Acute Kidney Injury Following Cardiac Surgery and Coronary Angiography

Incidence, Risk Factors and Outcome

Daði Helgason

Thesis for the degree of Philosophiae Doctor

Supervisor:
Tómas Guðbjartsson

Doctoral committee:
Ingibjörg Jóna Guðmundsdóttir

Martin Ingi Sigurðsson

Ólafur Skúli Indriðason

Runólfur Pálsson

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Bráður nýrnaskaði í kjölfar hjartaaðgerða og kransæðaþræðinga

Tíðni, áhættuþættir og afdrif

Daði Helgason

Ritgerð til doktorsgráðu

Umsjónarkennari og leiðbeinandi:

Tómas Guðbjartsson

Doktorsnefnd:

Ingibjörg Jóna Guðmundsdóttir

Martin Ingi Sigurðsson

Ólafur Skúli Indriðason

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Ágrip

Bráður nýrnaskaði (BNS) er vaxandi vandamál á heimsvísu og tengist hann aukinni sjúkdómsbyrði og dánartíðni. BNS er þekktur fylgikvilli eftir kransæðaþræðingar og opnar hjartaaðgerðir. Hann hefur verið tengdur við notkun skuggaefnis eftir þræðingar en undanfarið hefur verið deilt um mikilvægi þess í meinmyndun BNS. Áhættuþættir BNS eftir opnar hjartaaðgerðir geta verið bæði sjúklinga- og aðgerðartengdir en tími á hjarta- og lungnavél gegnir þar stóru hlutverki. BNS tengist verri lifun sjúklinga til skemmri tíma en skortur er á rannsóknum á langtíma afdrifum þessara sjúklinga, sérstaklega með tilliti til langtíma nýrnastarfsemi.

Markmið þessarar doktorsritgerðar var að kanna tíðni og áhættuþætti BNS eftir kransæðaþræðingar og þrjár mismunandi opnar hjartaaðgerðir: kransæðahjáveitu, ósæðarlokuskipti og viðgerð á ósæðarflysjun af gerð A. Jafnframt voru áhrif BNS á afdrif sjúklinga metin, sérstaklega með tilliti til langtíma lifunar og þróunar á langvinnum nýrnasjúkdómi (LNS).

Rannsóknirnar voru afturskyggnar þar sem rannsóknir I-III náðu til allra sjúklinga sem gengust undir kransæðaþræðingu eða hjartaaðgerðir á Íslandi en rannsókn IV var gerð á sjúklingum sem fóru í viðgerð á ósæðarflysjun af gerð A á átta háskólasjúkrahúsum í Danmörku, Finnlandi, Svíþjóð og á Íslandi. Gögnum var safnað úr miðlægum gagnasöfnum og sjúkraskrám sjúklinga. Skráðar voru ítarlegar upplýsingar um sjúklingatengda og aðgerðartengda þætti og afdrif sjúklinga eftir aðgerð. BNS var skilgreindur samkvæmt KDIGO skilmerkjum í rannsókn I og II en út frá RIFLE skilmerkjum í rannsókn III og IV. Forspárþættir BNS voru fundnir með fjölþátta aðhvarfsgreiningu. Afdrif sjúklinga með og án BNS voru borin saman og voru Cox líkön og propensity score pörun notuð til að meta tengsl BNS við langtíma lifun og þróun á LNS.

Tíðni BNS var frá 2% eftir kransæðaþræðingu upp í 41% í kjölfar aðgerðar á ósæðarflysjun. Aldur, þekktur nýrnasjúkdómur fyrir aðgerð, offita og blóðþurrð voru á meðal sjúklingatengdra áhættuþátta BNS. Skuggefnismagn tengdist aðallega aukinni hættu á BNS hjá sjúklingum með gaukulsíunarhraða < 45 mL/mín./1,73 m^2 fyrir þræðingu sem fengu > 150 mL af skuggaefni. Tími á hjarta- og lungnavél og gjöf rauðkornaþykknis voru áhættuþættir BNS eftir opnu hjartaaðgerðirnar.

Í öllum fjórum rannsóknunum höfðu sjúklingar sem fengu BNS verri langtímalifun en þeir sem ekki fengu BNS og var hann sjálfstæður forspárþáttur lifunar í kjölfar kransæðaþræðinga og aðgerða við ósæðarflysjun af gerð A. Eftir kransæðahjáveitu virtust tengsl BNS við lifun tengjast að verulegu leyti öðrum alvarlegum fylgikvillum. BNS var jafnframt sjálfstæður forspárþáttur fyrir því að sjúklingar þróuðu með sér LNS eftir kransæðaþræðingu og kransæðahjáveituaðgerð.

Rannsóknirnar staðfesta að BNS er alvarlegur fylgikvilli eftir bæði kransæðaþræðingar og opnar hjartaaðgerðir. Hugsanlega mætti hafa áhrif á suma þeirra áhættuþátta BNS sem fundnir voru og þannig draga úr líkum á BNS. BNS tengist ekki eingöngu síðri skammtímalifun sjúklinga heldur einnig langtíma lifun og jafnframt auknum líkum á að sjúklingar þrói með sér LNS.

Lykilorð:

Bráður nýrnaskaði, kransæðaþræðingar, opnar hjartaaðgerðir, áhættuþættir, langvinnur nýrnasjúkdómur, lifun.

Abstract

Acute kidney injury (AKI) is a growing problem worldwide and is associated with high morbidity and mortality. AKI is a known complication following cardiac operations and coronary angiography (CA). Following CA, AKI has been associated with contrast exposure but recently its importance in the development of AKI has been debated. Following open heart surgery, both patient-related and operative risk factors have been identified, where cardiopulmonary bypass (CPB) plays an important role. AKI has been associated with worse short-term survival. The association between AKI following cardiac procedures and patients´ long-term outcome has not been described as well, since many studies have lacked information on long-term follow-up, especially regarding long-term renal function and development of chronic kidney disease (CKD).

The aim of the work described in this thesis was to estimate the incidence and risk factors of AKI following CA and three different cardiac operations: coronary artery bypass grafting (CABG), surgical aortic valve replacement (SAVR) and repair of acute type A aortic dissection (ATAAD). Furthermore, the association between AKI and outcome of patients was evaluated, focusing especially on long-term survival and development or progression of CKD.

All the studies were retrospective; studies I–III included all the patients who underwent cardiac catheterisation or open heart procedures in Iceland, but study IV included patients who were operated with ATAAD repair at eight academic hospitals in Denmark, Finland, Sweden and Iceland. Data were gathered from national databases, medical record systems and hospital databases. Detailed information on patient characteristics together with intra- and post-procedural factors were registered. AKI was defined according to the KDIGO criteria in studies I and II and the RIFLE criteria in studies III and IV. Predictors of AKI were identified by using multivariable logistic regression models. Outcome of patients with and without AKI was compared and Cox models and propensity score matching were used to estimate the association between AKI and both long-term survival and kidney function.

The incidence of AKI ranged from 2% following CA to 41% after ATAAD repair. Among the patient-related risk factors for AKI were advanced age,

obesity, malperfusion and pre-procedural CKD. Contrast dose was mostly associated with AKI in patients who had eGFFR < 45 mL/min/1.73m^2 who received more than 150 mL of intra-arterial contrast. CPB was associated with AKI following the open cardiac surgeries, and also with number of transfusions of red blood cells administered perioperatively. Following the procedures, AKI was associated with inferior short-term and long-term survival and was an independent predictor of long-term survival following CA and ATAAD repair. The association between AKI following CABG and mortality appeared to be partially explained by its association with other major complications. Following CA and CABG, AKI was found to be a predictor of development of CKD.

The four studies highlight the fact that AKI is a severe complication following different cardiac procedures, and where the incidence is dependent on the complexity of the procedure and the severity of the underlying condition. Some of the identified risk factors of AKI could possibly be modified and may be useful in reducing the likelihood of AKI in high-risk patients. Furthermore, the studies have shown that AKI is not only associated with worse short-term patient outcome but also inferior long-term surival and increased risk of developing CKD.

Keywords:

Acute kidney injury, coronary angiography, cardiac surgery, risk factors, chronic kidney disease, survival.

