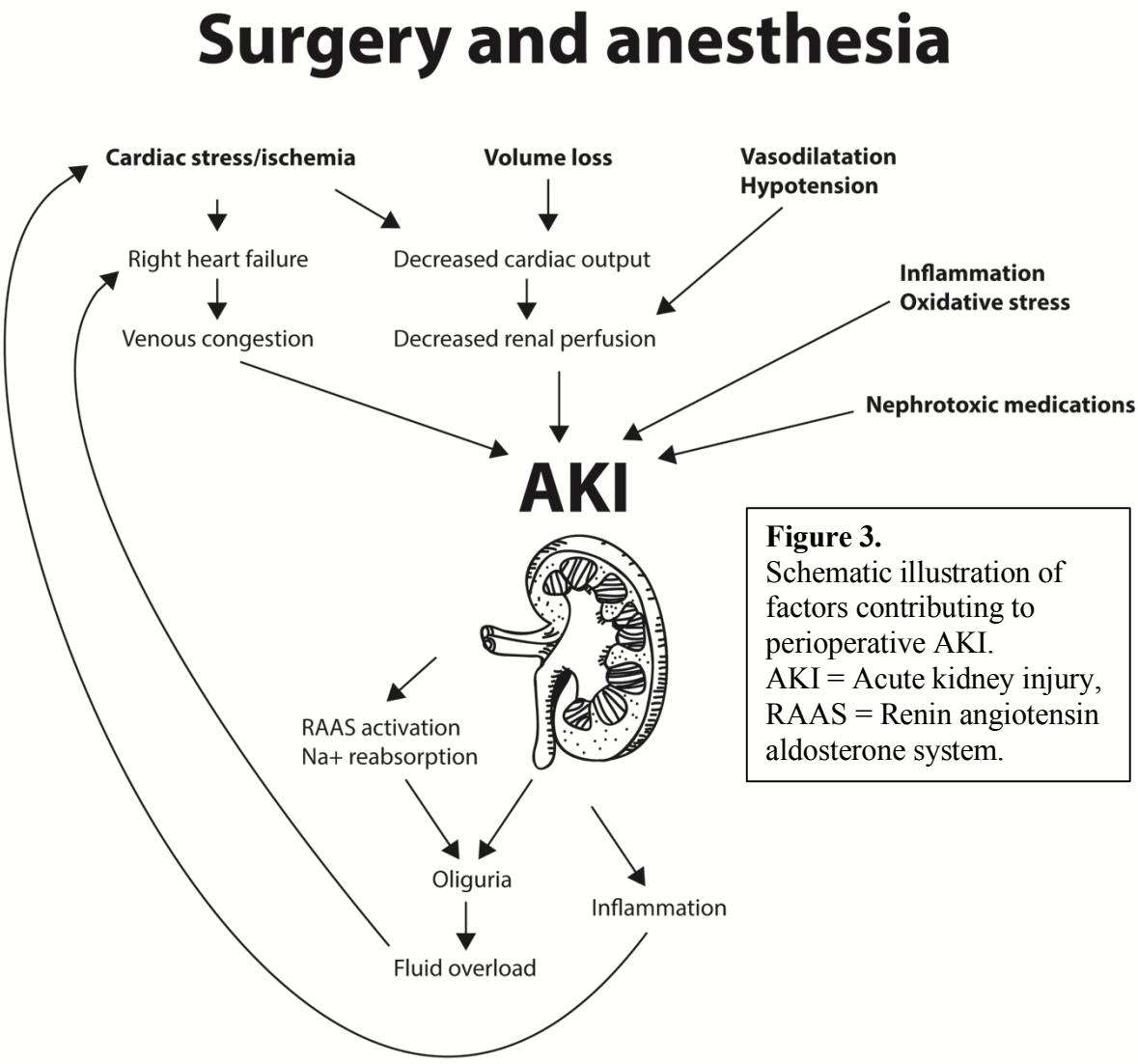

Figure 3.
Schematic illustration of factors contributing to perioperative AKI.
AKI = Acute kidney injury, RAAS = Renin angiotensin aldosterone system.

PREVENTION AND TREATMENT OF AKI

The principles of treatment for AKI can be divided into three categories: treatment of the underlying cause, optimization for recovery, and specific AKI treatment. This text will briefly mention the two latter categories and cover the most frequently discussed interventions.

Optimization for recovery

Optimization for AKI recovery involves volume and hemodynamic optimization, treatment of electrolyte disturbances, and dose adjustment or discontinuation of medications that are nephrotoxic or are dependent on renal elimination (21,71).

Hypoperfusion is an important factor in many patients with AKI, and hemodynamic optimization is a cornerstone of AKI treatment. The goal is to maintain adequate renal perfusion that allows for sufficient glomerular filtration and oxygenation of the renal tissue. The optimal blood pressure target in patients with AKI remains unknown, and few studies have investigated this issue. In noncardiac surgery populations, periods of a mean arterial pressure <55 to <60 mmHg have been associated with an increased risk for AKI (72,73). A

study on patients undergoing CABG showed that a mean target arterial pressure of 75 to 85 mmHg had no protective effect on the risk of AKI compared with a target pressure of 50 to 60 mmHg (74). In contrast, a study of patients with vasodilatory shock after cardiac surgery showed that restoration of the mean arterial pressure from 60 to 75 mmHg using norepinephrine was associated with an increased GFR and improved renal oxygen delivery (75). To be noted, there are likely individual differences and higher blood pressures might be needed in patients with chronic hypertension and possibly in patients with AKI with edema within the renal capsule.

The importance of fluid overload and venous congestion in patients with AKI has gained increasing attention. The kidneys are surrounded by a relatively inflexible capsule. Excessive fluid therapy in combination with AKI can cause high intracapsular pressure secondary to interstitial edema and a subsequent decrease in renal perfusion (76–78). I an animal model of ischemia-induced AKI, there was an association between subcapsular pressure and degree of AKI. Also, decapsulation improved renal function (77). The clinician must therefore administer fluid therapy to ensure adequate cardiac output while avoiding fluid overload. Venous congestion also decreases renal perfusion and is thus one of many problems in the panorama of the failing heart (cardiorenal syndrome [CRS] type 1). Various vasoactive drugs have been evaluated in favor of stricter fluid therapy. A possible treatment for patients with AKI and venous congestion is inotropic therapy. A study on the inotropic and vasodilating drug levosimendan showed an increased cardiac index, stroke volume index, renal blood flow, and GFR after cardiac surgery (79).

The choice of fluid in treatment of AKI has been widely discussed. There is evidence that fluids with a high chloride content (e.g. sodium chloride 0.9%) may be harmful to the kidney (80). An increased chloride concentration at the macula densa has been shown to increase tubuloglomerular feedback, causing vasoconstriction of the preglomerular arterioles and a subsequent decrease in renal perfusion (81). However, a recent randomized trial revealed no increased risk of AKI in patients treated with sodium chloride 0.9% compared with a buffered solution (82).

Synthetic colloids are used for intravascular expansion. A possible benefit of colloids is that more of the fluid remains in the blood vessels and does not enter the interstitium. Studies have shown that the synthetic colloid hydroxyethyl starch is associated with an increased risk of AKI, dialysis, and death compared with crystalloid solutions (83,84). Other colloids such as dextrans and gelatins have not been widely investigated, although some evidence points toward effects similar to those of hydroxyethyl starch (85,86). Albumin solutions are not associated with AKI but are expensive (87). There have not been demonstrated a benefit of using albumin compared to crystalloid solutions for volume expansion in the prevention of AKI (87,88).

Specific AKI prevention and treatment

Furosemide is a diuretic that blocks energy-consuming sodium channels in the renal tubules and thereby has potential renoprotective qualities by decreasing oxygen consumption and increasing washout of nephrotoxic molecules (89,90). However, the use of diuretics is associated with a risk of hypovolemia. Furosemide also acidifies the urine, which potentially increases the formation of obstructive proteins in certain cases such as in hemolysis and also increase the activity of reactive oxygen species (63,89). Studies have not shown that furosemide prevents AKI or improves AKI outcomes except in patients with fluid overload (89). The administration of furosemide to prevent AKI after cardiac surgery and exposure to contrast has been associated with higher risk of AKI (91,92).

Acetylcysteine has not been shown to prevent AKI in patients who have undergone cardiac surgery or in those with sepsis (93–95). Studies on acetylcysteine to prevent contrast-induced AKI have provided conflicting results, but meta-analyses have identified a tendency toward a protective effect, especially in high-risk patients (96,97). Many guidelines state that there might be a protective effect of acetylcysteine, but it is not generally recommended. Hydration with a isotonic crystalloid solution is the primary preventive medication against contrast-induced AKI (98–100).

Statins have not been found to prevent AKI in patients undergoing cardiac surgery and have even been associated with a higher risk of AKI in the intensive care setting (101–104). In contrast, statins have shown a possible preventive effect against contrast-induced AKI (105,106). Statins are not recommended for AKI prevention or treatment because of conflicting results (21).

Remote ischemic preconditioning is performed to induce ischemia in an extremity by short episodes of external compression. The hypothesis is that the ischemia will activate ischemic-protective mechanisms in remote organs such as the kidneys by processes such as cell-cycle arrest in the renal tubules. However, study results have been inconsistent. In summary, there has been found a small preventive effect against contrast-induced AKI and a small to nonexistent preventive effect against AKI after cardiac surgery (107–113).

The timing of dialysis initiation in patients with AKI has been widely discussed. The most recent randomized trial (*ELAIN* trial) showed that early initiation of renal replacement therapy in critically ill patients was associated lower mortality and duration of renal replacement therapy (114). The former *AKIKI* trial showed that early initiation of renal replacement therapy had no benefits (115). However, early dialysis initiation in *AKIKI* resembled late initiation in *ELAIN*, which might explain the contradictory results.

THE CARDIORENAL SYNDROME

Heart and kidney function are closely interconnected. Their physiological interaction maintains the body's hemodynamic homeostasis. Acute or chronic disease in one of these organs can induce acute injury or chronic worsening of function in the other. This co-

pathology between the heart and kidney has been described as the CRS, which is sub-classified according to which organ is primarily diseased and within what time frame the interaction is occurring (Table 4) (116). Both the heart and kidneys share several risk factors for disease. For example, hypertension, diabetes mellitus, and peripheral vascular disease are risk factors for both heart failure and CKD (29,117–119).

Table 4. Description of the cardiorenal syndromes (116).

CRS type	Name	Description	Example
I	Acute cardio-renal syndrome	Acute worsening of cardiac function leading to AKI	Acute de-compensated heart failure
II	Chronic cardio-renal syndrome	Chronic cardiac dysfunction leading to kidney dysfunction	Congestive heart failure
III	Acute reno-cardiac syndrome	AKI leading to heart injury or dysfunction.	AKI unspecified
IV	Chronic reno-cardiac syndrome	CKD leading to heart injury, disease or dysfunction.	CKD
V	Secondary cardio-renal syndromes	Systemic disorders causing both cardiac and renal dysfunction	Sepsis

AKI = acute kidney injury, CKD = chronic kidney disease, CRS = cardiorenal syndrome.

Cardiorenal syndrome type III

A few animal studies have investigated the acute effects of AKI on the heart. Robinson et al showed a reduced response to cardiac inotropes in rats with glycerol-induced AKI (120). Kelly studied the effects of renal artery occlusion in rats and found increased blood levels of tumor necrosis factor-α and interleukin-1, increased cardiac leukocyte infiltration, and echocardiographic changes in left ventricular function after 48 hours (121). Sumida et al. cross-clamped the renal arteries in mice for 30 minutes. After 72 hours, the authors observed cardiomyocyte apoptosis, mitochondrial fragmentation, increased expression of tumor necrosis factor-α, and cardiac dysfunction on echocardiography (122). Other reported effects of AKI include fluid overload, electrolyte imbalances, acidemia, uremic toxins, activation of the sympathetic nervous system, and activation of the renin-angiotensin-aldosterone system (123).

Cardiac depression is common in patients with severe sepsis and septic shock (124). Signs of reduced left ventricular contractility are found on echocardiography in such patients; this phenomenon is called septic cardiomyopathy (124). Studies have repeatedly identified tumor necrosis factor-α and interleukin-1 as important endogenic mediators (125). These inflammatory mediators were also identified in the animal models of CRS type III established by Kelly and Sumida et al. (122). It is possible that AKI-induced inflammation affects the heart via pathways similar to those in septic cardiomyopathy. However, the clinical importance of CRS type III is largely unknown. In human AKI studies, it is often difficult to determine which organ was affected first. Many studies might have described CRS types III and I. It is also possible that such injuries arise simultaneously and continue in a vicious circle.

AIMS OF THE THESIS

The overall aim of this thesis was to further investigate the risk factors for and outcomes of AKI in patients undergoing cardiac surgery. The specific aims were:

Study I To study the association between treatment with the antibiotic prophylaxis teicoplanin in cardiac surgery and the risk of developing perioperative AKI.

Study II To study the association between preoperative type 1 diabetes mellitus and type 2 diabetes mellitus, respectively, and the risk of developing AKI after CABG.

Study III To study the association between AKI after CABG and the long-term risk for a first hospitalization for heart failure.

Study IV To study the association between minimal increases of 0 to 26 μmol/L in postoperative SCr concentrations and the long- and short-term risk of death or the combined outcome of long-term mortality, heart failure, myocardial infarction, or stroke.

SUBJECTS AND METHODS

REGISTERS

Personal identity number

Since 1947, all permanent residents of Sweden have been assigned a unique personal identity number (PIN) (126). The PIN is a 10-digit number that is divided into 3 parts. The first six digits contain information on the date of birth, the next three constitute the birth number containing information on sex (odd numbers = men, even numbers = women), and the last number is a control digit generated by a modulus 10 method on the former digits (126). The birth number originally contained information on the county of birth, but since 1990, the numbers have been randomly selected. The PIN is maintained by the National Tax Board, and all Swedish residents are recorded in the Total Population Register (127). Those who do not qualify for a PIN are assigned a personal coordination number. The number is often described as unique, but the combination only leaves room for 500 males and 499 females on each birth date. This caused a shortage of PINs from 1 January to 1 July in the 1950s and 1960s, mainly because immigrants arrived without precise knowledge of their birth date. Those born within the first half of the year are assigned a birth date of January 1, and those born in the second half of the year are assigned a birth date of July 1. Therefore, PINs are reused (n = 15,887 in 2009) (126). The reuse of PINs is strictly controlled, and PINs that are reused are mainly those that were assigned to an individual earlier but were never used or were used for only a short time because of death. When extracting or merging data from registers, reused numbers can cause scenarios such as double death dates or double cancer diagnoses.

Studies III and IV included the outcomes heart failure, myocardial infarction, and stroke obtained from the National Patient Register. The date of hospital discharge is included with these diagnoses. This minimizes the risk of a double diagnosis because the former owner of the PIN likely developed the diagnosis before the study follow-up of the new owner.

The National Board of Health and Welfare used PINs to merge the two datasets used in Studies II to IV after approval from the local ethics committee in Stockholm. The registers used for Studies I to IV are listed in Table 6.

SWEDEHEART

All patients undergoing cardiac surgery in Sweden are registered in the Swedish Heart Surgery Register (128,129). This register was established in 1992 and includes all eight cardiac surgery sites in Sweden. It includes demographic, administrative, and perioperative data (130). In 2009, the Swedish Web-system for Enhancement and Development of Evidence-based care in Heart disease Evaluated According to Recommended Therapies (SWEDEHEART) was created by merging five quality registers on cardiac care: RIKS-HIA, the register on myocardial infarction care; SCAAR, the register for coronary angiography and percutaneous coronary intervention; SEPHIA, the register for secondary prevention following coronary intensive care; the percutaneous valve register; and the Swedish Heart Surgery Register (128). SWEDEHEART is financed by the local health care provider (Swedish Association of Local Authorities and Regions) (128).

The data quality of parts of SWEDEHEART is continually evaluated (128). Each year, a monitor randomly visits approximately 30 of the 74 hospitals and randomly selects about 30 patients for comparison of the data in SWEDEHEART with the data in the medical records (129). In 2007, RIKS-HIA exhibited 96% agreement with the medical records (128).

The (Swedish) National Patient Register

The National Patient Register was founded by the National Board of Health and Welfare in 1964 and has covered all of Sweden since 1987 (131). The register contains patient data (PIN, age, place of residence), geographical data (county, hospital/clinic), administrative data (locations and dates of admission and discharge), and medical data (primary and secondary discharge diagnoses, and performed procedures) (131). The diagnoses and performed procedures in the National Patient Register are classified according to the World Health Organization International Classification of Diseases (ICD).

Data on the outcome variables heart failure, myocardial infarction, and stroke in Studies III and IV were extracted from the National Patient Register. The validity of these diagnoses have been evaluated. Heart failure as a primary discharge diagnosis has been shown to be correct in 88% of cases (132,133). The diagnosis of myocardial infarction is correct in 98% to 100% of cases, and the proportion of myocardial infarctions identified through the register compared to various data sources ranges from 77% to 92% (133,134). The diagnosis of stroke is correct in 70% to 99% of cases, and the proportion of myocardial infarction identified through the register ranges from 84% to 95% (133).

The Cause of Death Register

The Cause of Death Register was founded by the National Board of Health and Welfare in 1954 with the aim of describing causes of death and following the trends of mortality from certain causes in Sweden (135). It registers all deceased Swedish residents and contains information on geographical data, age, time of death, and cause of death coded according to

the ICD (135). Since 2011, the register has also included individuals that are not Swedish residents but who died in Sweden.

The Swedish National Diabetes Register

In 1996, the Swedish Society of Diabetology initiated the Swedish National Diabetes Register with the main aim of reducing morbidity secondary to diabetes. This register is designed to compare the clinical results among all diabetes care units (136). The register contains data on demographics, the duration of diabetes, treatment indications and modalities, cardiovascular risk factors, and complications of diabetes (136,137). After comparison with the Prescribed Drug Register in 2014, the national coverage of the National Diabetes Register reached 90% (138). The validity of the diagnosis of T1DM was previously found to have 97% accuracy (139).