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Contents

List of abbreviations

ACS	acute coronary syndrome
AD	aortic dissection
ADQI	Acute Dialysis Quality Initiative
AKD	acute kidney disease
AKI	acute kidney injury
AKIN	Acute Kidney Injury Network
ARDS	acute respiratory distress syndrome
AS	aortic stenosis
ATAAD	acute type A aortic dissection
ATN	acute tubular necrosis
BMI	body mass index
CA	coronary angiography
CABG	coronary artery bypass grafting
CAD	coronary artery disease
CCS	Canadian Cardiac Society
CI	confidence interval
CI-AKI	contrast-induced acute kidney injury
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CPB	cardiopulmonary bypass
CRS	cardio-renal syndrome
CT	computed tomography
eGFR	estimated glomerular filtration rate
EACTA	European Association of Cardiothoracic Anaesthesiology
EACTS	European Association of Cardiothoracic Surgery
ESKD	end-stage kidney disease
ESRD	end-stage renal disease
EuroSCORE	European System for Cardiac Operative Risk Evaluation
GERAADA	German Registry for Acute Aortic Dissection Type A
GFR	glomerular filtration rate
HR	hazard ratio
IABP	intra-aortic balloon pump

ICD-10	International Classification of Diseases, 10th revision
ICU	intensive care unit
IHD	ischaemic heart disease
IRAD	International Registry of Acute Aortic Dissection
KDIGO	Kidney Disease: Improving Global Outcome
KIM-1	kidney injury molecule 1
LAD	left anterior descending
LIMA	left internal mammary artery
LVEF	left ventricular ejection fraction
MDRD	Modification in Diet and Renal Disease
MI	myocardial infarction
MOF	multiple organ failure
NAG	N-acetyl-β-glucosaminidase
NGAL	neutrophil gelatinase-associated lipocalin
NSTEMI	non-ST-elevation myocardial infarction
NYHA	New York Heart Association
OPCAB	off-pump coronary artery bypass
OR	odds ratio
PCI	percutaneous coronary intervention
PSM	propensity score matching
RAS	renin-angiotensin system
RBC	red blood cell
RIFLE	Risk, Injury, Failure, Loss of kidney function and End-stage kidney disease
RIMA	right internal mammary artery
RRT	renal replacement therapy
SAVR	surgical aortic valve replacement
SCAAR	Swedish Coronary Angiography and Angioplasty Registry
SCr	serum creatinine
STEMI	ST-elevation myocardial infarction
TAVI	transcatheter aortic valve implantation

List of figures

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List of original papers

This thesis is based on the following original publications, which are referred to in the text by their Roman numerals (I–IV):

I. Acute kidney injury following coronary angiography: a nationwide study of incidence, risk factors and long-term outcomes. Helgason D, Long TE, Helgadottir S, Palsson R, Sigurdsson GH, Gudbjartsson T, Indridason OS, Gudmundsdottir IJ, Sigurdsson MI. J Nephrol. 2018 Oct;31(5):721-730. doi: 10.1007/s40620-018-0534-y. Epub 2018 Sep 5.

II. Renal recovery and long-term survival following acute kidney injury after coronary artery surgery: a nationwide study. Helgadottir S, Sigurdsson MI, Palsson R, Helgason D, Sigurdsson GH, Gudbjartsson T. Acta Anaesthesiol Scand. 2016 Oct;60(9):1230-40. doi: 10.1111/aas.12758.

III. Acute kidney injury and outcome following aortic valve replacement for aortic stenosis. Helgason D, Helgadottir S, Viktorsson SA, Orrason AW, Ingvarsdottir IL, Geirsson A, Gudbjartsson T. Interact Cardiovasc Thorac Surg. 2016 Aug;23(2):266-72. doi: 10.1093/icvts/ivw117.

IV. Acute Kidney Injury Following Acute Repair of Type A Aortic Dissection. Helgason D, Helgadottir S, Ahlsson A, Gunn J, Hjortdal V, Hansson EC, Jeppsson A, Mennander A, Nozoharoor S, Zindovic I, Ohlsson C, Ragnarsson SO, Sigurdsson MI, Geirsson A, Gudbjartsson T. Manuscript.

In addition, some unpublished data have been presented.

All papers have been reprinted by kind permission of the publishers.

Declaration of contribution

For paper I, the doctoral student, Dadi Helgason, planned the research work with his co-authors, assisted with building of the dataset, performed the statistical analysis and drafted the full manuscript, which was revised by the co-authors.

For paper II, he participated in planning the research work, registering data in the dataset and revising the manuscript. Furthermore, he performed additional post-publication statistical analysis of the dataset for this thesis.

For paper III, he planned the research work with his supervisor, had a leading role in registering data in the dataset, performed all the statistical analysis and drafted the full manuscript, which was revised by the co-authors.

For study IV, the doctoral student planned the research work with his co-authors, performed the statistical analysis and drafted the whole manuscript, which was revised by the co-authors.

The doctoral student wrote this thesis under the guidance of his supervisor and the doctoral committee.

1 Introduction

Acute kidney injury (AKI) is defined as an abrupt deterioration of kidney function (Kidney Disease Improving Global Outcomes: (KDIGO) Acute Kidney Injury Work Group, 2012). It is a common problem in the hospital setting, for example following surgeries and procedures, and has been associated with adverse outcomes (Wang et al., 2012). Despite increased awareness, the incidence of AKI is rising globally and the mortality of patients who develop AKI remains high (Lameire et al., 2013). This thesis describes research on AKI following different cardiac procedures, coronary angiography (CA) and percutaneous coronary intervention (PCI), and also three types of open cardiac surgery (coronary artery bypass grafting [CABG], surgical aortic valve replacement [SAVR] and repair for acute type A aortic dissection [ATAAD]), with emphasis on incidence, risk factors, comorbidity and association with short-term and long-term outcome.

1.1 Kidney function and kidney disease

The kidneys have an important role in the excretion of waste products; in maintaining fluid balance, electrolyte and acid-base equilibrium; and in the production of hormones (Hall & Guyton, 2011). Blood flow to the two kidneys is normally about 20–25% of the cardiac output (1,100 mL/min) and each kidney contains approximately 1 million nephrons. Each nephron is composed of the glomerulus, through which large amounts of fluid are filtered from the blood, and a long tubule in which the filtered fluid is converted into urine before being delivered to the pelvis of the kidney (Hoenig & Zeidel, 2014). The net glomerular filtration is determined by the permeability of the glomerular capillary wall and the balance between hydrostatic pressure in the glomerular capillaries and the Bowman's capsule on the one hand and colloid osmotic pressure gradients on the other (Rennke & Dennker, 2014). The change in the glomerular capillary hydrostatic pressure is the primary influence of changes in glomerular filtration rate (GFR), which is determined by the arterial pressure and the afferent and efferent arteriolar resistance. However, due to autoregulation, the GFR remains almost constant over a wide range of renal arterial pressures (Hall & Guyton, 2011). The autoregulation involves changes in precapillary resistance, as in other capillary beds in the body, but also more complex mechanisms including the tubuloglomerular feedback and activation of the renin-angiotensin system (RAS) (Rennke & Dennker, 2014).

GFR is the best marker of renal function and is used in clinical practice. GFR can be measured by administration of exogenous compounds, e.g. inulin, that are able to achieve a stable plasma concentration, are freely filtered by the glomerulus and are not reabsorbed or secreted by the kidney (Hsu & Bansal, 2011). However, such measurements are both cumbersome and expensive, and are therefore not routinely used in daily practice. Thus, surrogate measurements have been used, for example creatinine, which is a waste product derived from the metabolism of creatine in skeletal muscles (Hall & Guyton, 2011). It has a relatively stable plasma concentration since it is filtered, but not reabsorbed, synthesized, or metabolised in the kidney and has been used as a measure of glomerular filtration(Rennke & Dennker, 2014). However, the concentration of serum creatinine (SCr) is determined by its generation and excretion, and although relatively stable in each individual, the generation is affected by age, sex, muscle mass and race—and tubular secretion accounts for up to 20% of its excretion (Hall & Guyton, 2011). In an attempt to adjust for these factors, GFR is most often evaluated by calculating creatinine clearance using the Cockroft-Gault formula (Cockcroft & Gault, 1976) or estimated glomerular filtration rate (eGFR) using either the Modification in Diet and Renal Disease (MDRD) equation (Levey et al., 1999) or the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation (Levey et al., 2009) where age, sex, weight and race are used to account for variability in creatinine generation.

1.1.1 Acute kidney injury (AKI)

AKI is characterised by a sudden deterioration in kidney function and often occurs in the hospital setting with a reported incidence ranging between 2% and 23% in different studies (Wang et al., 2012). In a meta-analysis of 312 studies worldwide, the pooled incidence of AKI was found to be 10.7% with a wide range depending on the clinical setting of the study and the definitions that were used (Susantitaphong et al., 2013). Sometimes AKI is divided into community-acquired AKI and hospital-acquired AKI; for example, in a study by Wonnacott et al., the overall incidence was 6.4% in hospitalised patients. Two-thirds of the patients had AKI on admission while one-third developed AKI during their hospital stay (Wonnacott et al., 2014). The causes of AKI can differ between countries and areas; in high-income countries, AKI is often associated with multimorbidity and polypharmacy in elderly patients in the hospital setting. In low-income countries, the disorder is predominantly community-acquired, affecting young and previously healthy people, and is associated with conditions such as diarrhea, HIV infection and tropical

infectious diseases (Lameire et al., 2013). Although the awareness and understanding of the pathogenesis of AKI and its adverse consequences have increased in recent years (Hoste et al., 2018), the incidence has been rising worldwide, in both high- and low-income countries (Lameire et al., 2013).

1.1.1.1 Pathophysiology

The causes of AKI are generally classified as prerenal, renal and postrenal (Ostermann & Joannidis, 2016). The AKI is most often caused by a generalised or localised reduction in renal blood flow, resulting from extracellular fluid volume depletion—for example, due to haemorrhage, or decreased effective circulating volume in conditions such as cirrhosis or congestive heart failure (CHF) (Bonventre & Yang, 2011) (**Figure 1**).

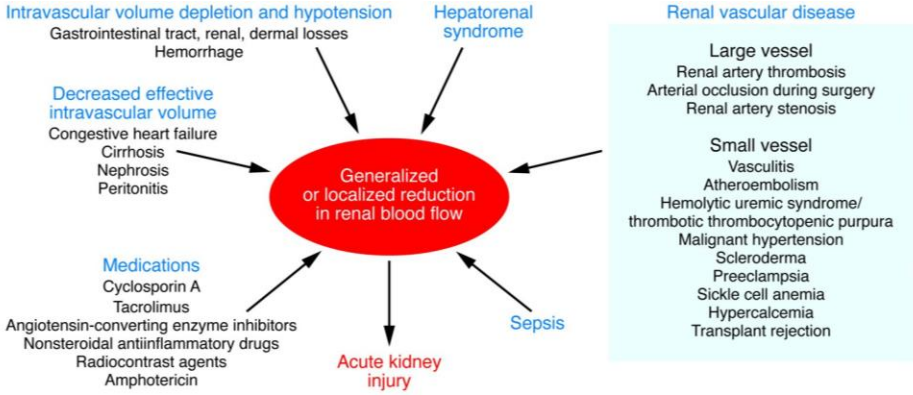

Figure 1. List of possible causes of a reduction in generalised or regional renal blood flow.
Reproduced with permission of American Society for Clinical Investigation, from (Bonventre & Yang, 2011).

These conditions can cause prerenal azotemia, characterised by decreased GFR without significant damage to the renal tissue, which is a common cause of community-acquired AKI (Wang et al., 2017). If severe and/or prolonged, the impairment in renal blood flow can also lead to a mismatch of oxygen supply and demand, causing acute renal tubular cell injury and death, a condition known as acute tubular necrosis (ATN) (Bonventre & Yang, 2011). However, a reduction in renal blood flow alone does not account for the entire reduction in GFR during AKI. The regional changes in blood flow are more important, where the flow to the outer medulla of the kidney is reduced disproportionately (Mason et al., 1984). In

sepsis—a common cause of AKI—patients can develop acute tubular injury, due to microvascular dysfunction among other factors, in the absence of overall renal hypoperfusion (Zarbock et al., 2014). ATN, which is the most common cause of hospital-acquired AKI, can cause severe kidney injury requiring renal replacement therapy (RRT) (Liano & Pascual, 1996). Following ATN, the tubular epithelium can be replenished and the patient can recover from the injury if the underlying condition is managed successfully. However, the repair process following ATN is often maladaptive and can result in kidney fibrosis (**Figure 2**) (Venkatachalam et al., 2010).

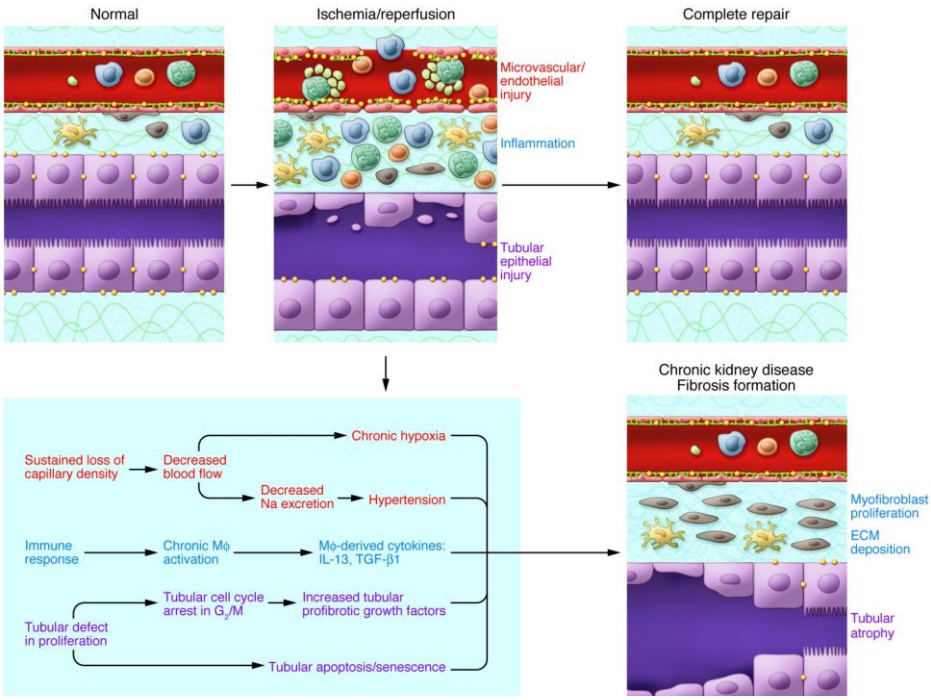

Figure 2. The repair process following ischaemic acute kidney injury.

The repair process following ischaemic acute kidney injury can be incomplete and result in fibrotic lesions, which may lead to a progressive decline in renal function. Chronic loss of peritubular microvessels can lead to long-term hypoxia and hypertension. In addition, persistent production of profibrotic cytokines including IL-13, arginase and TGF-β1 from the chronically activated macrophages (MΦ) contributes to the fibrosis. Renal tubular epithelial cells also have a critical role in the fibrosis formation with changes in their proliferation processes, including cell-cycle arrest in the G_2/M phase, which results in a secretory phenotype that enables the production of profibrotic growth factors by the epithelial cells. Together, these factors stimulate fibrogenesis and progression to chronic kidney disease is accelerated.
Reproduced with permission of American Society for Clinical Investigation, from (Bonventre & Yang, 2011).

Renal forms of AKI also include drug-induced nephrotoxicity, which accounts for 14–26% of AKI cases, and is more common in hospitalised patients (Perazella, 2018). Antimicrobial agents, chemotherapeutic drugs, analgesics and immunosuppressive agents are some of the most common nephrotoxic agents (Perazella, 2018). In addition, diseases affecting the glomeruli or the tubulointerstitial compartment can cause a rapid decline in kidney function consistent with AKI, and are termed rapidly progressive glomerulonephritis and acute interstitial nephritis, respectively (Arimura et al., 2016; Raghavan & Eknoyan, 2014). Finally, postrenal AKI is caused by obstruction of urine flow in the collecting system, for example due to kidney stones or tumours causing postrenal kidney injury (Hegarty et al., 2001; Nash et al., 2002).

1.1.1.2 Definition and staging of AKI

Over the years, different definitions and terms have been used to describe AKI, ranging from a mild elevation in SCr to requirement for RRT, hampering comparison of studies on the epidemiology of the disorder (Mehta & Chertow, 2003). In the following section, the three main classification systems, which are listed in **Table 1**, will be described.