The Swedish Renal Register

The active care of uremia was started to be registered by the Swedish Registry for Active Treatment of Uremia in 1991. The register was later merged with other Swedish renal registers to become the Swedish Renal Register (140). All patients with end-stage renal disease having renal replacement therapy or receiving a kidney transplant are expected to be reported into the register. The prevalence is ≈1000 per 1000 000 individuals in Sweden. All units that carry out renal replacement and kidney transplantation in Sweden report to the register (141).

The longitudinal Integration database for health Insurance and labor market studies

Since 1990, the Longitudinal Integration Database for Health Insurance and Labor Market Studies (LISA) has included all Swedish residents ≥16 years of age. The owner of the register is Statistics Sweden (Swedish name: Statistiska Centralbyrån), and the register is updated annually. The register contains information on employment, income, residence, and education (142).

The Total Population Register

Since 1968, Statistics Sweden has run the Total Population Register (Swedish name: Registret över toalbefolkningen). It contains data on sex, civil status, place of birth and residence, citizenship, and migration status (143,144). Since 2000, only those qualifying for a PIN have been included in the register (126). All deceased Swedish residents are reported in the register on a monthly basis.

Table 5 summarizes the study design and outcome measures of the studies in this thesis. The variables used in the thesis are summarized in Table 6.

Table 5. Methodological overview of studies I to IV

	Study I	Study II	Study III	Study IV
Running title	Teicoplanin and risk for AKI	Diabetes and risk for AKI	AKI and risk for heart failure	Minimal creatinine changes
Design	Observational cohort study	Nationwide observational cohort study		
Cohort	Adults, cardiac surgery, at Karolinska University Hospital 2010 to 2013	Adults, isolated CABG in Sweden 2003 to 2013	Adults, isolated CABG in Sweden 2000 to 2008	
Number of patients	2809	36 106	24 018	25 686
Source	Cohort: Local cardiac surgery register (part of SWEDEHEART) Additional data: Medical records	Cohort: SWEDEHEART Additional data: National Patient Register NDR Swedish Renal Register LISA	Cohort: SWEDEHEART Additional data: National Patient Register Cause-of-death register	Cohort: SWEDEHEART Additional data: National patient register Total population register
Exposure(s)	Teicoplanin	T1DM, T2DM	AKI, three stages: 1: 26-44 µmol/L 2: 44-88 µmol/L 3; >88 µmol/L	AKI, three groups: 1: 0 to 26 µmol/L 2: 26 to 44 µmol/L 3: >44 µmol/L
Outcome(s)	AKI according to AKIN stage 1: SCr increase ≥26 µmol/L or ≥50%.	AKI according to AKIN stage 1: SCr increase ≥26 µmol/L or ≥50%.	Heart failure	Long-term mortality, 30-day mortality, combined end-point of heart failure, mycardial infarction, stroke, or death
Follow-up	Postoperative stay	Until Dec 31, 2013	Until Dec 31, 2008	Short-term mortality: Until 30 days after surgery. Long-term mortality: Until Dec 2011. Cardiovascular outcomes: Until Dec 31, 2008
Statistical analysis	Logistic regression	Logistic regression	Survival analysis (Cox regression)	Logistic regression Survival analysis (Cox regression)

AKI = acute kidney injury, CABG = coronary artery bypass grafting, LISA = Longitudinal Integration Database for Health Insurance and Labor Market Studies, NDR = National Diabetes Register, SWEDEHEART = Swedish Web-system for Enhancement and Development of Evidence-based care in Heart disease Evaluated According to Recommended Therapies, T1DM = type 1 diabetes mellitus, T2DM = type 2 diabetes mellitus.

Table 6. Origin of variables used in Studies I to IV

Variable	Description/Definition	Used in study [a]			
		I	II	III	IV
SWEDEHEART					
Age		■	■	■	■
Sex		■	■	■	■
Weight		■	■		
Length		■	■		
Preoperative serum creatinine [b]	Usually taken within 24 hours before surgery.	■	■	■	■
Postoperative serum creatinine [b]	The highest value during postoperative stay.	■	■	■	■
Preoperative dialysis		■	■	■	■
Diabetes mellitus	Defined as ongoing treatment with insulin or oral hypoglycemic drugs	■	■	■	■
Left ventricular ejection fraction		■	■	■	■
Chronic obstructive pulmonary disease	Defined as ongoing treatment	■	■	■	■
Peripheral vascular disease	Defined as previous surgery on carotid or iliac artery, abdominal aorta or presence of claudication	■	■	■	■
Current smoking	Self reported			■	■
Hypertension	Defined as ongoing treatment		■	■	■
Hyperlipidemia	Defined as ongoing treatment		■	■	■
Preop. Hemoglobin concentration		■		■	
Prior stroke		■	■	■	■
Recent myocardial infarction within 90 days		■			
Prior PCI			■		
EuroSCORE			■		
Year of surgery		■	■	■	■
Waiting time to surgery					■
Emergent surgery	Surgery <24 hours from decision	■	■	■	■
Type of surgery		■	■	■	■
Previous cardiac surgery			■	■	■
Use of internal thoracic artery			■	■	■
Number of CABG grafts			■		
Number of arterial CABG grafts			■		
Radial artery CABG graft			■		
Bilateral internal mammary arteries			■		
Cardiopulmonary bypass		■	■	■	■
Deep hypothermic circulatory arrest		■			
Death within 30 days		■		■	■
Postoperative Creatine kinase MB		■			
Length of hospital stay			■	■	
Deep sternal wound infection		■			
Reoperation		■			

Table 6. (Continued)

Variable	Description/Definition	Used in study [a] I	II	III	IV
National Patient Register [c]					
Heart failure	ICD-8: 427 ICD-9: 428 ICD-10: I50 to I50.9				
Prior Stroke	ICD-7: 330-334 ICD-8 & ICD-9: 430-438 ICD-10: I60-I69.9				
Prior Mycardial infarction	ICD-7: 420 ICD-8 & ICD-9: 410 ICD-10: I21 to I21.9				
Chronic Obstructive Pulmonary Disease	ICD-7: 502 ICD-8 & ICD-9: 490-496 ICD-10: J44 to J44.9				
Alcohol abuse	ICD-9: 291, 303, 571 ICD-10: F10 to F10.9, K70 to K70.9				
Peripheral vascular disease	ICD-9: 440 to 446 ICD-10: I65 to I65.9, I71 to I71.9, I73.8, I73.9				
Atrial fibrillation	ICD-10: I48 to I48.9				
Hypertension	ICD-9: 401 to 405 ICD-10: I10 to I15.9				
Hyperlipidemia	ICD-9: 272 ICD-10: E78 to E78.9				
Cause-of-death register					
Date of death					
National Diabetes Register					
Type 1 diabetes					
Type 2 diabetes					
Duration of diabetes					
HbA1c					
Type 2 diabetes treatment regimens					
Svenskt njurregister					
End stage renal disease					
LISA Statistics Sweden					
Education					
Birth region					
Martial Status					
The Total Population Register					
Death date					
Medical records					
Teicoplanin treatment					

[a] Variables used in studies are marked with yellow.
[b] Analyzed according to Jaffé until 2005, thereafter enzymatic method.
[c] ICD-7 was used 1958-1968, ICD-8 & 9 was used in 1969-1996, and ICD-10 was used from 1997 until today.
CABG = Coronary artery bypass grafting, EuroSCORE = European System for Cardiac Operative Risk Evaluation, HbA1c = hemoglobin A1c, ICD = International Classification of Diseases, PCI = Percutaneous coronary intervention.

DATA COLLECTION AND STUDY POPULATION

Studies I to IV complied with the Declaration of Helsinki and were approved by the regional human research ethics committee in Stockholm, Sweden.

Study I

The cohort of Study I included all patients who underwent cardiac surgery from 1 January 2010 to 31 July 2013. On 6 December 2011, the institutional policy was changed and teicoplanin was added to the standard antibiotic prophylaxis regimen. This continued until 31 July 2013, when this change was reversed. Therefore, most of the patients treated with teicoplanin (exposed group) underwent surgery after December 6, 2011. The exclusion criteria for Studies I to IV are presented in Figure 4. Information on the patients was extracted from the local Heart Surgery Register at Karolinska University Hospital. Data on teicoplanin treatment were retrieved from the medical records.

Study II

Study II included all patients who underwent primary nonemergent isolated CABG in Sweden from 1 January 2003 to 31 December 2013. The exclusion criteria and number of excluded patients are shown in Figure 4. The cohort was retrieved from SWEDEHEART and cross-linked with the National Diabetes Register, the National Patient Register, LISA, and the Total Population Register. The origins of the included variables are shown in Table 6. The registers were linked by the National Board of Health and Welfare using PINs. The data was de-identified after linkage and the key was erased.

Study III and IV

In Studies III and IV, all patients who underwent CABG in Sweden from 1 January 2000 to 31 December 2008 were eligible for inclusion. The cohort was retrieved from SWEDEHEART and cross-linked with the National Patient Register and Cause of Death register using PINs. The included variables are shown in Table 6. The registers were linked by the National Board of Health and Welfare using PINs. The data was de-identified after linkage and the key was erased. The exclusion criteria and number of excluded patients are shown in Figure 4.

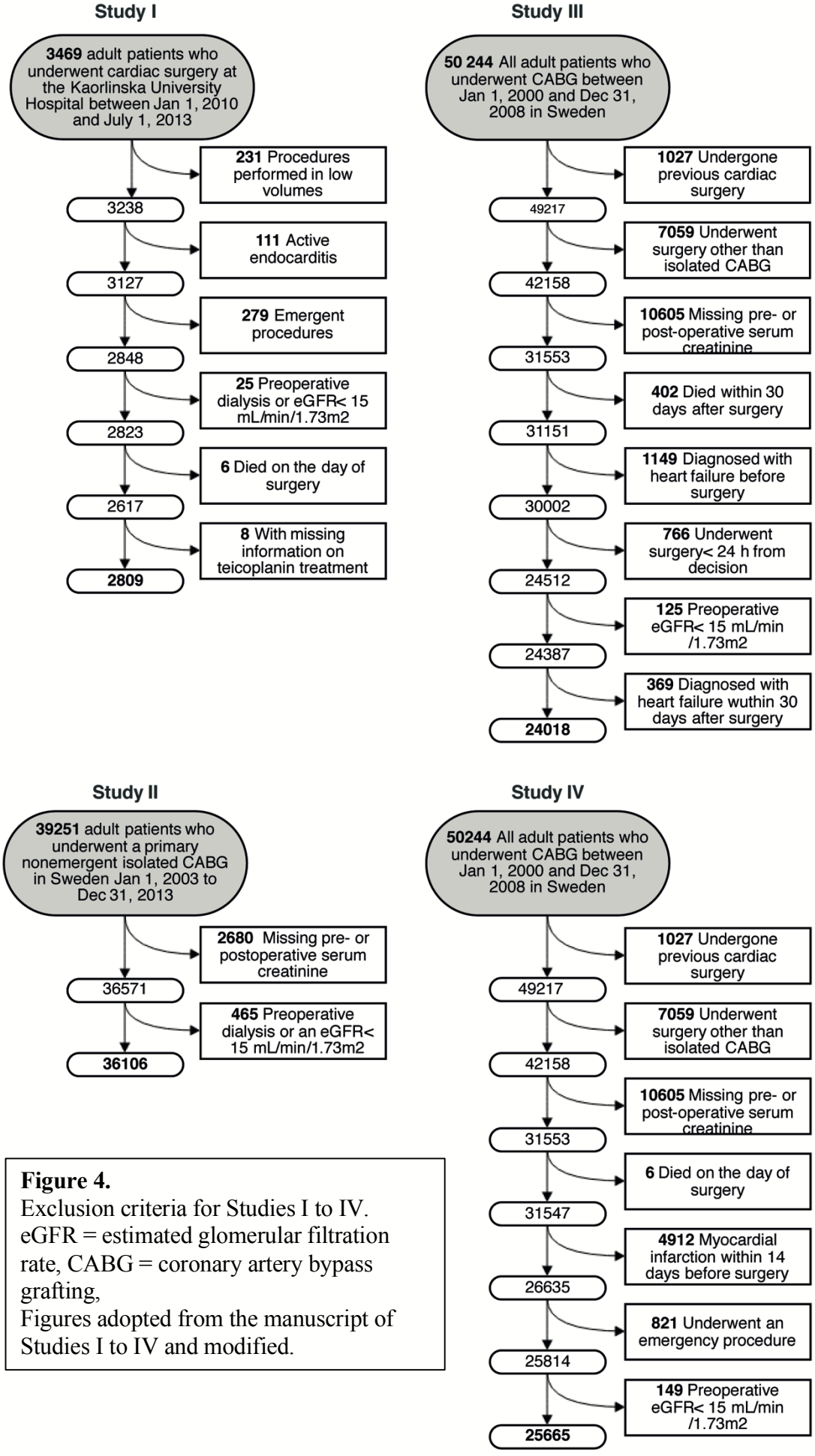

Figure 4.
Exclusion criteria for Studies I to IV. eGFR = estimated glomerular filtration rate, CABG = coronary artery bypass grafting,
Figures adopted from the manuscript of Studies I to IV and modified.

Exposure measures

Study I

The exposure in Study I was treatment with teicoplanin. On December 6, 2011, the institutional policy on antibiotic prophylaxis regimen was changed, and teicoplanin was added to the standard therapy which was cloxacillin. This regimen was as follows: 2 g of cloxacillin administered immediately before surgery, immediately after cardiopulmonary bypass, and every 8 hours thereafter until 48 hours postoperatively. In patients allergic to penicillin, cloxacillin was replaced with 600 mg of clindamycin. Teicoplanin was given as a single dose intravenously just before the start of the operation. The dose was 400 mg for patients weighing <80 kg and 600 mg for patients weighing >80 kg.

Study II

The exposure in Study II was either T1DM or T2DM. Information on diabetes was retrieved from the National Diabetes Register. T1DM was defined as an onset of diabetes before 30 years of age and treatment with insulin as the only glucose-lowering medication, which is a so-called epidemiological definition. T2DM was defined as isolated treatment with either diet or oral hypoglycemic medication, or onset of diabetes at >40 years of age with insulin treatment with or without oral hypoglycemic medication. Patients not included in the National Diabetes Register were defined as non-diabetics.

Studies III and IV

AKI was defined according to the absolute increase in post- compared to preoperative SCr concentration. The preoperative SCr was normally measured within 24 hours before surgery, and the postoperative SCr used was the highest value measured during the index hospitalization which in a previous study was the highest level within 48 hours of surgery in 92% of AKI cases (145).

The exposure in Study III was defined according to the three stages of AKI: stage 1, increase of 26 to 44 μmol/L; stage 2, increase of 44 to 88 μmol/L; and stage 3, increase of >88 μmol/L in postoperative SCr concentrations. This definition has been used in previous studies and was based on the AKIN criteria for stage 1 (26 μmol/L) and traditional arbitrary definitions (0.5 mg/dL = 44 μmol/L, 1 mg/dL = 88 μmol/L) (19,146). We also performed a secondary analysis with the same multivariable model but defined the exposure AKI according to the AKIN criteria: stage 1, increase of 26 to 44 μmol/L or relative increase of 50% to 100%; stage 2, 100% to 200% increase; and stage 3, >200% increase in postoperative SCr concentrations.

The exposure in Study IV was a redefined version of AKI that included minimal increases in postoperative SCr concentrations. The AKI stages are called AKI groups in this study to prevent confusion with common definitions of AKI, such as those used in the AKIN criteria. Three AKI groups were defined according to the increase in the SCr concentration from the preoperative to postoperative period: group 1, 0 to 26 μmol/L; group 2, 26 to 44 μmol/L; and

group 3, >44 μmol/L. The reference group had either no change or a decrease in the SCr concentration.

Outcome measures

Study I and II

The outcome in Studies I and II was AKI, which was defined as an absolute or relative increase in the SCr concentration from the preoperative to postoperative period of ≥26 μmol/L or ≥50%, respectively. This definition of the SCr increase is in line with the AKIN and KDIGO criteria for stage 1 (Table 1). However, the time frame differs. The preoperative SCr concentration was usually measured within 24 hours before surgery, and the postoperative SCr concentration was the highest value measured during the index hospitalization.

To further investigate the impact of T1DM and T2DM on the risk of AKI in Study II, secondary analyses were performed according to more severe AKI definitions. Three separate analyses were performed using three different definitions of AKI: the original definition of AKI, a definition according to AKIN stage II, and a definition according to AKIN stage III (Figure 5).

Study III

The primary outcome in Study III was hospitalization for the first time with heart failure as a primary discharge diagnosis in the National Patient Register. Patients with a preoperative diagnosis of heart failure were excluded from the study. Data on hospitalization for heart failure were retrieved from the National Patient Register using ICD codes (Table 6). The secondary outcome was the combined outcome of heart failure and death. The date of death was retrieved from the Swedish Cause of Death Register. Follow-up started on postoperative day 30 and ended at the time of hospitalization for heart failure, the time of death, or the end of the study (31 December 2008).

Study IV

The primary outcome in Study IV was long-term all-cause mortality. The two secondary outcomes were 30-day all-cause mortality and the combined outcome of long-term all-cause mortality, hospitalization for heart failure, myocardial infarction, or stroke. Information on survival was retrieved from the Total Population Register in February 2011. Data on heart failure, myocardial infarction, and stroke was retrieved from the National Patient Register using ICD codes. Follow-up ended on 31 December 2008.

Generated variables

Estimated GFR

The estimated GFR was calculated using information on preoperative SCr concentration, age and sex from SWEDEHEART. In Studies I, III, and IV, the estimated GFR was calculated using the simplified Modification of Diet in Renal Disease (MDRD) equation (53). In Study II, the estimated GFR was calculated using to the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation (55).

CKD-EPI equation

Female with SCr ≤62 μmol/L: $GFR_{CKD\text{-}EPI} = 144 \times (SCr/0.7)^{-0.329} \times 0.993^{age}$ [×1.159 if black]

Female with SCr >62 μmol/L: $GFR_{CKD\text{-}EPI} = 144 \times (SCr/0.7)^{-1.209} \times 0.993^{age}$ [×1.159 if black]

Male with SCr ≤80 μmol/L: $GFR_{CKD\text{-}EPI} = 141 \times (SCr/0.9)^{-0.411} \times 0.993^{age}$ [×1.159 if black]

Male with SCr >80 μmol/L: $GFR_{CKD\text{-}EPI} = 141 \times (SCr/0.9)^{-1.209} \times 0.993^{age}$ [×1.159 if black]

The simplified MDRD equation

$GFR_{MDRD} = 186 \times (SCr\ [\mu mol/L])^{-1.154} \times age^{-0.203}$ [×0.742 if female] [×1.210 if black]

Body mass index

Body mass index was calculated using data on weight and length obtained from SWEDEHEART.

Body mass index = weight (kg) / (length [cm]/100)^2

STATISTICAL ANALYSES

In Studies I to IV, the baseline characteristics are described using means and standard deviations for continuous variables and numbers and percentages for categorical variables.

Stata versions 12 and 13 (StataCorp LP, College Station, TX, USA) was used for the statistical analyses in Studies I to IV. R version 3.1.1 (R Foundation for Statistical Computing, Vienna, Austria) was used for data management in Study II.

Study I

Logistic regression was used to analyze the association between treatment with teicoplanin and the risk of developing AKI. ORs with 95% confidence intervals (CI) were calculated in a crude, adjusted for age and sex, and multivariable adjusted model. The multivariable adjusted model was constructed after considering all baseline characteristics presented in Table 7 and primary interaction terms. The final multivariable model included the variables age, sex, estimated GFR, left ventricular ejection fraction (LVEF), diabetes mellitus, deep hypothermic circulatory arrest, chronic obstructive pulmonary disease, preoperative hemoglobin concentration, postoperative creatine kinase MB concentration, and body mass index. All continuous variables (age, estimated GFR, hemoglobin concentration, body mass index, and creatine kinase MB concentration) were flexibly modeled using restricted cubic splines with three knots. Nonlinear associations with the outcome were identified by testing the null hypothesis that the second spline was significant at a p value of <0.05. Separate subgroup analyses were performed according to treatment dose, sex, estimated GFR, and type of surgical procedure and by excluding patients who developed a postoperative deep sternal wound infection.

Study II

Logistic regression was used to analyze the association between T1DM or T2DM and the risk of developing AKI. Patients without a diagnosis of diabetes comprised the reference group. ORs with 95% CIs were calculated. The multivariable adjusted model included all variables in Table 9 except duration of diabetes, hemoglobin A1c concentration, and European System for Cardiac Operative Risk Evaluation (EuroSCORE). The normal distribution of continuous variables was checked by formal analysis and visual examination. All continuous variables were flexibly modeled using restricted cubic splines with three knots at the 10^{th}, 50^{th}, and 90^{th} percentiles. We checked for primary interactions. Missing data were not imputed (Table 9). Observations with missing data for variables included in the models were excluded. As a sensitivity analysis, we imputed the missing data using multiple imputation by chained equations for comparison with the primary results.

We performed subgroup analyses according to the T2DM treatment regimens: dietary treatment only, oral hypoglycemic medication, or insulin with or without oral hypoglycemic medication. We also performed secondary analyses for the risk of AKI according to the three definitions of AKI representing increasing severity of AKI (Figure 5).

Study III

The association between AKI and the risk of first hospitalization for heart failure was studied using Cox proportional hazards regression (147). Hazard ratios with 95% CIs were calculated according to each stage of AKI compared with patients without AKI. Patients who died during follow-up were censored at the date of death. Those who did not develop heart failure and were alive at the end of follow-up (31 December 2008) were censored on this date. A multivariable model was constructed after considering all baseline characteristics. Age, sex, and estimated GFR was planned to be included from the start because we considered them to be of clinical importance in studies of AKI. Further variables were included using a manual stepwise forward and backward selection procedure and including variables that influenced the hazard ratio by ≥0.1. We also considered primary interaction terms. The final multivariable model included age, sex, estimated GFR, LVEF, diabetes mellitus, and myocardial infarction in the past or during follow-up. The proportionality assumption was tested and no violation was found. In the final model, there was missing data on LVEF (8%) and diabetes mellitus (29%). The missing data was regarded as missing at random and were imputed for the final multivariable model using multiple imputation by chained equations. A complete case analysis including 16,002 patients was also performed.

Study IV

The association between the AKI groups and the primary outcome of long-term mortality was studied using Cox proportional hazards regression (147). Cox regression was also used for the secondary combined outcome of long-term mortality, hospitalization for heart failure, myocardial infarction, or stroke. The association between AKI groups and 30-day mortality was analyzed using logistic regression. A multivariable model was constructed after considering all baseline characteristics (Table 14). A manual forward and backward selection procedure was used. Variables influencing a hazard ratio of ≥0.1 were included in the analysis. We checked for variable interaction. All variables were virtually complete except three variables that contained missing data: diabetes (29%), LVEF (8.3%), and peripheral vascular disease (8.0)%. Missing data was imputed using multiple imputation by chained equations. We also performed a complete case analysis in which only patients with complete information on all variables included in the final statistical model were included.

RESULTS AND METHODOLOGICAL DISCUSSIONS

STUDY I – TEICOPLANIN AND RISK FOR ACUTE KIDNEY INJURY

Results

In total, 2809 patients were included, and 62% patients were treated with teicoplanin. The patients' baseline characteristics are presented in Table 7. Patients treated with teicoplanin had a slightly higher preoperative estimated GFR. AKI developed in 32% of patients treated with teicoplanin and 29% of patients not treated with teicoplanin. The results of the primary analysis are presented in Table 8. Subgroup analyses showed signs of a dose-dependent relationship in which patients treated with a 600-mg dose of teicoplanin had an OR for AKI of 1.34 (CI, 1.05–1.70) and patients treated with a 400-mg dose had an OR for AKI of 1.46 (CI, 1.15–1.84). In the subgroup analysis that included only patients undergoing isolated CABG, the OR for AKI was 1.31 (CI, 0.99–1.73), and in the subgroup of patients undergoing procedures other than isolated CABG, the OR for AKI was 1.50 (CI, 1.18–1.92).

Discussion

This study showed that prophylactic treatment with teicoplanin in patients who underwent cardiac surgery was associated with an increased risk of AKI. The results were consistent even after adjustment for many known risk factors for AKI. In addition, subgroup analyses indicated a dose-dependent relationship with higher point estimates for AKI in the high-dose teicoplanin group. These results suggest that the negative influence of teicoplanin on renal function should be considered when developing antibiotic protocols in cardiac surgery.

A strength of this study is that the institutional policy of antibiotic prophylaxis changed from one day to another. This diminished the risk of selection bias. However, this study was based on a clinical observation that teicoplanin might cause AKI. During data collection, we found that 139 patients were not treated with teicoplanin during the teicoplanin period. It is possible that these patients were identified as those with a high risk of AKI and were therefore not treated with teicoplanin. Thus, this may have introduced confounding-by-indication, in this case meaning that treatment was withheld from the sicker patients, but given to the healthier ones. This suspicion is not supported by the data in Table 7, which show that patients treated with teicoplanin actually had a higher baseline estimated GFR. Also, we adjusted for most of the known risk factors for AKI, and the effect of this possible bias should have been reduced.

Due to the reason that the unexposed and the exposed group was operated during two different time periods, other causes of AKI than prophylactic treatment with teicoplanin might have emerged. To the best of the authors' knowledge, however, there were no changes in the preoperative, perioperative, or postoperative care policy that could explain the difference in the incidence of AKI. However, we tend to perform surgery on older and sicker patients. This might have resulted in a higher number of older and sicker patients in the

teicoplanin group. On the other hand, based on the data presented in Table 7, patients treated with teicoplanin appear neither older nor sicker. In addition, the analysis was adjusted for many the known risk factors for AKI, including age. The distribution of the type of surgical procedure might have also differed between the exposed and unexposed groups because we tended to perform fewer CABG operations. In the subgroup analysis of patients undergoing procedures other than isolated CABG, patients treated with teicoplanin had a significantly increased risk of AKI. In patients undergoing isolated CABG, the lower CI was 0.99. Considering all results in the study, the author argues that this lower CI was most likely due to insufficient statistical power. Additionally, Table 7 shows no significant differences regarding the surgical procedures.

The main limitation of this study is that it was not randomized. We cannot draw definitive conclusions regarding causality because there might have been confounding factors unknown to the authors that biased the association between treatment with teicoplanin and risk of AKI. A randomized controlled trial is needed to obtain a more definitive conclusion regarding teicoplanin and risk of AKI. Such study could also be designed to summarize risks and benefits e.g. regarding risk for infection contra risk for AKI and subsequent complications.

Table 7. Baseline characteristics of the study population in study I.

	All patients	Reference group [a]	Teicoplanin	p value
Number of patients	2809	1056	1753	
Percent of study population	100	38	62	
Age (SD), years	66 (12)	66 (12)	66 (11)	0.277
Female sex	26%	26%	26%	0.735
eGFR (SD), mL/min/1.73 m^2	82 (22)	80 (23)	84 (21)	<0.001
Preoperative SCr (SD), µmol/L	87 (24)	88 (25)	84 (23)	<0.001
Diabetes mellitus	21%	21%	20%	0.911
Peripheral vascular disease	8.8%	8.6%	9.0%	0.728
Hemoglobin concentration (SD), g/L	137 (15)	136 (15)	138 (15)	0.005
COPD	9.3%	9.6%	8.8%	0.462
Recent myocardial infarction	23%	23%	22%	0.291
Prior stroke	7.1%	6.9%	7.6%	0.466
Left ventricular ejection fraction				
Ejection fraction >0.5	66%	67%	65%	0.257
Ejection fraction 0.3-0.5	28%	26%	31%	0.010
Ejection fraction <0.3	6.1%	6.7%	4.6%	0.009
Type of surgery				
Isolated CABG	44%	44%	43%	0.665
Isolated valve surgery	32%	33%	31%	0.467
Other	24%	24%	26%	0.196
Cardiopulmonary bypass	99.5%	99.5%	99.5%	0.884
Deep hypothermic circulatory arrest	1.9%	1.5%	2.6%	0.043
CK-MB postop day 1 (SD), µg/L	22 (30)	22 (26)	22 (36)	0.479

[a] Patients not treated with teicoplanin.
The continuous variables age, glomerular filtration rate, and serum creatinine concentration are presented as mean with standard deviation.
CABG = coronary artery bypass grafting, COPD = chronic obstructive pulmonary disease, CK-MB = creatine kinase Mb, eGFR = estimated glomerular filtration rate, SCr = serum creatinine, SD = standard deviation.
Table adopted from the manuscript of Study I and modified.

Table 8. Risk of AKI following cardiac surgery according to teicoplanin antibiotic prophylaxis

	All patients	Reference group[a]	Teicoplanin
Number of patients (%)	2809 (100)	1753 (62)	1056 (38)
Number of events (%)	860 (31)	517 (29)	343 (32)
		Odds Ratio (95% CI)	
Crude		1.0	1.15 (0.98-1.36)
Adjustment for age and sex		1.0	1.20 (1.01-1.42)
Multivariable adjustment [b]		1.0	1.40 (1.18-1.68)

[a] Patients not treated with teicoplanin.
[b] Multivariable adjustment was made for age, sex, estimated glomerular filtration rate, left ventricular ejection fraction, diabetes mellitus, deep hypothermic circulatory arrest, chronic obstructive pulmonary disease, preoperative hemoglobin concentration, postoperative creatinine kinase MB, and body mass index.
AKI = Acute kidney injury, CI = confidence interval.
Table adopted from the manuscript of Study I and modified.

STUDY II - TYPE I AND TYPE II DIABETES AND RISK FOR AKI

Results

The study included 36,106 patients undergoing a primary nonemergent isolated CABG, of whom, 1.3% had T1DM and 14% had T2DM (Table 9). Patients with T1DM were younger, had a lower estimated GFR, were more likely to be female, and were more likely to have a history of heart failure than patients with no diabetes and patients with T2DM. Patients with T2DM had a lower estimated GFR and higher prevalence of heart failure and hypertension than did patients without diabetes (Table 9). AKI developed in 32% of patients with T1DM, 20% of patients with T2DM, and 13% of patients without diabetes. The ORs for AKI in patients with T1DM and T2DM compared with patients without diabetes are presented in Table 10. Patients with T1DM had an almost five-fold higher risk of AKI, and patients with T2DM had a small but significantly increased risk of AKI compared to patients without diabetes. The results of the secondary analyses using definitions representing more severe AKI are presented in Figure 5. The results from the secondary analyses according to T2DM treatment regimens is presented in Table 11. The results of the primary analyses but with imputed missing values were not different from the original model.

Discussion

The study showed that both T1DM and T2DM were associated with an increased risk of AKI in patients undergoing CABG. However, the association between T1DM and risk of AKI was considerably much higher than the association between T2DM and AKI. The secondary analysis using three definitions of AKI representing increasing AKI severity showed that patients with T1DM and T2DM were also at risk of major declines in renal function. To the authors' knowledge, this is the first study to investigate the association between subtypes of diabetes and the risk of AKI in patients who have undergone CABG. The results suggest that patients with diabetes, especially T1DM, may benefit from special consideration (e.g., avoidance of nephrotoxic drugs) when undergoing cardiac surgery.

Diabetes is strongly associated with the development of atherosclerosis and microvascular disease (117). The risk for AKI was markedly higher in patients with T1DM than in patients with T2DM. One can speculate that the duration of diabetes is an important factor in this case. The mean duration of diabetes was 44 years in patients with T1DM and 11 years in those with T2DM. The subgroup analyses according to the T2DM treatment regimens are in line with this theory of diabetes "dose" (Table 11). Those treated with insulin had the highest risk for AKI, and those who underwent only dietary treatment had the lowest risk. The differences between the treatment groups in terms of risk for AKI are likely not due to the medication itself; they are more likely due to confounding by indication. It is reasonable to think that patients who underwent only dietary treatment had the best metabolic control and that those required treatment with both insulin and oral hypoglycemic medication had the worst. One can argue that the primary results and the treatment regimen results show a dose-dependent/severity relationship between the diabetes and the risk for AKI.

The main strength of this study was that we were able to subgroup patients according to subtype of diabetes, i.e. T1DM or T2DM. Another strength of this study was the large number of patients, making it possible to perform analyses according to T2DM treatment regimens and also different AKI definitions. A limitation was that the reference group may have included patients with undiagnosed T2DM, leading to misclassification of the diagnosis. It is likely that patients with many comorbidities tend to be screened for diabetes mellitus more often than healthier individuals. It is therefore possible that our group of patients with T2DM is on an average sicker than they would have been if we screened all patients for T2DM before surgery. This possible differential misclassification of the exposure can lead to an overestimation of the effect of T2DM and the risk for AKI.

Table 9. Baseline characteristics of the study population in Study II

	All Patients	No Diabetes	T1DM	T2DM	Missing Data
No. of patients	36 106	30 525	457	5124	
Age, years, mean (SD)	67.4 (9.2)	67.3 (9.3)	58.8 (9.3)	68.4 (8.2)	
Female sex	21%	20%	44%	23%	
Diabetes diabetes, years, mean(SD)	13.7 (12)	0 (0)	44.0 (11)	10.8 (7.7)	
HbA1c					
IFCC (mmol/mol) <53	No data	No data	9.2%	43%	
NGSP <7.0					
IFCC 53–73	No data	No data	61%	45%	
NGSP 7.0–8.8					
IFCC >73	No data	No data	30%	12%	
NGSP >8.8					
BMI, kg/m^2, mean (SD)	27.4 (4.1)	27.1 (4.0)	26.1 (4.2)	28.9 (4.5)	5.4%
eGFR					
>60 mL/min/1.73 m^2	80%	81%	69%	75%	
45–60 mL/min/1.73 m^2	14%	14%	17%	16%	
30–45 mL/min/1.73 m^2	5.0%	4.5%	10%	7.5%	
15–30 mL/min/1.73 m^2	1.0%	0.8%	3.7%	1.8%	
Hypertension	41%	38%	48%	56%	
Hyperlipidemia	25%	24%	28%	31%	
Peripheral vascular disease	10%	9.5%	21%	14%	
Prior PCI	17%	16%	20%	20%	
COPD	7.9%	7.6%	5.3%	9.8%	
Prior myocardial infarction	55%	55%	53%	58%	
Heart failure	9.8%	9.1%	16%	14%	
Stroke	8.8%	8.3%	13%	12%	
Atrial fibrillation	6.4%	6.3%	2.6%	7.7%	
Left ventricular ejection fraction					2.2%
>50%	69%	70%	69%	65%	
30–50%	27%	26%	27%	30%	
<30%	4.2%	3.9%	4.3%	5.6%	
EuroSCORE, mean (SD)	4.1 (2.6)	4.0 (2.6)	3.2 (2.4)	4.5 (2.7)	
Alcohol dependency	2.3%	2.3%	1.3%	2.6%	
Birth region					
Nordic countries	90%	90%	97%	87%	
Other	10%	9.6%	2.8%	14%	
Education					2.4%
<10 years	43%	43%	35%	47%	
10–12 years	39%	39%	44%	39%	
>12 years	18%	18%	21%	15%	
Marital status					
Married	66%	66%	60%	66%	
Other	34%	34%	40%	34%	
Off-pump CABG	3.0%	3.2%	1.5%	2.0%	
No. of grafts					13%
1–2	19%	20%	18%	17%	
3–4	70%	70%	72%	73%	
>4	11%	11%	9.9%	11%	
Internal mammary artery	94%	94%	95%	93%	
Bilateral internal mammary arteries	1.1%	1.2%	0.7%	1.0%	
Radial artery	1.7%	1.7%	1.8%	1.4%	
>1 arterial graft	2.7%	2.8%	2.2%	2.3%	

BMI = body mass index, CABG = coronary artery bypass grafting, COPD = chronic obstructive pulmonary disease, eGFR = estimated glomerular filtration rate, HbA1c = hemoglobin A1c, IFCC = International Federation of Clinical Chemistry, NGSP = National Glycohemoglobin Standardization Program, PCI = percutaneous coronary intervention, SD = standard deviation, T1DM = type 1 diabetes mellitus, T2DM = type 2 diabetes mellitus. Table adopted from the manuscript of Study II and modified.