1.1.1.2.1 The RIFLE criteria

In an attempt to address the aforementioned problem of the variability in definitions, in 2004 the Acute Dialysis Quality Initiative (ADQI) group put forward a classification system for diagnosis and staging of AKI (formerly known as acute renal failure) called the RIFLE criteria (Bellomo et al., 2004). The diagnostic criteria consist of an SCr component, where AKI is defined as an increase in baseline SCr by at least 50%, a reduction in eGFR by at least 25% or an elevation in SCr to > 356.3 µmol/L (4 mg/dL) with an acute rise of at least 44 µmol/L (0.5 mg/dL), and a urinary output component, defined as urine flow of < 0.5 mL/kg/hour for more than 6 hours. The RIFLE criteria categorise AKI into three classes, with increasing severity of kidney injury: **R**isk, **I**njury and **F**ailure, based on the degree of increase in SCr over seven days. RIFLE also defines two outcome classes: **L**oss and **E**nd-stage kidney disease. The urinary output component has frequently been lacking in published reports, but large series of studies from all over the world have shown that AKI defined by the SCr component of the RIFLE criteria is associated with an increased risk of death (Ostermann & Chang, 2007; Uchino et al., 2006).

1.1.1.2.2 The AKIN criteria

In 2007, the Acute Kidney Injury Network (AKIN) proposed a modified version of the RIFLE AKI criteria (Mehta et al., 2007). The time frame was reduced from seven days to 48 hours and the AKI was defined as an absolute increase in SCr of more than 26.5 µmol/L (0.3 mg/dL), or as an increase in SCr of more than 50% or a reduction in urine output to less than 0.5 mL/kg/hour for more than 6 hours. The group of experts concluded that the diagnostic criteria should only be used after an optimal state of volume replacement has been achieved and the urine output criteria should only be applied when urinary tract obstruction has been excluded. The AKIN classes were called stage 1, 2 and 3 AKI instead of Risk, Injury and Failure, and AKI requiring RRT was classified as a stage 3 AKI, whereas the RIFLE outcome classes were removed.

1.1.1.2.3 The KDIGO criteria

In 2012, the Kidney Disease: Improving Global Outcome (KDIGO) work group proposed a new definition of AKI, combining the RIFLE and AKIN criteria. According to the KDIGO criteria, AKI is defined either as an increase in SCr of > 26.5mmol/L within 48 hours, a > 50% elevation in SCr within seven days, or a reduction in urine output to less than 0.5 mL/kg/hour for more than six hours (Kidney Disease Improving Global Outcomes: (KDIGO) Acute Kidney Injury Work Group, 2012). The KDIGO criteria have since been validated and have been shown to be comparable with the RIFLE criteria in predicting hospital mortality (Fujii et al., 2014).

Table 1. Comparison of the RIFLE (Bellomo et al., 2004), AKIN (Mehta et al., 2007) and KDIGO criteria (2012).

RIFLE		AKIN		KDIGO		All
Stage	SCr criteria	Stage	SCr criteria[a]	Stage	SCr criteria	Urine output criteria
Risk	↑SCr ≥ 1.5 × baseline or ↓eGFR > 25% from baseline	1	↑SCr ≥ 1.5–2 × baseline or ↑SCr ≥ 26.5 µmol/L	1	↑SCr ≥ 1.5–2 × baseline or ↑SCr ≥ 26.5 µmol/L[a]	< 0.5/mL/kg/h for > 6 h
Injury	↑SCr ≥ 2.0 × baseline or ↓eGFR > 50% from baseline	2	↑SCr > 2–3 × baseline	2	↑SCr > 2–3 × baseline	< 0.5/mL/kg/h for > 12 h
Failure	↑SCr > 3 × baseline or baseline > 354 µmol/L with an acute increase of ≥ 44 µmol/L or ↓eGFR > 75% from baseline	3	↑SCr > 3 × baseline or baseline > 354 µmol/L with an acute increase of ≥ 44 µmol/L or initiation of RRT	3	↑SCr > 3 × baseline or baseline > 354 µmol/L with an acute increase of ≥ 26.5 µmol/L or initiation of RRT	< 0.3/mL/kg/h for > 24 h or anuria for > 12 h
Loss	Complete loss of kidney function for > 4 weeks					
ESKD	End-stage kidney disease (> 3 months)					

AKIN, Acute Kidney Injury Network; eGFR, estimated glomerular filtraion rate; ESKD, end-stage kidney disease; KDIGO, Kidney Disease: Improving Global Outcome; RIFLE, Risk, Injury, Failure, Loss of kidney function and End-stage kidney disease; RRT, renal replacement therapy; SCr, serum creatinine.
[a]Within 48 h.

1.1.1.2.4 Limitations of the AKI classification systems

The AKI criteria are a step forward in the coordination of the definitions and staging of AKI. However, the criteria have several limitations, especially in the clinical setting. Firstly, they do not distinguish different aetiologies of AKI. Secondly, it can be difficult to determine the baseline kidney function as a recent SCr value is often missing when an acutely ill patient is being evaluated. The baseline SCr value used to define AKI has been the subject of discussion in recent years (Gaiao & Cruz, 2010), as the ideal baseline value would reflect the kidney function immediately before the development of AKI. A baseline SCr value that is too close to the AKI could lead to underestimation of the severity of AKI, since the deterioration of kidney function may already have begun. On the other hand, if older SCr values are used as surrogates for the baseline kidney function, overestimation of the incidence and severity of AKI could result. However, pre-existing SCr values are not always available. In such cases, the ADQI recommends using an estimation of baseline SCr derived from the MDRD equation, assuming an eGFR of 75 mL/min/1.73 m^2. This approach has been found to be inaccurate, as demonstrated by a study by Bagshaw et al.—which concluded that by estimating the baseline SCr, 19% of the AKI cases were misclassified (Bagshaw et al., 2009). Thus, the AKIN group suggested using the admission SCr as the baseline value for hospital-acquired AKI, because this approach is believed to better reflect the true baseline kidney function, for example in patients undergoing elective surgery or cardiac catheterisation (Gaiao & Cruz, 2010). However, diagnosis of community-acquired AKI is more difficult than that of hospital-acquired AKI. The urine output criteria, which are included in all three AKI classification systems described above, are of limited use in retrospective studies on the epidemiology of AKI as this information is often lacking.

It should be noted that when AKI occurs, the SCr and eGFR values poorly reflect the GFR at the time of assessment because there is a lag between the fall in GFR and the elevation in SCr (Waikar & Bonventre, 2009), which is why eGFR is not used during an AKI episode. In addition, the SCr levels in critically ill patients can also be affected by fluctuations in creatinine production, and alterations in total body water and the distribution volume of creatinine (Macedo et al., 2010).

Due to the limitations of SCr as a measure of the GFR in AKI, novel biomarkers for kidney function have been studied in recent years. Cystatin C is a cysteine protease inhibitor protein that is released by all cells at a

constant rate. Several studies have shown that cystatin C is a good marker of kidney function and even superior to SCr (Zhou et al., 2006). However, cystatin C is a marker of GFR and increases when renal damage with reduced GFR has occurred. Markers of injury that can be used to detect AKI earlier in the process have been studied, including neutrophil gelatinase-associated lipocalin (NGAL), N-acetyl-β-glucosaminidase (NAG) and kidney injury molecule 1 (KIM-1) with promising results (Teo & Endre, 2017; Vaidya et al., 2008).

1.1.2 Chronic kidney disease and end-stage renal disease

Chronic kidney disease (CKD) is defined as the presence of kidney damage or reduced kidney function for three or more months, and is classified into six stages according to eGFR (**Table 2**) (Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group, 2013).

CKD is a common disorder with a mean global prevalence of approximately 13%, and mainly affects the elderly (Hill et al., 2016). The global prevalence of CKD is rising, with the fastest growth in developing and low- and middle-income countries (George et al., 2017). It is associated with increased risk of hospitalisation, reduced quality of life, cardiovascular morbidity, progression to end-stage renal disease (ESRD, defined as kidney failure requiring maintenance dialysis or kidney transplantation for survival (Liyanage et al., 2015)) and premature mortality (Hill et al., 2016). Among the most common causes of CKD globally are diabetes, hypertension and glomerulonephritis but in many cases the aetiology is unknown (Levin et al., 2017).

Table 2. Definition and staging of chronic kidney disease (Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group, 2013).

Stage	GFR (mL/min/1.73 m^2)	Description
1	≥ 90	Normal or high[a]
2	60–89	Mildly decreased[a]
3A	45–59	Mildly to moderately decreased
3B	30–44	Moderately to severely decreased
4	15–29	Severely decreased
5	< 15	Kidney failure

[a]In the absence of evidence of kidney damage, neither GFR stage 1 nor 2 fulfil the criteria for chronic kidney disease.
GFR, glomerular filtration rate.

1.1.3 Renal recovery following AKI and the development of chronic kidney disease

It is now recognised that AKI and CKD are not always discrete entities, as patients who have had an episode of AKI have an increased risk of developing either new-onset CKD or progression of pre-existing CKD. Furthermore, patients with CKD are more likely to develop AKI (Chawla et al., 2014). The risk of AKI resulting in CKD is dependent on whether or not the patient recovers his/her kidney function after the AKI episode (Forni et al., 2017).