Table 10. Odds ratios with 95% CIs for AKI after CABG in patients with T1DM and T2DM

	All patients	No diabetes [a]	T1DM	T2DM
No. of patients	36 106	30 525	457	5124
No. of events (AKI) (%)	5199 (14)	4017 (13)	145 (32)	1037 (20)
			OR (95% CI)	
Risk for AKI (crude analysis)		1.00	3.07 (2.51-3.74)	1.67 (1.55-1.81)
Risk for AKI (multivariable adjusted [b])		1.00	4.89 (3.82-6.25)	1.27 (1.16-1.40)

[a] Reference category

[b] The final multivariable model included all variables presented in the table of characteristics (Table 9) except EuroSCORE, hemoglobin A1c concentration, and duration of diabetes.

Table adopted from the manuscript of Study II and modified.

AKI = Acute kidney injury, CABG = Coronary artery bypass grafting, CI = confidence interval, OR = Odds ratio, T1DM = Type 1 diabetes mellitus, T2DM = Type 2 diabetes mellitus.

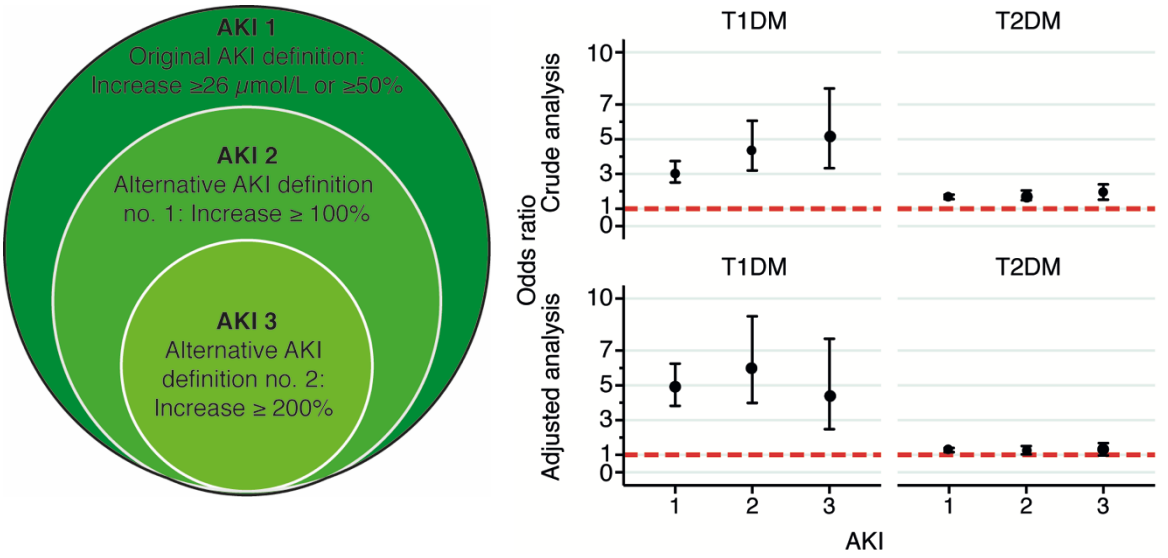

Figure 5.

The illustration to the left shows three separate definitions of AKI:

AKI 1, increase in SCr concentration of ≥26 µmol/L or ≥50%; reference group, increase of <26 µmol/L or <50%.

AKI 2, increase in SCr concentration of ≥100%; reference group, increase of <100%.

AKI 3, increase in SCr concentration of ≥200% µmol/L; reference group, increase of <200%.

The illustration to the right shows odds ratios with 95% confidence intervals for the risk of AKI from separate analyses according to the three definitions of AKI. The multivariable adjusted analysis included all variables in Table 9 except EuroSCORE, hemoglobin A1c concentration, and duration of diabetes.

All analyses showed significant results except the multivariable adjusted analysis of T2DM and the risk of the AKI 3 with an OR of 1.27 (95% CI, 0.97–1.68).

The figure was adopted from the manuscript of Study IV and modified.

AKI = Acute kidney injury, SCr = Serum creatinine, T1DM = Type 1 diabetes mellitus, T2DM = Type 2 diabetes mellitus.

Table 11. Odds ratios for risk for AKI according to T2DM treatment regimens.

		T2DM		
	Reference group [a]	Diet treatment only	Oral hypoglycemic medication	Insulin treatment with or without oral hypoglycemic medication
No. of patients	30 525	999	2321	1804
No. of events (%)	4017 (13)	182 (18)	413 (18)	442 (25)
	Odds Ratio (95% Confidence Interval)			
Risk for AKI (crude analysis)	1.00	1.47 (1.25–1.73)	1.43 (1.28–1.60)	2.14 (1.91–2.40)
Risk for AKI (multivariable adjusted [b])	1.00	1.13 (0.93–1.38)	1.23 (1.08–1.41)	1.82 (1.61–2.06)

[a] No diabetes diagnosis. [b] The multivariable adjusted model included all variables in Table 9, except diabetes duration, hemoglobin A1c, and EuroSCORE. Table adopted and modified from the manuscript of study II.
AKI = Acute kidney injury, T2DM = Type 2 diabetes mellitus.

STUDY III – AKI AND RISK OF HEART FAILURE

Results

In total, 24,018 patients were included in the study, and the overall incidence of AKI was 12%. Patients with AKI were older, had a lower estimated GFR, and were more likely to have diabetes mellitus, hypertension, peripheral vascular disease, a severely reduced LVEF, and prior myocardial infarction or stroke. The patients' characteristics are presented in Table 12. During a mean follow-up of 4.1 ± 2.4 years, 5.5% of the patients were hospitalized for heart failure. A total of 12.0% of patients with AKI were hospitalized for heart failure compared with 4.7% of patients without AKI. The results of the primary analysis are presented in Table 13, and the Kaplan–Meier curve on the cumulative incidence of heart failure is presented in Figure 6. There was a significant association between AKI and risk of heart failure, and the hazard ratio increased with each stage of AKI even after multivariable adjustment (Table 13).

The median length of hospital stay was 6 days for patients without AKI and 7, 7, and 9 days for patients with AKI stages 1, 2, and 3, respectively. The complete case analysis showed results similar to those of the primary analysis with hazard ratios of 1.57 (CI, 1.27–1.95), 1.72 (CI, 1.35–2.18), and 1.83 (CI, 1.33–2.51) for AKI stages 1, 2, and 3, respectively. The results from the analysis using a definition of AKI according to the AKIN criteria were similar to the primary definition. These results are presented in the supplementary table in the manuscript of Study III. The mortality rate during follow-up was 14% for no AKI, 21% for stage 1 AKI, 28% for AKI stage 2, and 38% for AKI stage 3. The multivariable adjusted hazard ratios for the secondary outcome of heart failure or death for AKI stages 1, 2, and 3 compared with patients with no AKI was 1.31 (CI, 1.17–1.46), 1.60 (CI, 1.42–1.80), and 2.13 (CI, 1.82–2.49), respectively.

Discussion

The main finding in Study III is that AKI after CABG is associated with an increased long-term risk of developing heart failure. This finding was consistent even after adjustment for several risk factors for both AKI and heart failure.

During follow-up, 5.5% of the patients developed heart failure. It is possible that we underestimated the true incidence of heart failure because some patients who developed heart failure might not have been hospitalized during follow-up. These patients may have been cared for in an out-patient setting. Also, sicker patients tend to develop AKI to a greater extent than healthier. It is possible that sicker patients are more sensitive to mild symptoms of heart failure and thereby tend to seek hospital care to a greater extent during follow-up. This can lead to an overestimation on the association between AKI and heart failure. On the other hand, it is not sure that they will be diagnosed with heart failure and that it will be the primary discharge diagnosis. There might also be fatal events of heart failure that was not included in the study. This could bias the results if either the AKI group or the no AKI group tend to develop fatal heart failure to a greater extent. However, the incidence of fatal heart failure was likely rather low and would therefore not alter the results significantly.

Patients who underwent surgery close to the end of follow-up, might have contributed with person-years but did not have time to develop heart failure symptoms. The induction time of heart failure after AKI might have caused an underestimation of the association between AKI and long-term risk of heart failure in this study. The curves in Figure 6 show that the derivative/slope of the curves are higher in each stage of AKI during the first year. This difference in the incidence rates during the first year indicate a risk of underestimation of the association if the time from surgery to the end of follow-up was shorter than 1 year.

A strength of the study is the large study base and the long follow-up. The study was national and represented the Swedish population of CABG patients in the 21st century. A limitation is that we had no information on medications before surgery or during follow-up. For example, physicians who identified AKI after CABG might have stopped the prescription of angiotensin-converting enzyme inhibitors, which also have preventive effects on heart failure. These medications may have confounded the association.

Table 12. Baseline characteristics of the study population in Study III

			AKI stage[a]		
	All patients	**No AKI**	**1**	**2**	**3**
Number of patients	24 018	21 239	1428	927	424
Percent of study population	100	88	6.0	3.9	1.8
Age (SD), y	67 (9)	66 (9)	70 (9)	71 (9)	70 (9)
Female sex	21%	21%	20%	21%	20%
Estimated GFR (SD), ml/min/1.73 m^2	77 (21)	78 (20)	73 (23)	68 (26)	58 (25)
Preoperative SCr (SD), µmol/L	92 (26)	90 (22)	98 (33)	107 (40)	131 (64)
Diabetes mellitus	23%	22%	27%	33%	37%
Hypertension	57%	56%	65%	72%	77%
Hyperlipidemia	61%	60%	61%	62%	70%
Peripheral vascular disease	8.9%	8.3%	13%	13%	18%
Current smoking	18%	18%	15%	18%	15%
Prior MI	36%	35%	40%	43%	52%
Prior stroke	4.8%	4.4%	6.9%	7.0%	12%
Left ventricular ejection fraction					
Ejection fraction >50%	73%	74%	68%	64%	61%
Ejection fraction 30% to 50%	24%	23%	28%	32%	33%
Ejection fraction <30%	2.7%	2.5%	3.7%	4.0%	6.2%
Internal thoracic artery use	94%	94%	95%	94%	93%
CABG without cardiopulmonary bypass	5.9%	5.6%	6.7%	7.9%	8.7%
Year of surgery					
2000-2004	56%	56%	56%	59%	55%
2005-2008	44%	44%	44%	41%	45%

[a]AKI was defined according to an absolute increase in the SCr concentration: stage 1, 26 to 44 µmol/L; stage 2, 44 to 88 µmol/L; stage 3, >88 µmol/L.
AKI = acute kidney injury, CABG = coronary artery bypass grafting, eGFR = estimated glomerular filtration rate, MI = myocardial infarction, SCr = serum creatinine, SD = standard deviation.
Table adopted from the manuscript of Study III and modified.

Table 13. Hazard ratios of first hospitalization for Heart Failure with 95% CIs in relation to AKI[a]

		AKI [a]		
	No kidney injury[b]	**Stage 1**	**Stage 2**	**Stage 3**
No. of patients %	21 239	1428	927	424
Per cent of population	88.4	5.6	3.9	1.8
No. of events, %	997 (4.7)	141 (9.9)	122 (13.2)	65 (15.3)
	Hazard ratio (95% CI)			
Crude	1.00	2.22 (1.86-2.65)	3.10 (2.57-3.74)	3.95 (3.08-5.08)
Adjustment for age and sex	1.00	1.87 (1.57-2.23)	2.48 (2.05-2.99)	3.29 (2.56-4.23)
Multivariable adjustment[c]	1.00	1.60 (1.34-1.92)	1.87 (1.54-2.27)	1.98 (1.53-2.57)

[a] AKI classified according to absolute increase in serum creatinine concentration: stage 1, 26 to 44 µmol/L; stage 2, 44 to 88 µmol/L; stage 3, >88 µmol/L.
[b] Reference category
[c] Multivariable adjustment was made for age, sex, diabetes mellitus, left ventricular ejection fraction, estimated glomerular filtration rate, and pre- and postoperative myocardial infarction.
AKI = Acute kidney injury, CI = confidence interval.
Table adopted from the manuscript of Study III and modified.

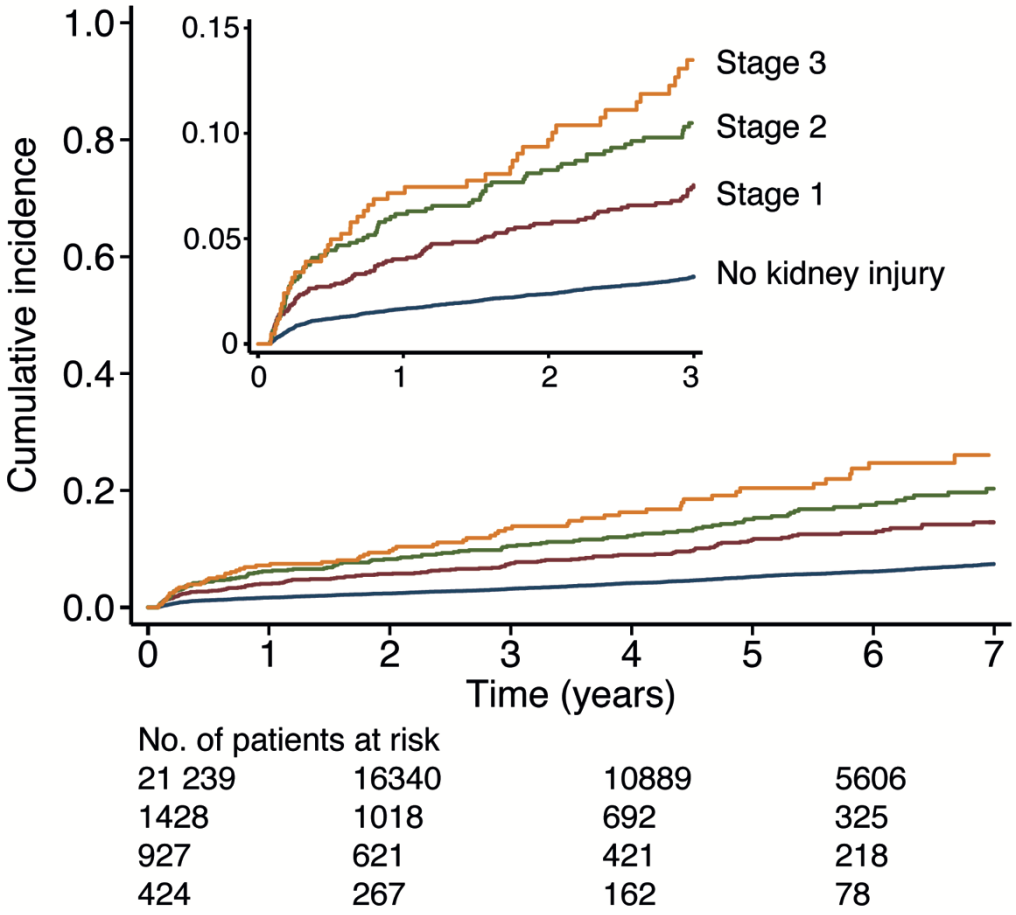

Figure 6.
Kaplan-Meier curve showing the cumulative incidence for a first hospitalization of heart failure according to stage of acute kidney injury. The inset presents the same data zoomed in on the first three years. Figure adopted and modified from the manuscript of study III.

STUDY IV – MINIMAL CHANGES IN SERUM CREATININE

Results

The study included 25,665 patients. Among these, 40% developed AKI group 1, 6.4% developed AKI group 2, and 6.4% developed AKI group 3. Patients who developed AKI were older, and had a higher prevalence of a reduced estimated GFR, and had a higher prevalence of previous myocardial infarction, stroke, and heart failure (Table 14). The relative risks for long-term mortality, 30-day mortality, and the composite outcome of long-term mortality, myocardial infarction, heart failure, and stroke are presented in Table 15.

Long-term mortality

During a mean follow-up of 6.0 years, 17% of the patients died. The long-term mortality was 14% in patients without AKI. The long-term mortality in patients with group 1, 2, and 3 AKI was 16%, 25%, and 40%, respectively. The cumulative incidence of long-term mortality is illustrated by the Kaplan–Meier curve in Figure 7.

30-day mortality

The 30-day mortality was 1.0% among all patients. The 30-day mortality among patients with group 1, 2, and 3 AKI was 0.5%, 2.8%, and 8.4%, respectively. The 30-day morality according to changes in the SCr concentrations is illustrated in Figure 8.

Combined outcome of long-term mortality, heart failure, myocardial infarction, and stroke

During a mean follow-up of 3.7 years, 28% of patients died or were hospitalized for myocardial infarction, heart failure, or stroke. The absolute risk of reaching the composite outcome during follow-up was 24% among patient without AKI, and in group 1, 2, and 3 AKI it was 26%, 39%, and 54%, respectively.

Discussion

The main finding in Study IV was that a minimal increase in the SCr concentration of 0 to 26 μmol/L after CABG was associated with an increased risk of long-term mortality and cardiovascular outcomes, and a small but not minimal increase of 26 to 44 μmol/L was associated with 30-day mortality.

Figure 8 shows that the 30-day mortality curve has an exponential shape and starts to accelerate at approximately 18 μmol/L. However, we found no significant association between a minimal increase in the SCr concentration of 0 to 26 μmol/L and 30-day mortality. A significant association was on the other hand found in the analyses on long-term mortality, and the combined outcome. AKI group 2, which corresponded to the absolute increase in the SCr criteria for AKIN and KDIGO stage 1, was associated with increased risk of all outcomes in the study. The author therefore argues that the results validate the absolute SCr criteria for AKIN and KDIGO and that a lower threshold is not valuable due to conflicting results. The conflicting results suggest that there might be something happening to the kidneys that is not always showing clinical changes in GFR. Upcoming AKI biomarkers might in the future work as a complement in the group of patients with minimal increases in SCr.