The definition of renal recovery has been the subject of several recent studies. Even so, there is no widely accepted definition of renal recovery (Chawla et al., 2017). Thus, different definitions have been used, ranging from freedom from dialysis (Bagshaw et al., 2005) to absolute cut-off values of SCr or eGFR (Macedo et al., 2012; Pannu et al., 2013), or relative changes in SCr or eGFR. (Macedo et al., 2008; Pannu et al., 2013). In a recent study by Long et al., several different definitions of renal recovery in patients who developed AKI following surgery were studied. The risk of development or progression of CKD was increased if SCr did not decrease to < 1.25 × baseline SCr × baseline range within 30 days. Furthermore, the risk of inferior long-term survival was increased if patients did not achieve a reduction in SCr of < 1.5 × baseline SCr within 30 days (Long et al., 2019).

The three-month period from the AKI episode to the possible development of CKD has been identified as a critical period of vulnerability of the kidneys, and the term acute kidney disease (AKD) has been proposed. In 2017, a consensus report was published in an attempt to increase awareness and to highlight the importance of thorough follow-up of patients during this period (Chawla et al., 2017). The report defined persistent AKI as an episode lasting more than 48 hours, and the conclusion was that early identification of persistent AKI is important in order to initiate an extended evaluation and management to avoid further kidney damage and associated mortality. It was also concluded that the care of AKI patients after hospital discharge is often inadequate and that further investigations are needed, for example to identify modifiable risk factors for persistent kidney injury and adverse outcome.

1.2 Heart disease

1.2.1 Coronary artery disease

Coronary artery disease (CAD) is the leading cause of mortality and morbidity in Europe and accounts for 19–20% of all deaths (Wilkins E, 2017). Over the past 30 years, the mortality rates from cardiovascular diseases have been declining in Europe, including Iceland, mainly due to a decreased prevalence of risk factors for CAD such as hypercholesterolemia, hypertension and smoking (Aspelund et al., 2010). At the same time, the prevalence of other risk factors such as obesity and diabetes has been steadily increasing, attenuating the decline in premature deaths—a development which could possibly lead to increased cardiovascular mortality in the future (Andersen et al., 2017). The main cause of CAD is atherosclerosis, which can theoretically affect any artery in the body but is mainly located in the coronary, cerebral and lower extremity arteries (Glagov et al., 1988). This is a progressive inflammatory disorder that involves the accumulation of lipids, activation of inflammatory cells and migration of smooth muscle cells from the media to the intima of the arterial wall. This complex process can lead to plaque formation and cause stenoses in the coronary arteries (Libby & Theroux, 2005) (**Figure 3**). CAD can remain stable and slowly progressive (stable ischaemic heart disease [IHD]) or it can present abruptly as in acute coronary syndrome (ACS), consisting of ST-elevation myocardial infarction (STEMI), non-ST-elevation myocardial infarction (NSTEMI) and unstable angina. The clinical presentation, diagnosis and treatment differ between stable IHD and ACS. In both categories, patients' symptoms and clinical signs can be suggestive of the diagnosis. In ACS, ischaemic changes can be seen on an electrocardiogram and elevation of plasma biomarkers such as troponin T and creatine kinase MB (CK-MB) observed. When ACS is suspected, a CA, which accurately diagnoses and maps the extent of CAD, is recommended (Neumann et al., 2019). CA is also useful in symptomatic patients where stable IHD is suspected, which is sometimes preceded by noninvasive testing such as stress test or computed tomography (CT) angiography of the coronary arteries (Members et al., 2013). The treatment of CAD is multi-factorial and consists of pharmacological therapy, including antianginal agents such as nitroglycerine and beta blockers, and also drugs that prevent further progression of the disease, e.g. statins and antiplatelet drugs (Montalescot et al., 2013). When significant stenoses of coronary arteries are identified, especially in patients with ACS, PCI can often be successfully applied. In complex CAD, CABG is sometimes indicated (Neumann et al., 2019).

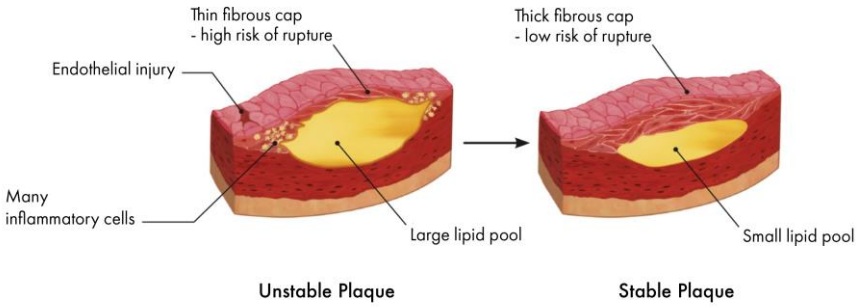

Figure 3. Atherosclerosis. Comparison of stable and unstable coronary artery plaques.
Design: Hjördís Bjartmars.

1.2.1.1 Coronary angiography and percutaneous coronary intervention

The first CA was performed in 1958 and the first PCI in 1977 (Meier et al., 2003). Ten years after that, the first PCI was performed at Landspitali (the National University Hospital of Iceland) and today, around 1,600–1,900 coronary angiographies and 700–800 PCIs are performed there annually (Helgason et al., 2018). The procedure involves insertion of a catheter through a sheath in either the radial or the femoral artery, which is placed in the ostium of the coronary arteries. Contrast medium is then injected through the catheter and the coronary arteries are visualised using fluoroscopy. This gives a detailed picture of the lumen of the coronary arteries. A significant stenosis can most often be treated with PCI. However, it can be difficult to assess whether a stenosis is functionally significant, causing limitation of blood flow with angiography alone. To evaluate the stenosis further, the flow can be estimated by measuring the pressure gradient across it (Gotberg et al., 2017). In PCI, a wire is guided through the stenotic area, which is subsequently dilated. In the first years of PCI, stenoses were solely dilated with a balloon, but later, metal stents emerged, which improved the outcome of PCI significantly and reduced the rate of restenosis (Serruys et al., 1994) (**Figure 4**). Even so, the vascular injury caused by stent implantation could lead to in-stent restenosis requiring repeated revascularisation within a year in up to 20% of patients (McDonald et al., 2015). When the drug-eluting stents emerged in the early 1990s, the risk of restenosis was reduced

further—by approximately 80% (Holmes et al., 2004)—through inhibition of smooth muscle proliferation and neointimal hyperplasia (Leon & Bakhai, 2003).

PCI is the cornerstone of treatment for patients with STEMI where the aim is to treat the occluded vessel within 90 minutes from first medical contact (Ibanez et al., 2017). In NSTEMI, CA is usually performed within 2–72 hours of presentation, depending on the ischaemic risk profile of the patient (Neumann et al., 2019). In patients with a stable CAD and non-flow-limiting lesions, PCI does not improve symptoms and outcome compared with those patients who are only treated medically (Pijls et al., 2007).

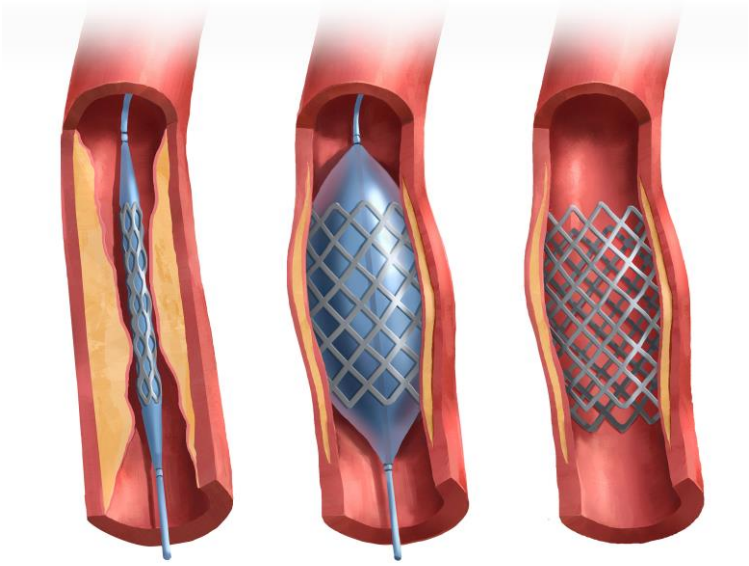

Figure 4. Dilation and stenting of a stenotic coronary artery.
Design: Emil H. Valgeirsson.

1.2.1.2 Coronary artery bypass grafting

Based on the extent and distribution of the CAD and comorbidities of the patient, CABG can in some cases be a better option than PCI (Neumann et al., 2019). The first CABG procedure was performed in 1960 (Head et al., 2013) and the first CABG in Iceland was performed 26 years later (Sigurjonsson et al., 2012).

The procedure begins with a sternotomy and is most often performed using cardiopulmonary bypass (CPB) (**Figure 5**), which revolutionised cardiac surgery when it was introduced in 1953 (Hessel, 2014). During CPB,

the venous blood from the right atrium is transferred to the CPB machine, where the blood is oxygenated and then transferred back to the patient's arterial circulation, usually into the ascending aorta. Alternatively, the femoral and axillary arteries can be used for cannulation, for example, in procedures of the ascending aorta and aortic arch (Sarkar & Prabhu, 2017). The choice of cannulation site is also influenced by the distribution of atherosclerotic disease, to minimise the risk of embolisation of atheromatous debris (El-Sherief et al., 2013). Following cannulation, the heart is then stopped with cardioplegia, a potassium-rich solution which allows the surgeon to perform the bypass on a flaccid heart (Machin & Allsager, 2006). Subsequently, the left internal mammary artery is usually anastomosed to the left anterior descending artery (LAD) and veins from the lower limb of the patient used to bypass stenoses in other arteries (Giannoglou et al., 2001). Alternatively, other arterial conduits such as the right internal mammary artery (RIMA) or the radial artery can be used, or even the lesser saphenous vein (Steinbruchel, 2000; Taggart et al., 2017). The length of time spent on CPB varies between procedures and is affected by the number of anastomoses and training of the surgeon, but it is often around 60–90 minutes (Sigurjonsson et al., 2012).

CABG can also be performed without the use of CPB—that is, on a beating heart—often called off-pump coronary artery bypass (OPCAB) (Khan et al., 2004). Initial studies on the OPCAB technique, which were usually non-randomised, suggested that it had lower rates of complications such as perioperative bleeding and stroke (Gold et al., 2004). Since then, several randomised trials have shown that the short-term outcomes of CABG using this technique is comparable to that of the conventional CABG with CPB, including rates of stroke, myocardial infarction (MI) and 30-day mortality (Dieberg et al., 2016). Furthermore, several randomised studies have indicated that long-term survival is inferior following OPCAB compared with CABG performed on-pump (Shroyer et al., 2009; Takagi & Umemoto, 2014).

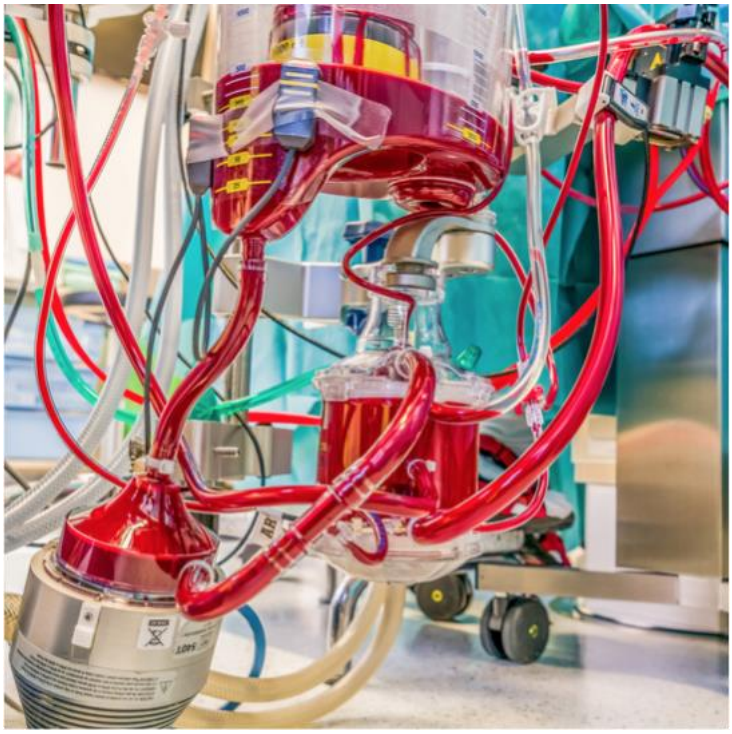

Figure 5. Cardiopulmonary bypass machine.
Photo: Ragnar Th. Sigurdsson.

Following the aforementioned developments in PCI techniques, CABG procedures became less frequently used as a treatment for CAD. In the United States, CABG rates dropped from 1,742 procedures/million adults/year in 2001 to 1,081 procedures/million adults/year in 2007 (Epstein et al., 2011). Another study showed that the PCI/CABG ratio increased from 2002 to 2013, but then levelled out (Blumenfeld et al., 2017). Compared with PCI, patients undergoing CABG generally require a longer hospital stay with associated higher cost (Weintraub et al., 2004). However, CABG is still indicated for patients with severe CAD and a high SYNTAX score—an angiographic scoring tool to determine the complexity of CAD (Serruys et al., 2009). This applies particularly to patients with diabetes and extensive disease, and to patients with heart failure. Furthermore, CABG is often indicated in patients who are having heart valve surgery (Neumann et al., 2019).

1.2.2 Aortic stenosis

Aortic stenosis (AS) is the most common heart valve disease in developed countries (Maganti et al., 2010). The prevalence increases with age, but it is estimated that 2–4% of individuals aged 65 years or more have AS (Carabello & Paulus, 2009). The pathogenesis is not fully understood. In the past it was believed that the disease was degenerative, mostly resulting from wear and tear of the leaflets, but studies have shown that AS is an active disease caused by lipoprotein deposition, chronic inflammation and active leaflet calcification (Freeman & Otto, 2005). There is some overlap in risk factors for AS and CAD, i.e. dyslipidemia, chronic kidney disease and smoking (Freeman & Otto, 2005). Around 1–2% of people are born with a bicuspid aortic valve, which is a strong risk factor for AS. This defect can be caused by a mutation in the NOTCH1 gene and newly discovered genetic alterations at loci on chromosome 1p21 (Garg et al., 2005; Helgadottir et al., 2018). These patients develop AS at a faster rate and usually require surgery 10–20 years earlier than those with a tricuspid aortic valve (Roberts & Ko, 2005). In addition, patients with a bicuspid valve often have concurrent aortopathy, which makes them prone to develop aortic aneurysm and aortic dissection (AD) (Michelena et al., 2011).

In AS, calcification of the valve leaflets increases over time, leading to narrowing of the valve area and decreased motility of the valve, which causes left ventricular pressure overload (Calin et al., 2015). Development of hypertrophy of the left ventricle is believed to be the main compensatory mechanism in AS, allowing the left ventricular ejection fraction (LVEF) to be preserved. As the stenosis increases, the LVEF declines (Spaccarotella et al., 2011). In the earlier stages, AS is usually asymptomatic. As the disease progresses, symptoms emerge, including dyspnea, angina, syncope on exertion and sudden death. The overall mortality rate in asymptomatic AS patients is low. However, once symptoms appear, the mortality rate approaches 25% per year (Carabello & Paulus, 2009).

1.2.2.1 Surgical aortic valve replacement

Although risk factors for AS are well described, pharmacological therapies targeting these factors have failed to slow the progression of AS (Freeman & Otto, 2005). Before CPB emerged, no treatment that improved the survival of patients with AS was available (Carabello & Paulus, 2009). Since then, the golden standard treatment for AS has been SAVR (Maganti et al., 2010). However, in recent years transcatheter aortic valve implantation (TAVI) has emerged as an alternative treatment option (Baumgartner et al., 2017).

SAVR is the second most common open heart surgery after CABG in the western world. Similar to CABG, as described above, a sternotomy is performed and the patient is connected to CPB. Then a cross-clamp is placed on the aortic root and an incision is made in the aortic root followed by removal of the stenotic aortic valve, together with surrounding calcification. A valve prosthesis is then sutured in the annulus of the aortic root. Finally, the aortic root is closed, the patient is weaned from CPB and the sternum is closed with steel wires (Ramlawi et al., 2014).