The mean follow-up time was 6.0 years in the primary analysis of long-term mortality, and 3.7 years in the secondary analysis in which hospitalization for heart failure, myocardial infarction, and stroke were added to the death as outcome. Notably, 28% of patients developed the combined outcome before end of follow-up. The follow-up time from the analysis might seem short; however, calculation of the time from surgery to the date on which no more data on outcomes were available (February 2011 for survival status and December 2008 for heart failure, myocardial infarction, and stroke) shows that the patients had a mean time of 4.5 years to develop myocardial infarction, heart failure, and stroke and 6.6 years for long-term mortality.

A weakness of the study is that we did not perform separate analyses on the cardiovascular outcomes. Different associations may exist between various diseases and AKI. Another

weakness is that we had no information on the amount of fluids given during or after surgery and were therefore unable to estimate the degree of hemodilution after surgery.

Table 14. Baseline characteristics of the study population in Study IV.

Variable	All patients	No AKI	AKI groups[a]		
			1	2	3
Number of patients	25 665	12 066	10 322	1631	1646
Percent of study population	100	47	40	6,4	6,4
Women	21%	23%	20%	20%	21%
eGFR (ml/min/1.73 m^2), mean (SD)	77 (21)	75 (19)	82 (21)	72 (23)	63 (26)
Preoperative SCr concentration (µmol/L), mean (SD)	92 (27)	93 (23)	87 (22)	99 (33)	117 (50)
Diabetes mellitus	24%	21%	23%	28%	36%
Hypertension	58%	54%	58%	64%	72%
Hyperlipidemia	61%	60%	60%	60%	65%
Peripheral vascular disease	9.4%	8.4%	8.9%	13%	16%
Current smokers	18%	19%	17%	14%	17%
Chronic obstructive pulmonary disease	6.2%	6.4%	5.6%	6.9%	8.4%
Previous MI	36%	35%	36%	40%	48%
Previous stroke	5.0%	4.3%	4.8%	7.6%	9.1%
Previous congestive heart failure	4.1%	3.4%	3.6%	6.3%	10%
Left ventricular ejection fraction					
Ejection fraction >50%	71%	73%	72%	65%	58%
Ejection fraction 30% to 50%	25%	24%	24%	29%	35%
Ejection fraction <30%	3.8%	3.3%	3.5%	5.3%	7.6%
Internal thoracic artery use	94%	94%	94%	94%	94%
CABG without cardiopulmonary bypass	5.8%	5.5%	5.8%	6.7%	7.5%
Waiting time <7 days	23%	22%	23%	25%	27%

[a]AKI groups were defined according to an absolute increase in SCr conentration: no AKI, <0 µmol/L; group 1, 0 to 26 µmol/L; group 2, 26 to 44 µmol/L; group 3 >44 µmol/L.
AKI = acute kidney injury, CABG = coronary artery bypass grafting, eGFR = estimated glomerular filtration rate, MI = myocardial infarction, SD = standard deviation, SCr = Serum Creatinine.
Table adopted an modified from the manuscript of study IV.

Table 15. Relative risks in relation to AKI group 1 to 3[a] for all-cause mortality within 30 days, long-term mortality, and the combined outcome of long-term death, myocardial infarction, heart failure, and stroke

Outcome	No kidney injury	AKI groups		
		1	2	3
Number of patients	25 665	10 322	1631	1646
30-day all-cause mortality		**Odds ratio (95% CI)**		
Crude		1.34 (0.91-1.99)	4.63 (2.91-7.38)	23.4 (16.7-32.7)
Multivariable adjustment[b]		1.37 (0.84-2.21)	3.64 (2.07-6.38)	15.4 (9.98-23.9)
Long-term all-cause mortality		**Hazard ratio (95% CI)**		
Crude		1.16 (1.08-1.24)	1.93 (1.73-2.15)	3.75 (3.43-4.10)
Multivariable adjustment[b]		1.07 (1.00-1.15)	1.33 (1.19-1.48)	2.11 (1.92-2.32)
Combined end-point[c]		**Hazard ratio (95% CI)**		
Crude		1.15 (1.10-1.22)	1.86 (1.71-2.03)	3.12 (2.90-3.37)
Multivariable adjustment[b]		1.09 (1.03-1.15)	1.39 (1.27-1.52)	1.99 (1.84-2.16)

[a]Acute kidney injury groups were defined according to the increase in the serum creatinine concentration from the preoperative to postoperative periods: group 1, 0 to 26 µmol/L; group 2, 26 to 44 µmol/L; group 3, >44 µmol/L; and no kidney injury, ≤0 µmol/L (reference group).
[b]Multivariable adjustments were made for age, chronic obstructive pulmonary disease, heart failure, diabetes mellitus, estimated glomerular filtration rate, left ventricular ejection fraction, myocardial infarction, peripheral vascular disease, sex, and stroke (all prior to surgery).
[c]The combined outcome includes heart failure, stroke, myocardial infarction, and long-term death.
Table adopted from the manuscript of Study IV and modified.
AKI = Acute kidney injury, CI = confidence interval.

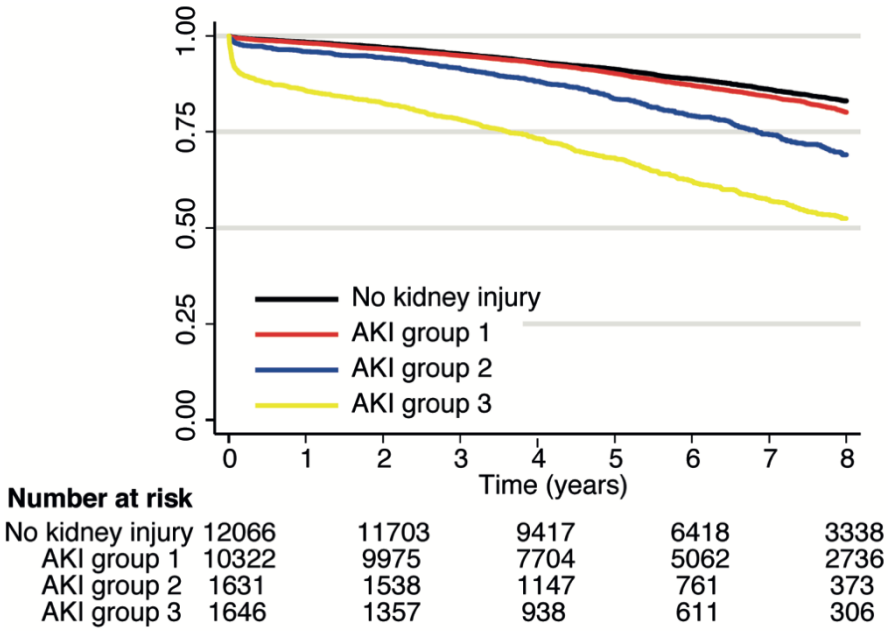

Figure 7.
Kaplan–Meier curve on the cumulative incidence of long-term death according to acute kidney injury group. AKI = acute kidney injury. Adopted from the manuscript of Study IV and modified.

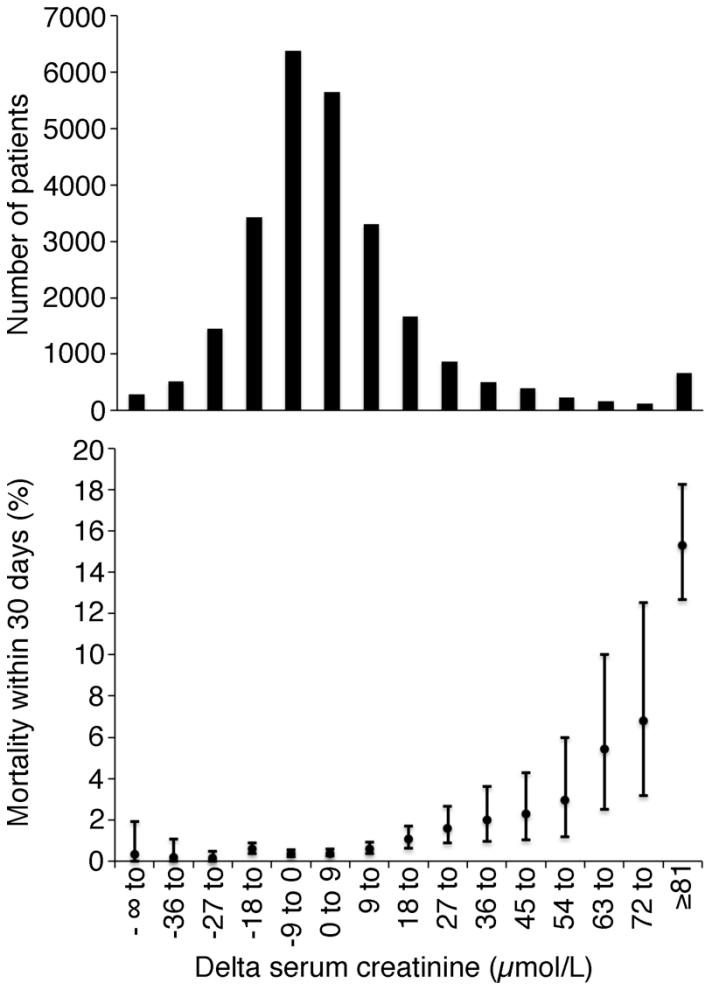

Figure 8.
Illustration of the 30-mortality and number of patients according to change in post-compared to pre-operative serum creatinine concentrations. Figure adopted and modified from the manuscript of study IV.

INTERPRETATION AND OVERALL DISCUSSION

SUMMARY OF FINDINGS

In this thesis of observational cohort studies, we identified risk factors for and outcomes of AKI in patients undergoing cardiac surgery. We also investigated the prognostic value of minimal increases in postoperative SCr concentrations. Treatment with teicoplanin and a comorbidity of diabetes were associated with the development of AKI. AKI after surgery was associated with increased long- and short-term mortality, heart failure and a combined outcome of long-term mortality, heart failure, myocardial infarction, or stroke. Minimal increases in SCr of 0 to 26 micromol/L was associated with an increased long-term mortality and cardiovascular outcomes, but not 30-day mortality. Due to the conflicting results of prognosis in relation to minimal increases in SCr, it is not motivated to include minimal increases in SCr in the AKI stage 1 criteria according to KDIGO or AKIN.

METHODOLOGICAL CONSIDERATIONS

Internal validity

A main goal in performing Studies I to IV was to obtain the most accurate results possible and coming close to the true associations between the exposures and outcomes. However, epidemiologic studies are associated with several pitfalls, many of which have been named and categorized for a better understanding and prevention. As discussed below, the accuracy of study results can decrease due to systematic error and random error.

Systematic error (bias)

Systematic error, also called bias, is a built-in error that makes all study results incorrect to a certain extent. A systematic error is not dependent on the size of the study. Therefore, unlike random error, systematic error cannot be mended by increasing the sample size which is the case with random error. Systematic error is comparable to a good sniper using an incorrectly calibrated sniper scope that causes all shots to be close to one another but located alongside the bullseye. Systematic error is dependent on the study design. In general, systematic error in epidemiologic studies can be divided into three broad categories: selection bias, information bias, and confounding (148). Systematic error may not be fixed afterward, but the extent of it may be estimated. Thus, the best way to handle systematic error is to avoid it.

Selection bias is a systematic error related to factors that influence participation in either the exposed group or the unexposed group. For example, patients with a hereditary disposition for cancer might be more interested in participating in a new cancer screening program. Comparison of the screened patients (exposed group) with unscreened patients might seem to indicate that the screening program identifies more patients with cancer, but the true cause of the higher number of identified is that this group had a higher baseline risk of cancer (148).

In Studies II to IV, we excluded patients with missing preoperative or postoperative SCr concentrations. Exclusion of patients with missing information can introduce selection bias if the excluded population differs from patients with complete information. In this case, the selection bias will affect the results if there is a different association between the exposure and the outcome in the excluded group as compared to the group included in the study. No such systematic error was identified in our data. In fact, our research group investigated the patients with missing values in the cohorts of Studies III and IV. Patients with missing data had the same baseline characteristics and risk of long-term mortality as did patients with complete information on the SCr concentration (unpublished data).

Information bias arises when the gathered data on the study subjects is incorrect (148). There are many categories of information bias, and one example is misclassification. Misclassification of dichotomous variables arises when the study subjects are assigned to the wrong category. Using Study III as an example, some patients might have been diagnosed with heart failure but did not fulfill all criteria for heart failure. If the tendency to overdiagnose the outcome of heart failure is higher in the exposed group (AKI group), the risk of developing heart failure would be overestimated and the misclassification would be a differential misclassification of the outcome. If the tendency to overdiagnose heart failure is equal in the exposed and unexposed groups, the risk would not be overestimated and the misclassification would be nondifferential. A nondifferential misclassification does not result in overestimation or underestimation of the effect, but because more patients would be classified as having heart failure unrelated to whether they were exposed or not, the association would seem weaker. The effect size would thereby be diluted and the relative risk would approach 1. All epidemiological studies are affected by nondifferential misclassification to some extent.

Our studies were dependent on valid diagnoses to obtain accurate results. Classification of AKI was based on values from laboratory analyses, and the laboratories were blinded to the patients' status. However, the frequency of obtaining blood samples might have been higher in sicker patients or patients with postoperative complications. Therefore, we might have identified more cases of AKI in the sicker group because of increased sampling. This misclassification of the exposure can lead to overestimation of the association between AKI and morbidity and mortality. On the other hand, we used the highest postoperative SCr concentration during the entire postoperative period. Thus, the diagnosis of AKI in the healthier population was not likely to have been missed to a great extent.

A confounder is a factor that is associated with the exposure and outcome but is not part of the causal pathway (Figure 9) (148). For example, an association may be present between cocaine use and myocardial infarction. However, age could be a confounder in this case because the risk of myocardial infarction increases with higher age, and younger individuals tend to use cocaine to a greater extent. Age is thereby related to both the studied exposure and outcome. If we adjust for age, we can estimate the effect of cocaine use regardless of age. If cocaine use leads to tachycardia with subsequent cardiac ischemia and myocardial infarction,

tachycardia would be an intermediate factor in a causal pathway. When investigating the association between cocaine use and the risk of myocardial infarction, it would be incorrect to adjust for tachycardia because this is the mechanism which mediates the causal relationship between cocaine and myocardial infarction.

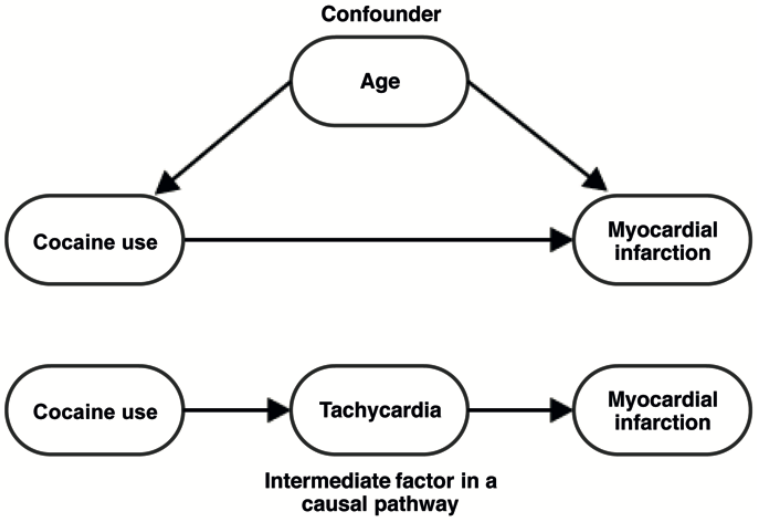

Figure 9.
Illustration showing a confounder and an intermediate factor and their relationships to an exposure (cocaine use) and outcome (myocardial infarction).

In Studies I to IV, we handled confounding using multivariable statistical models and stratified analyses. These are statistical methods to handle confounding. There are also methods during data collection to decrease confounding such as randomization, restriction, and matching (148). These methods were not used because we used already-sampled data. The analyses in Studies I to IV were adjusted for the most important risk factors for perioperative AKI described in the literature (30). However, we cannot rule out the presence of residual confounding. In Studies II to IV, we did not adjust for perioperative risk factors for AKI such as the use of cardiopulmonary bypass or the cross-clamp time because these factors can be part of a causal pathway of AKI and cardiovascular outcomes. In Study I, we investigated a specific causal pathway, and the perioperative risk factors were thereby eligible for inclusion in the multivariable model. Deep hypothermic circulatory arrest was included in the final model.

Random error - Precision

Random error is variability in the study data that cannot be explained. The random error is thereby derived from a lack of knowledge or lack of detail of the data. For example, if a rubber ball is thrown onto an irregular surface, the direction in which the ball will bounce is difficult to predict and might be interpreted as random. If the ball is thrown 10,000 times and the outcome is measured, it would be possible to draw conclusions regarding the most likely angle and distance the next time the ball is thrown. The most likely intervals of direction and length within which the ball will stay can also be calculated. If the exact angle, force, and configuration of the surface can be measured, then the direction in which the ball bounces would not be random and the results could be predicted with higher precision.

The precision of the point estimates in Studies I to IV was indicated by the 95% CIs. Simplified, this means that there is a 95% likelihood that the true value is within this interval. Notably, calculated precision does not take systematic error into account. When a CI does not include the null hypothesis (often a relative risk of 1), the result is considered statistically significant. The p value is traditionally used for hypothesis testing. The definition according to Fisher, who promoted the widespread use of p values in medical statistics, can be summarized as follows: "the probability that the null hypothesis is true according to an observation, plus more extreme values" (149). The CI and p value can be calculated from the same equation, and presenting both a p value to a CI does not add information. The 95% CI and a p value of <0.05 are somewhat arbitrary levels of confidence commonly used in medical research (148).

Of importance, a significant result is neither equal to the effect size nor clinical importance. A study of 36,106 patients, as in Study II, will in this case provide plentiful significant results when comparing variables. In this study, we found that T1DM and T2DM had a multivariable adjusted hazard ratio of 4.89 and 1.27, respectively. The importance of the calculated effect size depends on the clinical context, specifically how common the exposure is and the severity of the outcome or secondary consequences. The hazard ratio of 1.27 found in Study II might seem low, but considering that 14% of the patients who underwent CABG had T2DM and that the consequences of perioperative AKI are severe in terms of associated complications and health care costs, the author argues that this rather low hazard ratio has an important impact on patients undergoing cardiac surgery.

External validity / Generalizability

External validity also called generalizability, is the ability to apply the results from a sample or cohort to other samples or cohorts, for example, among other hospitals, an entire country, other countries, or other ethnic and socioeconomic groups. Study I was a single-center study of a general cardiac surgery population. Studies II to IV were nation-wide studies; they included patients who underwent nonemergent CABG from all cardiac surgery sites in Sweden. In Sweden, there is no policy to send sicker adult patients to a certain center for CABG or regular valve surgery. The characteristics of the patients in Study I should therefore not differ significantly from those of the patients in Studies II to IV. The patient's characteristics were similar between Study I and Studies II to IV (Tables 7, 9, 12, 14). Additionally, the demographics and comorbidities were comparable between patients in Studies I to IV and cohorts from European studies, Australia, and the United States (150–152). The cardiac surgery procedures in Sweden are also largely standardized and comparable with those in other countries with similar health care. Therefore, the author believes and that our results are generalizable to other countries with similar health care.

Whether the results of Studies I to IV are generalizable to populations undergoing other types of surgical procedures, such as major abdominal surgery or orthopedic surgery, is uncertain. The use of perioperative cardiopulmonary bypass is unique to cardiac surgery, and whether the AKI-associated outcomes following cardiac surgery are similar to those following other

procedures is not answered in our studies. Separate studies in other surgical settings are needed to draw general conclusions regarding this issue. In fact, results from other surgical settings such as major abdominal and orthopedic surgery have shown that AKI is associated with increased mortality and complications (153,154). The results of our studies thereby show consistency not only with prior studies in cardiac surgery (155,156), but also with other surgical settings (153,154).

INTERPRETATION OF FINDINGS

The strong association between AKI, CKD, cardiovascular disease, and their risk factors makes it difficult to interpret what perioperative AKI really means and causes. In Study II, we found that both T1DM and T2DM are risk factors for AKI. Diabetes is also a general risk factor for the development of CKD and cardiovascular disease even outside the cardiac surgery setting (117–119). In Studies III and IV, we found an association between AKI and the risk of developing heart failure as well as between AKI and the composite outcome of long-term mortality, heart failure, myocardial infarction, and stroke. One might wonder if perioperative AKI is more a *sign* of cardiovascular disease than an important event on its own. Does AKI really *cause* disease? Is AKI during surgery merely a cardiovascular and renal stress test comparable to the cardiologist's exercise stress test that reveals ischemic heart disease? Irrespective of this, AKI remains of interest because it provides information on the patient's prognosis; however, would research on AKI prevention and treatment be meaningful? The schematic illustration in Figure 10 shows the associations found by our research group and indicates that all pathways could bypass a causal effect of AKI and outcomes. These speculations challenge the two assumptions held by many AKI researchers: that the frequency of perioperative AKI is modifiable and that a decreased incidence of perioperative AKI will improve patients' outcomes. Based on the pathways illustrated in Figure 10, it might be easy to reject the above-mentioned assumptions. Unfortunately, it will be difficult to perform a human study that allows for identification of a causal pathway from AKI to, for example, cardiac injury (CRS type III or IV). What we can do, however, is to use the currently available evidence and step by step reason regarding a possible causal pathway:

- AKI can be caused by factors that do not primarily injure any organs except the kidneys. These causes of AKI are not dependent upon risk factors for either cardiovascular disease or AKI, nor are they dependent upon a systemic disease. For example, primarily nephrotoxic factors include exposure to different toxins such as orellanine from mushroom poisoning, snake bites, or rhabdomyolysis (157–159). It is fully reasonable that medications can also be primarily nephrotoxic. In Study I, we showed that teicoplanin was associated with AKI. Correct medical treatment can likely modify the frequency of perioperative AKI.

- AKI can lead to CKD, and there is a dose-dependent relationship between the severity of AKI and long-term renal function in various clinical settings including cardiac surgery, intoxications, rhabdomyolysis, and sepsis (4,158–161).

- Studies have shown that renal transplantation can reverse a decreased LVEF and left ventricular hypertrophy (162). A recent study also showed that healthy kidney donors later developed signs of increased left ventricular mass, an increased mass–volume ratio, and increased serum concentrations of troponin T (163). This implies a causal relationship between chronic loss of renal function and cardiovascular disease. There are also functions unique to the kidney that can cause distant organ effects. A decrease in urine production is associated with a risk of fluid overload, electrolyte disturbances, and accumulation of metabolites that can stress distant organs such as a failing heart (116).

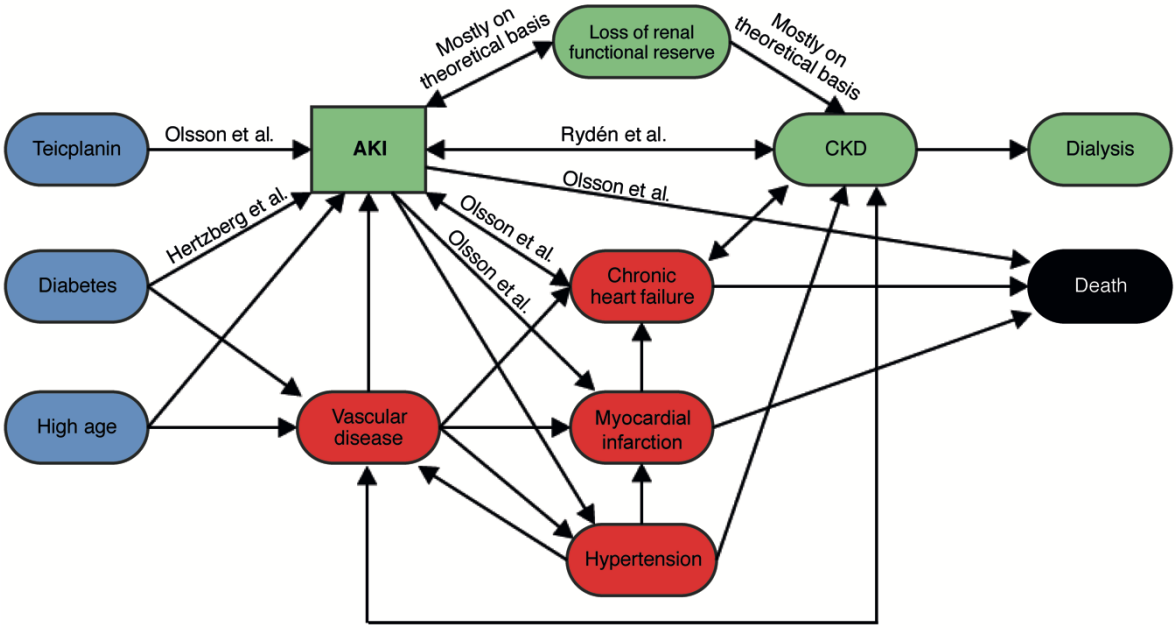

Figure 10.
Illustration of selected associations found in epidemiological studies of AKI suggesting several possible causal connections and confounding factors. Green boxes represent renal outcomes, red boxes represent cardiovascular outcomes, and blue boxes represent risk factors for either renal or cardiovascular outcomes. The text above the arrows are examples of studies that found the stated association.
AKI = acute kidney injury, CKD = chronic kidney disease.

Considering the above statements, one can argue that AKI is not only a sign of cardiovascular disease but that it can also have long-term causative effects. The evidence regarding the acute effects of AKI is weaker. In Study IV, we found that the development of AKI after CABG was associated with 30-day mortality. Is this due to a primary cardiac injury leading to decreased cardiac output or to other factors external to the kidneys that run parallel with AKI? Or does AKI have an impact on 30-day mortality on its own? As mentioned in the background section, animal studies have shown that AKI causes acute distant organ effects

not only by fluid overload and electrolyte disturbances (122). These studies found that the inflammatory mediators involved in AKI are the same as those involved in toxic cardiomyopathy. Additionally, even if the primary cause of AKI is reduced cardiac function, it is possible that AKI will further worsen the cardiac function by inflammation, fluid overload, and activation of the renin-angiotensin-aldosterone system (60).

In summary, the author argues that there is a strong association between perioperative AKI and a worse prognosis. This is likely due to a combination of both AKI as a sign of cardiovascular disease and AKI as a cause of cardiovascular disease with CKD or decreased renal functional reserve as intermediate steps. There may also be short-term effects of AKI that influence the outcome. The abovementioned assumptions of AKI research are plausible, and interventional AKI studies are meaningful. Further exploration on the casual pathway of AKI should be performed by interventional studies in which a decreased incidence of AKI is followed up with respect to associated complications.

FUTURE RESEARCH

Improved interventional studies

The impact of AKI on patients' prognosis is receiving increasingly more attention in research. AKI has been found to be associated with a worse prognosis in various settings such as intensive care, major abdominal surgery, and orthopedic surgery (153,154,164). In Studies I to IV, we further investigated AKI in the cardiac surgery setting. A natural next step would be studies on the prevention and treatment of AKI. Two very common clinical settings in which prevention of AKI could be effective are cardiac surgery and administration of iodinated contrast media (165). However, no studies have identified effective preventive interventions in these settings. In many cases, studies have shown severe methodological limitations (165). A challenge inherent to the study of perioperative AKI is its multifactorial causes. It is unlikely that one single intervention will lead to a great decrease in the incidence of AKI. Thus, interventional studies must be large to ensure sufficient statistical power. Many of the interventional AKI studies with absent or inconclusive statistical significance included around 50 to 500 patients (166–168). These studies were likely deemed to fail from the beginning considering the following power calculation example:

In Study II, the baseline incidence of AKI was around 14%. If the effect size of a potential intervention is assumed to reduce the risk of AKI by 25%, the event rate in the treatment group would be 10.5%. A power calculation using $\alpha = 0.05$ and $1 - \beta = 0.8$ (80% power) would result in a required sample size of 2866 patients. If the intervention instead would be assumed to reduce the risk of AKI by 50% (huge effect), the required sample size would be 656 patients.

Large interventional studies are expensive. The sample size can be decreased using risk stratification scores that increase the baseline incidence of AKI in the cohort. If we could use

a prediction score to identify a cohort in which the baseline risk of AKI is 50% and we assume an effect size of a 50% reduction in AKI, the required sample size would be 524 patients. Hence, good AKI prediction models are needed. New biomarkers might play an important role in the future for improved prediction models. Also, we are likely often too late and have missed the opportunity for AKI treatment. Biomarkers may improve the timing of the intervention and thereby improving the effect size.

To ensure a progress in AKI prevention and treatment studies, the author argues that there are needed studies with adequate statistical power, improved prediction scores, and further exploration of AKI biomarkers.

Follow up studies

Several ideas for follow-up studies emerged in the aftermath of performing Studies I to IV. In Study I, treatment with teicoplanin was associated with the development of AKI after surgery. It would be interesting to perform a long-term follow-up study to determine whether teicoplanin treatment is associated with the development of CKD, cardiovascular outcomes, death, and postoperative infections. This will help to evaluate the costs and benefits of teicoplanin treatment. Such a study could also provide insight regarding a causal relationship between AKI and outcomes of cardiac surgery. However, a challenge in this follow-up study would be adequate statistical power because the incidence of AKI between the teicoplanin and reference group differed by only 3 percentage units, and the cumulative incidence of heart failure, myocardial infarction, stroke, and death was around 28%. Another challenge is the fact that teicoplanin treatment was not randomized.

In Study III, we found an association between AKI and a long-term risk of heart failure. It would be interesting to determine how much of this long-term risk of developing heart failure is explained by an intermediate step of CKD. Such a study could use SCr from laboratory registers for identification of CKD.

Study settings for cardio-renal syndrome type III investigations

The causal relationship between AKI and outcomes is difficult to study in humans because we do not want to induce AKI in a randomized group of patients. For further conclusions on the acute effects of AKI (CRS type III), we must identify clinical settings that could simulate an experimental setting. In this thesis, we used cardiac surgery as a model for AKI. Interesting settings for investigating the acute effects of AKI are renal transplantation and nephrotoxin exposures:

Transplantation surgery

CKD is associated with cardiac abnormalities such as ventricular hypertrophy, systolic and diastolic dysfunction, and left ventricular dilatation (162). A recent study revealed improved cardiac function and structure in a long-term follow-up after kidney transplantation (169). This group of patients would be interesting to study further. When inserting a new (likely ischemic) kidney in patients with renal failure, will the same inflammatory markers be

released as in animal models of ischemic kidney disease? Will this have an effect on graft prognosis or future cardiovascular disease? Will sensitive measurements of cardiac function reveal any acute changes?

Kidney donors exhibit a sudden decline in GFR. Will there be acute hemodynamic alterations and changes in the renal angiotensin aldosterone system? Will there be acute changes in cardiac function?

Acute kidney injury from toxin exposure

Exposure to various nephrotoxins, such as orellanine intoxication, may lead to severe AKI and subsequent CKD. Some patients have no cardiovascular risk factors before exposure. Do these intoxications have short-term effects on cardiac function and structure or on blood inflammatory markers? What is the long-term risk of cardiovascular disease?

CONCLUSIONS

The overall aim of this thesis was to further investigate the risk factors for and outcomes of AKI in patients undergoing cardiac surgery. The main findings were as follows.

Study I Antibiotic prophylaxis with teicoplanin in patients undergoing cardiac surgery was associated with an increased risk of developing AKI.

Study II T1DM and T2DM were associated with an increased risk of AKI in patients undergoing CABG irrespective of their preoperative renal function. The risk of developing AKI was higher in patients with T1DM than in patients with T2DM.

Study III The development of AKI after CABG was associated with an increased long-term risk of developing heart failure

Study IV A minimal increase in the SCr concentration of 0 to 26 μmol/L was associated with increased long-term mortality and an increased risk of the combined outcome of long-term mortality, heart failure, myocardial infarction, and stroke. A minimal increase in the SCr concentration was not associated with 30-day mortality, but those having a minor increase in SCr of 26 to 44 μmol/L had a significantly increased 30-day mortality.

ACKNOWLEDGEMENTS

The author is thankful to the steering committees of SWEDEHEART, the Swedish National Diabetes Register, and the Swedish Renal Registry for making their registers available for the purpose of our studies. I also want to thank the Swedish Heart-Lung foundation for financial support making it possible to go to international conferences. In addition, I would like to thank the Swedish Medical Society for grants that made the assembly of the datasets used in this thesis possible.

The journey until this thesis have been great and I have learned a lot. There are many people that I would like to thank for being part of my development in science. I want to express my gratitude to all who supported me and contributed to this thesis, especially:

Supervisors

Huvudhandledare **Martin Holzmann.** Tack för din undervisning och guidning, för din entusiasm, energi och kloka råd. Tack för din generositet, omtanke, och för roliga fester och middagar. Jag hoppas att vi får fortsätta med nya spännande forskningsprojekt framöver!

Bihandledare **Ulrik Sartipy**. Tack för alla goda råd och undervisning. Tack för att man alltid känner sig välkommen när man kommer förbi ditt kontor för att be om hjälp, och att problemen alltid är lösta när man går därifrån. Tack för din tid och ditt engagemang.

Mentor **Johan Holmdahl.** Tack för fina samtal, goda råd och perspektiv på tillvaron.

Collaborators and co-authors

Linda Rydén. Tack för all positiv feedback och uppmuntran. För roliga middagar och resor!

Marcus Liotta. Tack för roliga stunder och intressanta diskussioner i Treviso, Philadelphia och Stockholm.

Indirect collaborators and friends

Adam Stenman. Du är en sann glädjespridare och inspiratör. Tack för alla goda råd och för din hjälp. Du är grym på det mesta men ändå ödmjuk. Det är inte säker att jag börjat forska om det inte varit för att du fanns där och peppade. Tack för alla skratt och roliga upptåg. För simturer runt Kungsholmen, mellan öarna utanför Hunnebo och klättring på Karlbergsmuren.

Mina kurskamrater genom läkarprogrammet **Karolin Petersson**, **Erik & Linnea Malgerud**, **Oskar Kövamees**, **Ingrid Liljefors**, **Johanna Andersson**, **Tor Karlsson**, **Niklas Tångring och Emil Boström**. Tack för alla roliga stunder och ambitiösa studier.

Mina vänner **Axel Andersson**, **Hans Larson**, **Sebastian & Astrid Jönsson, Anna & Björn Johannessen, Annika Christensson, Hedvig Almgren, Terje Vikingsson.** Tack för allt kul vi haft ihop. Utan er hade jag inte varit den person jag är idag.

My family

Mina föräldrar **Barbro och Per-Olof.** Tack för er villkorslösa kärlek och ert stöd. För glädje och engagemang. Tack mina fantastiska syskon och förebilder Anna, Mattias, Peter. Tack för all glädje och tålamod genom åren. Tack till svåger Lasse, svägerskor Sara och Karolina och alla barnen Mikaela, Jesper, Mia, Noa, Astrid, Elin, Edwin, Wilmer. Det är fantastiskt att se hur familjen bara expanderar med alla underbara personer.

Tack till svärmor och svärfar och respektive, svägerskor, svågrar och familjer. Det har varit fantastiskt roligt att lära känna er alla!

Cecilia. Min livs kärlek och fru. Tack för din kärlek och ditt tålamod. Jag ser fram emot vår framtid tillsammans!

REFERENCES

1. Boron WF, Boulpaep EL, editors. Medical physiology: a cellular and molecular approach. 2nd ed., International ed. Philadelphia, PA: Saunders/Elsevier; 2009. 1337 p.

2. Susantitaphong P, Cruz DN, Cerda J, Abulfaraj M, Alqahtani F, Koulouridis I, et al. World incidence of AKI: a meta-analysis. Clin J Am Soc Nephrol. 2013;8(9):1482–93.

3. Hoste EAJ, Schurgers M. Epidemiology of acute kidney injury: how big is the problem? Crit Care Med. 2008;36(4 Suppl):S146–51.

4. Rydén L, Sartipy U, Evans M, Holzmann MJ. Acute kidney injury after coronary artery bypass grafting and long-term risk of end-stage renal disease. Circulation. 2014;130(23):2005–11.