The first SAVR using a prosthetic valve was performed around 1960 and the first such operation was performed in Iceland in 1987 (Arnórsson, 2013). In the first SAVR surgeries, a mechanical valve called “ball within a cage” was used. A second generation of mechanical valves emerged approximately ten years later, the so-called “tilt disk valve” and finally, bi-leaflet valves appeared and are now the most commonly used mechanical valves. Today, however, bioprostheses made either of porcine tissues or bovine tissues are much more commonly used than mechanical prostheses (Viktorsson et al., 2016) (**Figure 6**). Other biological valve options, such as homografts and autografts (Ross procedure) are used much less frequently (Chaikof, 2007). The mechanical valves have great durability, but the patients require life-long anticoagulation therapy to reduce the risk of thromboembolic events (Nishimura et al., 2017). On the other hand, the patients who receive biological valves do not need life-long anticoagulation, but the valves do not last as long as mechanical valves (Pibarot & Dumesnil, 2009). Recently, a minimally invasive approach was developed whereby a suture-less biological aortic valve is used, which requires shorter cross-clamp and CPB times than the conventional method (Di Eusanio & Phan, 2015). In the era of emerging alternative procedures, it is important to study the outcome of the conventional surgeries and to identify risk factors for adverse outcome.

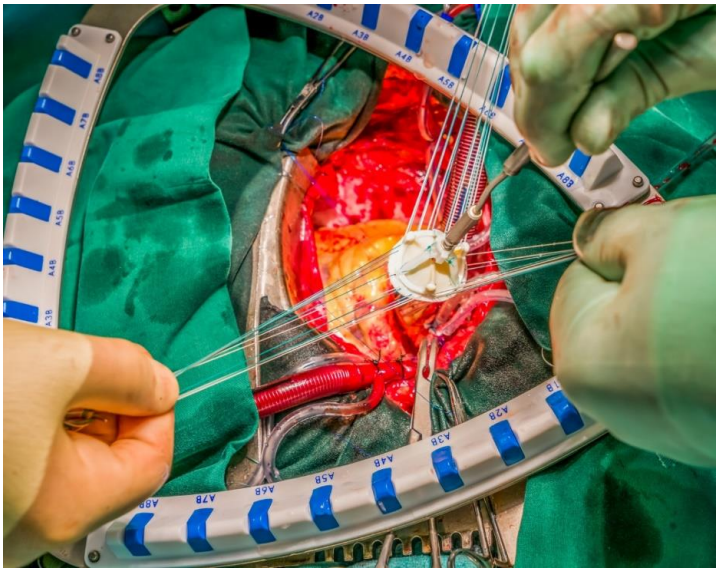

Figure 6. Surgical aortic valve replacement where a stented biological valve is inserted and sewn to the aortic annulus.
Photo: Ragnar Th. Sigurdsson.

1.2.2.2 Transcatheter aortic valve implantation (TAVI)

While SAVR is an established and durable option for AS, up to one-third of patients are not considered fit for surgery due to high operative risks (Iung et al., 2005). In 2002, a novel technique called TAVI was used for the first time in a human. This minimally invasive procedure involves implantation of a prosthetic aortic valve that is inserted via a catheter through the femoral artery. Alternatively, the subclavian artery, a direct aortic approach or implantation through the apex of the heart can be used (Cribier, 2012). When placed in the aortic annulus, the biological prosthetic valve can either be balloon-expandable or self-expandable within a metal grid, and pushes the native valve leaflets into the aortic annulus. Since the first procedure, the rate of TAVI has grown rapidly and it is estimated that over 300,000 procedures have been performed worldwide (Cahill et al., 2018). At the same time, the outcome of TAVI has improved regarding short-term mortality and complications (Walther et al., 2015). TAVI is now recommended for high-risk patients who are unsuitable for conventional SAVR but have suitable access for TAVI, as well as for intermediate-risk older individuals. Again, as with revascularisation, the aim is to find the most suitable treatment for the patient based on comorbidities and overall risk, which is often not accounted for in

traditional risk scores. TAVI can also be an option for valve-in-valve implantation, used for treating degenerated bioprostheses previously implanted with SAVR (Baumgartner et al., 2017). TAVI has also been compared with SAVR in intermediate-risk patients showing non-inferiority. Building on the results of intermediate-risk trials, several trials are currently active, with the aim of evaluating outcomes after TAVI in patients who are at low to intermediate operative risk. Recently published results from one of these trials have shown promising results in favour of TAVI regarding the rate of the composite endpoint of death, stroke, or re-hospitalisation at one year (Mack et al., 2019).

In the early days of TAVI, clinical studies that compared the outcome of patients with those who underwent SAVR showed a higher risk of stroke following TAVI. However, a recent meta-analysis has shown that the incidence of stroke is now comparable between the two procedures (Davlouros et al., 2018). Still, in contrast to SAVR, the durability of the TAVI valves is still not known. Furthermore, complications such as moderate to severe paravalvular leakage, which has been seen in up to 24% of patients before discharge with previous generations of valves (Genereux et al., 2013), and conduction disorders that require pacemaker implantation in 9–26% of patients, remain a concern (Leon et al., 2016; Reardon et al., 2017).

1.2.3 Aortic dissection

AD is a grave condition with high morbidity and mortality (Hagan et al., 2000). The pathogenesis is complex and the dissection is the end result of many different processes that cause weakening of—or increased stress on—the aortic wall. Most cases are thought to develop from intimal tearing preceded by atherosclerotic ulcers (Sundt, 2007). The tearing allows the blood to enter the media of the arterial wall, creating a false lumen that can expand in an antegrade or retrograde manner (Nienaber & Clough, 2015). The most common risk factors for AD are a history of hypertension, atherosclerosis, previous cardiovascular surgery and old age. AD is also associated with several genetic conditions including Marfan's syndrome, Ehlers-Danlos syndrome and congenital bicuspid valve, which is also an important risk factor for AS (Byers et al., 2017; De Paepe et al., 1996; Wojnarski et al., 2015). Over the past decades, the incidence of AD has been increasing from roughly 3 cases/100,000/year to 6 cases/100,000/year (Howard et al., 2013; Meszaros et al., 2000). AD is most often classified anatomically, according to the Stanford classification, into type A or B—involving or sparing the ascending aorta, respectively (Daily et al., 1970). The DeBakey classification

subdivides the dissection process differently: type I dissection involves the entire aorta, type II dissection involves the ascending aorta and type III dissection spares the ascending aorta and the arch (DeBakey et al., 1966) (**Figure 7**). Patients with Stanford type B AD are often managed medically in an intensive care unit (ICU) with the goal of reducing blood pressure and preventing aortic rupture, and progression of the dissection. Open surgery, however, has been reserved for patients with aortic rupture or signs of malperfusion (Golledge & Eagle, 2008). Endovascular management of type B AD is now more frequently used in complicated type B AD, both in the chronic and acute forms. The aim of the endovascular therapy is to direct the blood flow to the true lumen and to promote remodelling of the aorta (Di Tommaso et al., 2018). Patients with complicated AD who undergo endovascular treatment have a lower 30-day mortality than those who are treated medically or surgically (Nienaber & Clough, 2015). Patients with type B AD are at risk of neurological complications and conversion to type A dissection (Fattori et al., 2013). They are also at risk of developing AKI, mainly due to hypoperfusion of the kidneys. However, contrast used in the endovascular treatment could also play a role in the pathogenesis of AKI (Pisimisis et al., 2010).

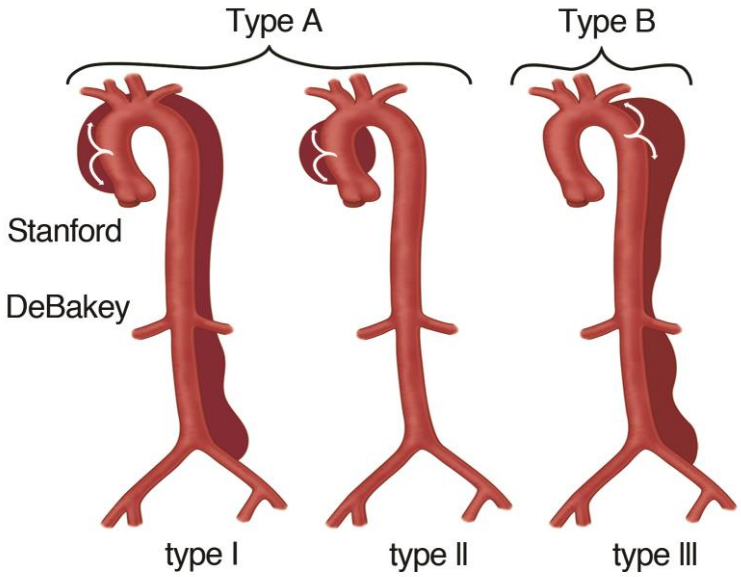

Figure 7. Aortic dissection according to the Stanford classification (types A and B) and DeBakey classification (types I, II and III). See text for details.
Design: Hjördís Bjartmars.