5. Jones J, Holmen J, De Graauw J, Jovanovich A, Thornton S, Chonchol M. Association of complete recovery from acute kidney injury with incident CKD stage 3 and all-cause mortality. Am J Kidney Dis. 2012;60(3):402–8.

6. Goldstein SL, Chawla L, Ronco C, Kellum JA. Renal recovery. Crit Care. 2014;18(1):301.

7. Goren O, Matot I. Update on perioperative acute kidney injury. Curr Opin Crit Care. 2016;22(4):370–8.

8. Haase M, Shaw A. Acute kidney injury and cardiopulmonary bypass: special situation or same old problem? Contrib Nephrol. 2010;165:33–8.

9. Dunn JS, McNee JW. A CONTRIBUTION TO THE STUDY OF WAR NEPHRITIS. Br Med J. 1917;2(2971):745–51.

10. Beall D, Bywaters EGL, Belsey RHR, Miles JAR. Crush Injury with Renal Failure. Br Med J. 1941;1(4185):432–4.

11. Novis BK, Roizen MF, Aronson S, Thisted RA. Association of preoperative risk factors with postoperative acute renal failure. Anesth Analg. 1994;78(1):143–9.

12. Ricci Z, Ronco C, D'Amico G, De Felice R, Rossi S, Bolgan I, et al. Practice patterns in the management of acute renal failure in the critically ill patient: an international survey. Nephrol Dial Transplant. 2006;21(3):690–6.

13. Bellomo R, Ronco C, Kellum JA, Mehta RL, Palevsky P, Acute Dialysis Quality Initiative workgroup. Acute renal failure - definition, outcome measures, animal models, fluid therapy and information technology needs: the Second International Consensus Conference of the Acute Dialysis Quality Initiative (ADQI) Group. Crit Care. 2004;8(4):R204–12.

14. Kuitunen A, Vento A, Suojaranta-Ylinen R, Pettilä V. Acute renal failure after cardiac surgery: evaluation of the RIFLE classification. Ann Thorac Surg. 2006;81(2):542–6.

15. Arnaoutakis GJ, Bihorac A, Martin TD, Hess PJ, Klodell CT, Ejaz AA, et al. RIFLE criteria for acute kidney injury in aortic arch surgery. J Thorac Cardiovasc Surg. 2007;134(6):1554–60; discussion 1560–1.

16. Hoste EAJ, Clermont G, Kersten A, Venkataraman R, Angus DC, De Bacquer D, et al. RIFLE criteria for acute kidney injury are associated with hospital mortality in critically ill patients: a cohort analysis. Crit Care. 2006;10(3):R73.

17. Ricci Z, Cruz D, Ronco C. The RIFLE criteria and mortality in acute kidney injury: A systematic review. Kidney Int. 2008;73(5):538–46.

18. Uchino S, Bellomo R, Bagshaw SM, Goldsmith D. Transient azotaemia is associated with a high risk of death in hospitalized patients. Nephrol Dial Transplant. 2010;25(6):1833–9.

19. Mehta RL, Kellum JA, Shah SV, Molitoris BA, Ronco C, Warnock DG, et al. Acute Kidney Injury Network: report of an initiative to improve outcomes in acute kidney injury. Crit Care. 2007;11(2):R31.

20. Joannidis M, Metnitz B, Bauer P, Schusterschitz N, Moreno R, Druml W, et al. Acute kidney injury in critically ill patients classified by AKIN versus RIFLE using the SAPS 3 database. Intensive Care Med. 2009;35(10):1692–702.

21. Kellum JA, Lameire N, KDIGO AKI Guideline Work Group. Diagnosis, evaluation, and management of acute kidney injury: a KDIGO summary (Part 1). Crit Care. 2013;17(1):204.

22. Md Ralib A, Pickering JW, Shaw GM, Endre ZH. The urine output definition of acute kidney injury is too liberal. Crit Care. 2013;17(3):R112.

23. Siew ED, Matheny ME, Ikizler TA, Lewis JB, Miller RA, Waitman LR, et al. Commonly used surrogates for baseline renal function affect the classification and prognosis of acute kidney injury. Kidney Int. 2010;77(6):536–42.

24. Ricci Z, Cruz DN, Ronco C. Classification and staging of acute kidney injury: beyond the RIFLE and AKIN criteria. Nat Rev Nephrol. 2011;7(4):201–8.

25. Pickering JW, Frampton CM, Walker RJ, Shaw GM, Endre ZH. Four hour creatinine clearance is better than plasma creatinine for monitoring renal function in critically ill patients. Crit Care. 2012;16(3):R107.

26. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. Am J Kidney Dis. 2002;39(2 Suppl 1):S1–266.

27. KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. 2013;3(1).

28. Go AS, Chertow GM, Fan D, McCulloch CE, Hsu C. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. N Engl J Med. 2004;351(13):1296–305.

29. Gargiulo R, Suhail F, Lerma EV. Cardiovascular disease and chronic kidney disease. Dis Mon. 2015;61(9):403–13.

30. KDIGO AKI Workgroup. Kidney Disease: Improving Global Outcomes (KDIGO) clinical practise guideline for acute kidney injury. Kidney Int Suppl. 2012;2:1–138.

31. Kiil F, Aukland K, Refsum HE. Renal sodium transport and oxygen consumption. Am J Physiol. 1961;201:511–6.

32. Brezis M, Rosen S, Silva P, Epstein FH. Selective vulnerability of the medullary thick ascending limb to anoxia in the isolated perfused rat kidney. J Clin Invest. 1984;73(1):182–90.

33. Persson PB, Ehmke H, Nafz B, Kirchheim HR. Sympathetic modulation of renal autoregulation by carotid occlusion in conscious dogs. Am J Physiol. 1990;258(2 Pt 2):F364–70.

34. Wyss M, Kaddurah-Daouk R. Creatine and creatinine metabolism. Physiol Rev. 2000;80(3):1107–213.

35. Traynor J, Mactier R, Geddes CC, Fox JG. How to measure renal function in clinical practice. BMJ. 2006;333(7571):733–7.

36. Thomas ME, Blaine C, Dawnay A, Devonald MAJ, Ftouh S, Laing C, et al. The definition of acute kidney injury and its use in practice. Kidney Int. 2015;87(1):62-73

37. Waikar SS, Bonventre JV. Creatinine kinetics and the definition of acute kidney injury. J Am Soc Nephrol. 2009;20(3):672–9.

38. Kellum JA, Devarajan P. What can we expect from biomarkers for acute kidney injury? Biomark Med. 2014;8(10):1239–45.

39. Schrezenmeier EV, Barasch J, Budde K, Westhoff T, Schmidt-Ott KM. Biomarkers in acute kidney injury - pathophysiological basis and clinical performance. Acta Physiol (Oxf). 2016;[Epub ahead of print]

40. Ostermann M, Philips BJ, Forni LG. Clinical review: Biomarkers of acute kidney injury: where are we now? Crit Care. 2012;16(5):233.

41. Charlton JR, Portilla D, Okusa MD. A basic science view of acute kidney injury biomarkers. Nephrol Dial Transplant. 2014;29(7):1301–11.

42. Endre ZH, Pickering JW. Acute kidney injury: cell cycle arrest biomarkers win race for AKI diagnosis. Nat Rev Nephrol. 2014;10(12):683–5.

43. Hoste EAJ, McCullough PA, Kashani K, Chawla LS, Joannidis M, Shaw AD, et al. Derivation and validation of cutoffs for clinical use of cell cycle arrest biomarkers. Nephrol Dial Transplant. 2014;29(11):2054–61.

44. Bihorac A, Chawla LS, Shaw AD, Al-Khafaji A, Davison DL, Demuth GE, et al. Validation of cell-cycle arrest biomarkers for acute kidney injury using clinical adjudication. Am J Respir Crit Care Med. 2014;189(8):932–9.

45. Musso CG, Álvarez-Gregori J, Jauregui J, Macías-Núñez JF. Glomerular filtration rate equations: a comprehensive review. Int Urol Nephrol. 2016;48(7):1105–10.

46. Delanaye P, Schaeffner E, Ebert N, Cavalier E, Mariat C, Krzesinski J-M, et al. Normal reference values for glomerular filtration rate: what do we really know? Nephrol Dial Transplant. 2012;27(7):2664–72.

47. Berg UB. Differences in decline in GFR with age between males and females. Reference data on clearances of inulin and PAH in potential kidney donors. Nephrol Dial Transplant. 2006;21(9):2577–82.

48. Lindeman RD, Tobin J, Shock NW. Longitudinal studies on the rate of decline in renal function with age. J Am Geriatr Soc. 1985;33(4):278–85.

49. Murphy DP, Hsu C. Estimating glomerular filtration rate: is it good enough? And is it time to move on? Curr Opin Nephrol Hypertens. 2013;22(3):310–5.

50. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron. 1976;16(1):31–41.

51. Verhave JC, Fesler P, Ribstein J, du Cailar G, Mimran A. Estimation of renal function in subjects with normal serum creatinine levels: influence of age and body mass index. Am J Kidney Dis. 2005;46(2):233–41.

52. Froissart M, Rossert J, Jacquot C, Paillard M, Houillier P. Predictive performance of the modification of diet in renal disease and Cockcroft-Gault equations for estimating renal function. J Am Soc Nephrol. 2005;16(3):763–73.

53. Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. Ann Intern Med. 1999;130(6):461–70.

54. Björk J, Bäck S-E, Sterner G, Carlson J, Lindstrom V, Bakoush O, et al. Prediction of relative glomerular filtration rate in adults: new improved equations based on Swedish Caucasians and standardized plasma-creatinine assays. Scand J Clin Lab Invest. 2007;67(7):678–95.

55. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF 3rd, Feldman HI, et al. A new equation to estimate glomerular filtration rate. Ann Intern Med. 2009;150(9):604–12.

56. Bell M, SWING, Granath F, Schön S, Ekbom A, Martling C-R. Continuous renal replacement therapy is associated with less chronic renal failure than intermittent haemodialysis after acute renal failure. Intensive Care Med. 2007;33(5):773–80.

57. Kasper DL. Harrison's principles of internal medicine. 19th ed. New York: McGraw Hill Education; 2015. Chapter 279, Acute Kidney Injury.

58. Hertzberg D, Rydén L, Sartipy U, Holzmann M. Viktigt utreda orsaken till akut njurskada - Behandlingen ska sikta på att begränsa skadan och förhindra progress. [In Process Citation]. Läkartidningen. 2016;113.

59. Thakar CV. Perioperative acute kidney injury. Adv Chronic Kidney Dis. 2013;20(1):67–75.

60. Legrand M, Payen D. Case scenario: Hemodynamic management of postoperative acute kidney injury. Anesthesiology. 2013;118(6):1446–54.

61. O'Sullivan KE, Byrne JS, Hudson A, Murphy AM, Sadlier DM, Hurley JP. The effect of obesity on acute kidney injury after cardiac surgery. J Thorac Cardiovasc Surg. 2015;150(6):1622–8.

62. Grams ME, Astor BC, Bash LD, Matsushita K, Wang Y, Coresh J. Albuminuria and estimated glomerular filtration rate independently associate with acute kidney injury. J Am Soc Nephrol. 2010;21(10):1757–64.

63. Haase M, Haase-Fielitz A, Bellomo R. Cardiopulmonary bypass, hemolysis, free iron, acute kidney injury and the impact of bicarbonate. Contrib Nephrol. 2010;165:28–32.

64. Gaffney AM, Sladen RN. Acute kidney injury in cardiac surgery. Curr Opin Anaesthesiol. 2015;28(1):50–9.

65. Seabra VF, Alobaidi S, Balk EM, Poon AH, Jaber BL. Off-pump coronary artery bypass surgery and acute kidney injury: a meta-analysis of randomized controlled trials. Clin J Am Soc Nephrol. 2010;5(10):1734–44.

66. Lamy A, Devereaux PJ, Prabhakaran D, Taggart DP, Hu S, Paolasso E, et al. Off-pump or on-pump coronary-artery bypass grafting at 30 days. N Engl J Med. 2012;366(16):1489–97.

67. Lamy A, Devereaux PJ, Dorairaj P, Taggart DP, Hu S, Paolasso E, et al. Effects of Off-Pump and On-Pump Coronary-Artery Bypass Grafting at 1 Year. N Engl J Med. 2013;

68. Garg AX, Devereaux PJ, Yusuf S, Cuerden MS, Parikh CR, Coca SG, et al. Kidney function after off-pump or on-pump coronary artery bypass graft surgery: a randomized clinical trial. JAMA. 2014;311(21):2191–8.

69. Chawla LS, Zhao Y, Lough FC, Schroeder E, Seneff MG, Brennan JM. Off-pump versus on-pump coronary artery bypass grafting outcomes stratified by preoperative renal function. J Am Soc Nephrol. 2012;23(8):1389–97.

70. Sartipy U, Holzmann MJ, Hjalgrim H, Edgren G. Red Blood Cell Concentrate Storage and Survival After Cardiac Surgery. JAMA. 2015;314(15):1641–3.

71. Harty J. Prevention and management of acute kidney injury. Ulster Med J. 2014;83(3):149–57.

72. Walsh M, Devereaux PJ, Garg AX, Kurz A, Turan A, Rodseth RN, et al. Relationship between intraoperative mean arterial pressure and clinical outcomes after noncardiac surgery: toward an empirical definition of hypotension. Anesthesiology. 2013;119(3):507–15.

73. Sun LY, Wijeysundera DN, Tait GA, Beattie WS. Association of intraoperative hypotension with acute kidney injury after elective noncardiac surgery. Anesthesiology. 2015;123(3):515–23.

74. Azau A, Markowicz P, Corbeau JJ, Cottineau C, Moreau X, Baufreton C, et al. Increasing mean arterial pressure during cardiac surgery does not reduce the rate of postoperative acute kidney injury. Perfusion. 2014;29(6):496–504.

75. Redfors B, Bragadottir G, Sellgren J, Swärd K, Ricksten S-E. Effects of norepinephrine on renal perfusion, filtration and oxygenation in vasodilatory shock and acute kidney injury. Intensive Care Med. 2011;37(1):60–7.

76. Prowle JR, Kirwan CJ, Bellomo R. Fluid management for the prevention and attenuation of acute kidney injury. Nat Rev Nephrol. 2014;10(1):37–47.

77. Herrler T, Tischer A, Meyer A, Feiler S, Guba M, Nowak S, et al. The intrinsic renal compartment syndrome: new perspectives in kidney transplantation. Transplantation. 2010;89(1):40–6.

78. Mohmand H, Goldfarb S. Renal dysfunction associated with intra-abdominal hypertension and the abdominal compartment syndrome. J Am Soc Nephrol. 2011;22(4):615–21.

79. Bragadottir G, Redfors B, Ricksten S-E. Effects of levosimendan on glomerular filtration rate, renal blood flow, and renal oxygenation after cardiac surgery with cardiopulmonary bypass: a randomized placebo-controlled study. Crit Care Med. 2013;41(10):2328–35.

80. Yunos NM, Bellomo R, Hegarty C, Story D, Ho L, Bailey M. Association between a chloride-liberal vs chloride-restrictive intravenous fluid administration strategy and kidney injury in critically ill adults. JAMA. 2012;308(15):1566–72.

81. Chowdhury AH, Cox EF, Francis ST, Lobo DN. A randomized, controlled, double-blind crossover study on the effects of 2-L infusions of 0.9% saline and plasma-lyte® 148 on renal blood flow velocity and renal cortical tissue perfusion in healthy volunteers. Ann Surg. 2012;256(1):18–24.

82. Young P, Bailey M, Beasley R, Henderson S, Mackle D, McArthur C, et al. Effect of a Buffered Crystalloid Solution vs Saline on Acute Kidney Injury Among Patients in the Intensive Care Unit: The SPLIT Randomized Clinical Trial. JAMA. 2015;314(16):1701–10.

83. Myburgh JA, Finfer S, Bellomo R, Billot L, Cass A, Gattas D, et al. Hydroxyethyl starch or saline for fluid resuscitation in intensive care. N Engl J Med. 2012;367(20):1901–11.

84. Perner A, Haase N, Guttormsen AB, Tenhunen J, Klemenzson G, Åneman A, et al. Hydroxyethyl starch 130/0.42 versus Ringer's acetate in severe sepsis. N Engl J Med. 2012;367(2):124–34.

85. Schick MA, Isbary TJ, Schlegel N, Brugger J, Waschke J, Muellenbach R, et al. The impact of crystalloid and colloid infusion on the kidney in rodent sepsis. Intensive Care Med. 2010;36(3):541–8.

86. Dickenmann M, Oettl T, Mihatsch MJ. Osmotic nephrosis: acute kidney injury with accumulation of proximal tubular lysosomes due to administration of exogenous solutes. Am J Kidney Dis. 2008;51(3):491–503.

87. Moritz ML, Ayus JC. Maintenance Intravenous Fluids in Acutely Ill Patients. N Engl J Med. 2015;373(14):1350–60.

88. SAFE Study Investigators, Finfer S, McEvoy S, Bellomo R, McArthur C, Myburgh J, et al. Impact of albumin compared to saline on organ function and mortality of patients with severe sepsis. Intensive Care Med. 2011;37(1):86–96.

89. Ahmed US, Iqbal HI, Akbar SR. Furosemide in Acute Kidney Injury–A Vexed Issue. Austin J Nephrol Hypertens. 2014;1(5):1025.

90. Swärd K, Valsson F, Sellgren J, Ricksten S-E. Differential effects of human atrial natriuretic peptide and furosemide on glomerular filtration rate and renal oxygen consumption in humans. Intensive Care Med. 2005;31(1):79–85.

91. Kelly AM, Dwamena B, Cronin P, Bernstein SJ, Carlos RC. Meta-analysis: effectiveness of drugs for preventing contrast-induced nephropathy. Ann Intern Med. 2008;148(4):284–94.

92. Patel NN, Angelini GD. Pharmacological strategies for the prevention of acute kidney injury following cardiac surgery: an overview of systematic reviews. Curr Pharm Des. 2014;20(34):5484–8.

93. Song JW, Shim JK, Soh S, Jang J, Kwak YL. Double-blinded, randomized controlled trial of N-acetylcysteine for prevention of acute kidney injury in high risk patients undergoing off-pump coronary artery bypass. Nephrol Carlton Vic. 2015;20(2):96–102.

94. Szakmany T, Hauser B, Radermacher P. N-acetylcysteine for sepsis and systemic inflammatory response in adults. Cochrane Database Syst Rev. 2012;(9):CD006616.

95. Adabag AS, Ishani A, Koneswaran S, Johnson DJ, Kelly RF, Ward HB, et al. Utility of N-acetylcysteine to prevent acute kidney injury after cardiac surgery: a randomized controlled trial. Am Heart J. 2008;155(6):1143–9.

96. Wu M-Y, Hsiang H-F, Wong C-S, Yao M-S, Li Y-W, Hsiang C-Y, et al. The effectiveness of N-Acetylcysteine in preventing contrast-induced nephropathy in patients undergoing contrast-enhanced computed tomography: a meta-analysis of randomized controlled trials. Int Urol Nephrol. 2013;45(5):1309–18.

97. Wang N, Qian P, Kumar S, Yan TD, Phan K. The effect of N-acetylcysteine on the incidence of contrast-induced kidney injury: A systematic review and trial sequential analysis. Int J Cardiol. 2016;209:319–27.

98. National Clinical Guideline Centre (UK). Acute Kidney Injury: Prevention, Detection and Management Up to the Point of Renal Replacement Therapy [Internet]. London: Royal College of Physicians (UK); 2013 Aug. (NICE Clinical Guidelines, No. 169.) Available from: https://www.ncbi.nlm.nih.gov/books/NBK247665/

99. Lameire N, Kellum JA, KDIGO AKI Guideline Work Group. Contrast-induced acute kidney injury and renal support for acute kidney injury: a KDIGO summary (Part 2). Crit Care. 2013;17(1):205.

100. Ad-hoc working group of ERBP, Fliser D, Laville M, Covic A, Fouque D, Vanholder R, et al. A European Renal Best Practice (ERBP) position statement on the Kidney Disease Improving Global Outcomes (KDIGO) clinical practice guidelines on acute kidney injury: part 1: definitions, conservative management and contrast-induced nephropathy. Nephrol Dial. 2012;27(12):4263–72.

101. Lewicki M, Ng I, Schneider AG. HMG CoA reductase inhibitors (statins) for preventing acute kidney injury after surgical procedures requiring cardiac bypass. Cochrane Database Syst Rev. 2015;(3):CD010480.

102. Billings FT, Hendricks PA, Schildcrout JS, Shi Y, Petracek MR, Byrne JG, et al. High-Dose Perioperative Atorvastatin and Acute Kidney Injury Following Cardiac Surgery: A Randomized Clinical Trial. JAMA. 2016;315(9):877–88.

103. Zheng Z, Jayaram R, Jiang L, Emberson J, Zhao Y, Li Q, et al. Perioperative Rosuvastatin in Cardiac Surgery. N Engl J Med. 2016;374(18):1744–53.

104. National Heart, Lung, and Blood Institute ARDS Clinical Trials Network, Truwit JD, Bernard GR, Steingrub J, Matthay MA, Liu KD, et al. Rosuvastatin for sepsis-associated acute respiratory distress syndrome. N Engl J Med. 2014;370(23):2191–200.

105. Gandhi S, Mosleh W, Abdel-Qadir H, Farkouh ME. Statins and contrast-induced acute kidney injury with coronary angiography. Am J Med. 2014;127(10):987–1000.

106. Cheungpasitporn W, Thongprayoon C, Kittanamongkolchai W, Edmonds PJ, O'Corragain OA, Srivali N, et al. Periprocedural effects of statins on the incidence of contrast-induced acute kidney injury: a systematic review and meta-analysis of randomized controlled trials. Ren Fail. 2015;37(4):664–71.

107. Zarbock A, Schmidt C, Van Aken H, Wempe C, Martens S, Zahn PK, et al. Effect of remote ischemic preconditioning on kidney injury among high-risk patients undergoing cardiac surgery: a randomized clinical trial. JAMA. 2015;313(21):2133–41.

108. Hausenloy DJ, Candilio L, Evans R, Ariti C, Jenkins DP, Kolvekar S, et al. Remote Ischemic Preconditioning and Outcomes of Cardiac Surgery. N Engl J Med. 2015;373(15):1408–17.

109. Zhang L, Diao Y, Chen G, Tanaka A, Eastwood GM, Bellomo R. Remote ischemic conditioning for kidney protection: A meta-analysis. J Crit Care. 2016;

110. Walsh M, Whitlock R, Garg AX, Légaré J-F, Duncan AE, Zimmerman R, et al. Effects of remote ischemic preconditioning in high-risk patients undergoing cardiac surgery (Remote IMPACT): a randomized controlled trial. CMAJ. 2016;188(5):329–36.

111. Zhao B-C, Deng W-T, Li B-C, Deng Q-W, Xia Z-Q, Li Y-Y, et al. Remote ischemic preconditioning for preventing acute kidney injury following cardiovascular surgery: A meta-analysis with trial sequential analysis. Int J Cardiol. 2016;203:842–4.

112. Zuo B, Wang F, Song Z, Xu M, Wang G. Using remote ischemic conditioning to reduce acute kidney injury in patients undergoing percutaneous coronary intervention: a meta-analysis. Curr Med Res Opin. 2015;31(9):1677–85.

113. Er F, Nia AM, Dopp H, Hellmich M, Dahlem KM, Caglayan E, et al. Ischemic preconditioning for prevention of contrast medium-induced nephropathy: randomized pilot RenPro Trial (Renal Protection Trial). Circulation. 2012;126(3):296–303.

114. Zarbock A, Kellum JA, Schmidt C, Van Aken H, Wempe C, Pavenstädt H, et al. Effect of Early vs Delayed Initiation of Renal Replacement Therapy on Mortality in Critically Ill Patients With Acute Kidney Injury: The ELAIN Randomized Clinical Trial. JAMA. 2016;315(20):2190–9.

115. Gaudry S, Hajage D, Schortgen F, Martin-Lefevre L, Pons B, Boulet E, et al. Initiation Strategies for Renal-Replacement Therapy in the Intensive Care Unit. N Engl J Med. 2016;

116. Ronco C, McCullough P, Anker SD, Anand I, Aspromonte N, Bagshaw SM, et al. Cardio-renal syndromes: report from the consensus conference of the acute dialysis quality initiative. Eur Heart J. 2010;31(6):703–11.

117. Duran-Salgado MB, Rubio-Guerra AF. Diabetic nephropathy and inflammation. World J Diabetes. 2014;5(3):393–8.

118. Tsai W-C, Wu H-Y, Peng Y-S, Ko M-J, Wu M-S, Hung K-Y, et al. Risk Factors for Development and Progression of Chronic Kidney Disease: A Systematic Review and Exploratory Meta-Analysis. Medicine (Baltimore). 2016;95(11):e3013.

119. Gregg EW, Li Y, Wang J, Burrows NR, Ali MK, Rolka D, et al. Changes in diabetes-related complications in the United States, 1990-2010. N Engl J Med. 2014;370(16):1514–23.

120. Robinson SC, Bowmer CJ, Yates MS. Cardiac function in rats with acute renal failure. J Pharm Pharmacol. 1992;44(12):1007–14.

121. Kelly KJ. Distant effects of experimental renal ischemia/reperfusion injury. J Am Soc Nephrol. 2003;14(6):1549–58.

122. Sumida M, Doi K, Ogasawara E, Yamashita T, Hamasaki Y, Kariya T, et al. Regulation of Mitochondrial Dynamics by Dynamin-Related Protein-1 in Acute Cardiorenal Syndrome. J Am Soc Nephrol. 2015;26(10):2378-87

123. Clementi A, Virzì GM, Brocca A, de Cal M, Pastori S, Clementi M, et al. Advances in the pathogenesis of cardiorenal syndrome type 3. Oxid Med Cell Longev. 2015;2015:148082.

124. Vieillard-Baron A. Septic cardiomyopathy. Ann Intensive Care. 2011;1(1):6.

125. Muller-Werdan U, Buerke M, Ebelt H, Heinroth KM, Herklotz A, Loppnow H, et al. Septic cardiomyopathy - A not yet discovered cardiomyopathy? Exp Clin Cardiol. 2006;11(3):226–36.

126. Ludvigsson JF, Otterblad-Olausson P, Pettersson BU, Ekbom A. The Swedish personal identity number: possibilities and pitfalls in healthcare and medical research. Eur J Epidemiol. 2009;24(11):659–67.

127. Ludvigsson JF, Almqvist C, Bonamy A-KE, Ljung R, Michaëlsson K, Neovius M, et al. Registers of the Swedish total population and their use in medical research. Eur J Epidemiol. 2016;31(2):125–36.

128. Jernberg T, Attebring MF, Hambraeus K, Ivert T, James S, Jeppsson A, et al. The Swedish Web-system for enhancement and development of evidence-based care in heart disease evaluated according to recommended therapies (SWEDEHEART). Heart. 2010;96(20):1617–21.

129. Emilsson L, Lindahl B, Köster M, Lambe M, Ludvigsson JF. Review of 103 Swedish healthcare quality registries. J Intern Med. 2015;277(1):94–136.

130. Olsson C, Eriksson N, Ståhle E, Thelin S. The Swedish Heart Surgery Register: data quality for proximal thoracic aortic operations. Scand Cardiovasc J. 2006;40(6):348–53.

131. Patientregistret [Internet]. [cited 2016 Aug 23]. Available from: http://www.socialstyrelsen.se/register/halsodataregister/patientregistret

132. Ingelsson E, Arnlöv J, Sundström J, Lind L. The validity of a diagnosis of heart failure in a hospital discharge register. Eur J Heart Fail. 2005;7(5):787–91.

133. Ludvigsson JF, Andersson E, Ekbom A, Feychting M, Kim J-L, Reuterwall C, et al. External review and validation of the Swedish national inpatient register. BMC Public Health. 2011;11:450.

134. Linnersjö A, Hammar N, Gustavsson A, Reuterwall C. Recent time trends in acute myocardial infarction in Stockholm, Sweden. Int J Cardiol. 2000;76(1):17–21.

135. Dödsorsaksregistret [Internet]. [cited 2012 Feb 21]. Available from: http://www.socialstyrelsen.se/register/dodsorsaksregistret

136. Nationella Diabetesregistret [Internet]. [cited 2016 Aug 24]. Available from: https://www.ndr.nu/#/om-ndr

137. Gudbjörnsdottir S, Cederholm J, Nilsson PM, Eliasson B, Steering Committee of the Swedish National Diabetes Register. The National Diabetes Register in Sweden: an implementation of the St. Vincent Declaration for Quality Improvement in Diabetes Care. Diabetes Care. 2003;26(4):1270–6.

138. Nationella Diabetesregistret [Internet]. [cited 2016 Aug 24]. Available from: https://www.ndr.nu/#/arsrapport

139. Eeg-Olofsson K, Cederholm J, Nilsson PM, Zethelius B, Svensson A-M, Gudbjörnsdóttir S, et al. Glycemic control and cardiovascular disease in 7,454 patients with type 1 diabetes: an observational study from the Swedish National Diabetes Register (NDR). Diabetes Care. 2010;33(7):1640–6.

140. SNR | Om registret [Internet]. [cited 2016 Oct 6]. Available from: http://www.medscinet.net/snr/about.aspx?lang=1

141. Schön S, Ekberg H, Wikström B, Odén A, Ahlmén J. Renal replacement therapy in Sweden. Scand J Urol Nephrol. 2004;38(4):332–9.

142. Statistiska Centralbyrån. Longitudinal integration database for health insurance and labour market studies (LISA by Swedish acronym) [Internet]. [cited 2016 Aug 24]. Available from: http://www.scb.se/en_/Services/Guidance-for-researchers-and-universities/SCB-Data/Longitudinal-integration-database-for-health-insurance-and-labour-market-studies-LISA-by-Swedish-acronym/

143. Startpage [Internet]. Statistiska Centralbyrån. [cited 2016 Aug 24]. Available from: http://www.scb.se/en_/

144. Registret över totalbefolkningen (RTB) [Internet]. Statistiska Centralbyrån. [cited 2016 Aug 24]. Available from: http://www.scb.se/sv_/Vara-tjanster/Bestalla-mikrodata/Vilka-mikrodata-finns/Registret-over-totalbefolkningen-RTB/

145. Rydén L, Ahnve S, Bell M, Hammar N, Ivert T, Holzmann MJ. Acute kidney injury following coronary artery bypass grafting: early mortality and postoperative complications. Scand Cardiovasc J. 2012;46(2):114–20.

146. Fox CS, Muntner P, Chen AY, Alexander KP, Roe MT, Wiviott SD. Short-term outcomes of acute myocardial infarction in patients with acute kidney injury: a report from the national cardiovascular data registry. Circulation. 2012;125(3):497–504.

147. Cox DR. Regression Models and Life-Tables. J R Stat Soc. 1972;34(2):187–220.

148. Rothman KJ. Epidemiology: An Introduction. New York: Oxford University Press; 2002.

149. Kyriacou DN. The Enduring Evolution of the P Value. JAMA. 2016;315(11):1113–5.

150. Gallagher S, Jones DA, Lovell MJ, Hassan S, Wragg A, Kapur A, et al. The impact of acute kidney injury on midterm outcomes after coronary artery bypass graft surgery: a matched propensity score analysis. J Thorac Cardiovasc Surg. 2014;147(3):989–95.

151. Ahmed WA, Tully PJ, Baker RA, Knight JL. Survival after isolated coronary artery bypass grafting in patients with severe left ventricular dysfunction. Ann Thorac Surg. 2009;87(4):1106–12.

152. Mehta RH, Honeycutt E, Patel UD, Lopes RD, Shaw LK, Glower DD, et al. Impact of recovery of renal function on long-term mortality after coronary artery bypass grafting. Am J Cardiol. 2010;106(12):1728–34.

153. O'Connor ME, Kirwan CJ, Pearse RM, Prowle JR. Incidence and associations of acute kidney injury after major abdominal surgery. Intensive Care Med. 2016;42(4):521–30.

154. Nadkarni GN, Patel AA, Ahuja Y, Annapureddy N, Agarwal SK, Simoes PK, et al. Incidence, Risk Factors, and Outcome Trends of Acute Kidney Injury in Elective Total Hip and Knee Arthroplasty. Am J Orthop (Belle Mead NJ). 2016;45(1):E12–9.

155. Tolpin DA, Collard CD, Lee V-V, Virani SS, Allison PM, Elayda MA, et al. Subclinical changes in serum creatinine and mortality after coronary artery bypass grafting. J Thorac Cardiovasc Surg. 2012;143(3):682–8.e1.

156. Lassnigg A, Schmidlin D, Mouhieddine M, Bachmann LM, Druml W, Bauer P, et al. Minimal changes of serum creatinine predict prognosis in patients after cardiothoracic surgery: a prospective cohort study. J Am Soc Nephrol. 2004;15(6):1597–605.

157. Milani Júnior R, Jorge MT, de Campos FP, Martins FP, Bousso A, Cardoso JL, et al. Snake bites by the jararacuçu (Bothrops jararacussu): clinicopathological studies of 29 proven cases in São Paulo State, Brazil. QJM. 1997;90(5):323–34.

158. Holmdahl J, Blohmé I. Renal transplantation after Cortinarius speciosissimus poisoning. Nephrol Dial Transplant. 1995;10(10):1920–2.

159. Bosch X, Poch E, Grau JM. Rhabdomyolysis and acute kidney injury. N Engl J Med. 2009;361(1):62–72.

160. Rimes-Stigare C, Frumento P, Bottai M, Mårtensson J, Martling C-R, Walther SM, et al. Evolution of chronic renal impairment and long-term mortality after de novo acute kidney injury in the critically ill; a Swedish multi-centre cohort study. Crit Care. 2015;19:221.

161. Chawla LS, Amdur RL, Amodeo S, Kimmel PL, Palant CE. The severity of acute kidney injury predicts progression to chronic kidney disease. Kidney Int. 2011;79(12):1361–9.

162. Zolty R, Hynes PJ, Vittorio TJ. Severe left ventricular systolic dysfunction may reverse with renal transplantation: uremic cardiomyopathy and cardiorenal syndrome. Am J Transplant. 2008;8(11):2219–24.

163. Moody WE, Ferro CJ, Edwards NC, Chue CD, Lin ELS, Taylor RJ, et al. Cardiovascular Effects of Unilateral Nephrectomy in Living Kidney Donors. Hypertension. 2016;67(2):368–77.

164. Bagshaw SM, Lapinsky S, Dial S, Arabi Y, Dodek P, Wood G, et al. Acute kidney injury in septic shock: clinical outcomes and impact of duration of hypotension prior to initiation of antimicrobial therapy. Intensive Care Med. 2009;35(5):871–81.

165. Weisbord SD, Palevsky PM. Design of Clinical Trials in Acute Kidney Injury: Lessons from the Past and Future Directions. Semin Nephrol. 2016;36(1):42–52.

166. Ho KM, Morgan DJR. Meta-analysis of N-acetylcysteine to prevent acute renal failure after major surgery. Am J Kidney Dis. 2009;53(1):33–40.

167. Wang J, Gu C, Gao M, Yu W, Yu Y. Preoperative Statin Therapy and Renal Outcomes After Cardiac Surgery: A Meta-analysis and Meta-regression of 59,771 Patients. Can J Cardiol. 2015;31(8):1051–60.

168. Tie H-T, Luo M-Z, Luo M-J, Zhang M, Wu Q-C, Wan J-Y. Sodium bicarbonate in the prevention of cardiac surgery-associated acute kidney injury: a systematic review and meta-analysis. Crit Care. 2014;18(5):517.

169. Hawwa N, Shrestha K, Hammadah M, Yeo PSD, Fatica R, Tang WHW. Reverse Remodeling and Prognosis Following Kidney Transplantation in Contemporary Patients With Cardiac Dysfunction. J Am Coll Cardiol. 2015;66(16):1779–87.