1.2.3.1 Acute type A aortic dissection

ATAAD accounts for two-thirds of ADs (Criado, 2011) and most commonly presents in the seventh and eighth decades of life (Hagan et al., 2000). Two-thirds of the cases are males and the patients generally present with a severe tearing chest pain or back pain with an abrupt onset. In contrast, up to 10% of patients do not complain of having chest pain (Collins et al., 2004). Furthermore, around one-quarter of all patients present with hypotension or shock and approximately one-third of patients with ATAAD have some degree of malperfusion syndrome on presentation, which can affect the brain, coronary arteries, liver, small or large bowel, kidneys and the extremities, depending on the arterial branches affected (Czerny et al., 2015). Malperfusion in ATAAD is associated with an increased risk of early mortality (Czerny et al., 2015). The Penn classification categorises the extent of malperfusion into four stages; Aa (no organ ischaemia), Ab (localised ischaemia), Ac (generalised ischaemia) and Abc (localised and generalised ischaemia together) (Augoustides et al., 2009). This classification has been proven to be a good predictor of survival (Augoustides et al., 2009).

Prompt diagnosis based on early suspicion of ATAAD is mandatory for a successful outcome. The quickest and most accurate method of confirming the diagnosis is CT angiography of the thoracic aorta (Rogers et al., 2011). Without treatment, more than half of patients die due to aortic rupture, valvular dysfunction, pericardial tamponade, or arch vessel occlusion causing end-organ malperfusion (Nienaber & Clough, 2015).

1.2.3.1.1 Surgery for acute type A aortic dissection

Since mortality rates with medical treatment alone are high, there is a general consensus that emergency open surgical repair is the standard of care in ATAAD. The surgery aims at preventing aortic rupture, development of pericardial effusion and tamponade, but also at eliminating aortic regurgitation and preventing MI (Erbel et al., 2001). The surgery usually involves resecting the ascending aorta and, if involved, the aortic arch and then replacing it with a prosthetic graft (Erbel et al., 2001). The exact surgical approach depends on various factors such as the preoperative condition of the patient; the extent of the intimal tear; the state of the aortic root, valves and coronary arteries; and the preference of the surgeon. Despite there being a decrease in early mortality following ATAAD repair, the in-hospital mortality following these procedures is high, ranging from 10% to 22%. In addition, postoperative complications are common (Orihashi, 2012; Yuan et al., 2017).

While the long-term survival of these patients is inferior to that of patients without ATAAD, with nearly a threefold mortality risk (Olsson et al., 2006), a recent Nordic study showed that medium-term survival is improving (Olsson et al., 2017).

1.3 The interaction between cardiac and renal disease

The heart supplies the organs and tissues with blood and the kidneys play a vital role in sodium homeostasis, fluid balance and blood pressure regulation (Shah & Greaves, 2011). As expected, cardiac and renal diseases frequently co-exist and disorders affecting one of these organs often results in

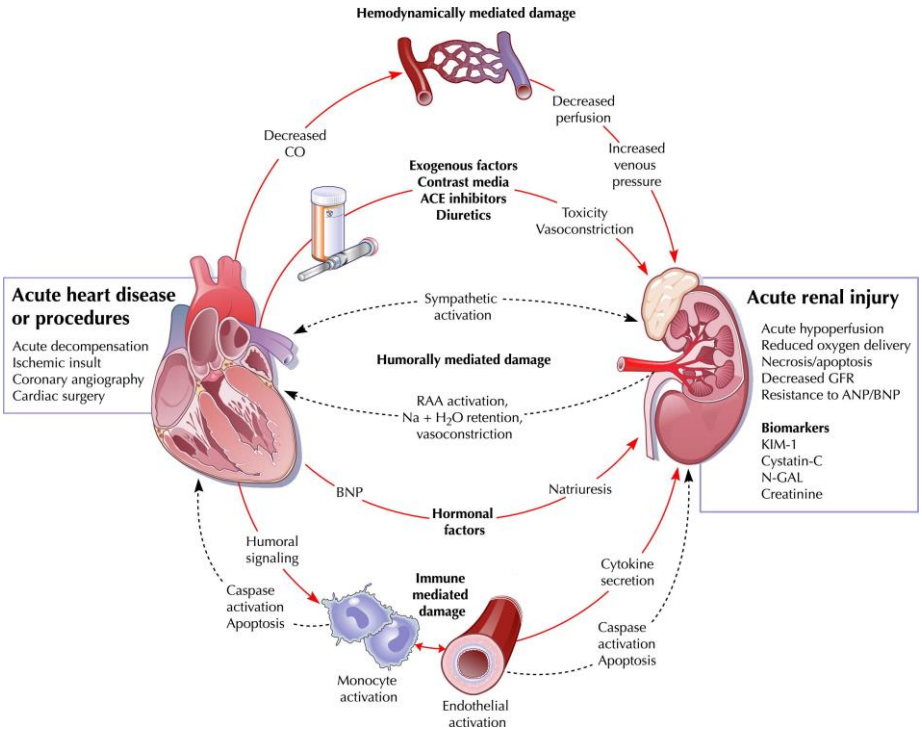

Figure 8. Cardiorenal syndrome type 1.

ACE, angiotensin-converting enzyme; ANP, atrial natriuretic peptide; BNP, B-type natriuretic peptide; CO, cardiac output; GFR, glomerular filtration rate; KIM, kidney injury molecule; N-GAL, neutrophil gelatinase-associated lipocalin; RAA, renin angiotensin aldosterone.
Reproduced with permission of Elsevier, from (Ronco et al., 2008).

secondary dysfunction of the other (Forman et al., 2004). In 2010, the ADQI published a consensus statement on the definition of cardio-renal syndrome (CRS), classifying it into five types. Type 1 includes conditions where there is a sudden worsening of heart function that results in kidney injury, such as

ACS leading to AKI (**Figure 8)**. In type 2, chronic cardiac abnormalities cause kidney injury, most often a chronic deterioration in kidney function. In type 3, there is a sudden decline in kidney function that leads to acute cardiac disorders, such as heart failure with pulmonary oedema and arrhythmias. Type 4 covers conditions where CKD leads to heart disease, but a meta-analysis showed that there is an exponential relationship between the severity of CKD and the risk of all-cause mortality, especially cardiovascular death (Tonelli et al., 2006). Finally, Type 5 CRS is a systemic disease that leads to both cardiac and renal dysfunction, for example sepsis and diabetes (Ronco et al., 2010).

1.3.1 AKI following cardiac procedures

In CRS type 1, haemodynamic changes play an important role in the development of AKI but there are also other contributory factors, including the sympathetic nervous system, the RAS and reactive oxygen species. AKI following cardiac procedures has been classified as one of the subgroups of CRS type 1 (Vandenberghe et al., 2016). In these cases, an injury to the kidneys is related to the underlying cardiac disease and the procedure. In the following sections, AKI following different cardiac procedures will be discussed further.

1.3.1.1 AKI following coronary angiography

AKI is a known complication of CA. The disorder has been associated with the use of contrast media and is often referred to as contrast-induced nephropathy or contrast-induced AKI (CI-AKI) (McCullough et al., 2016). The incidence of AKI following CA has declined in recent years (McCullough, 2008), although it has varied between studies because of differences in study cohorts, in definitions of AKI and in the development of contrast agents. The reported incidence ranges from 2% to 25% (Solomon & Dauerman, 2010). A recent multi-centre study of more than 1.3 million patients who underwent PCI found an incidence of 7% (Amin et al., 2017), whereas a study including all CAs in Alberta Canada found an incidence of 10%; both studies defined AKI by using the AKIN criteria (James et al., 2011).

There are several types of contrast medium, which are often classified based on the degree of ionization and osmolality and whether they are monomeric or dimeric. They all have iodine concentrations of 270–400 mg/mL, which provides adequate radiographic opacification, but vary in osmolality and viscosity. The first contrast agents used in angiographies in the 1950s were so-called high-osmolar ionic contrast agents with an

osmolality of up to 1,500–2,000 mOsm/kg H_2O (Khasawneh et al., 2013). In addition to the iodine, these types of contrast medium have osmotically active ions of sodium or meglumine salts (Barrett et al., 1992). In the early 1990s, the low-osmolar contrast media emerged, where the osmolality was lowered by making the molecules non-ionic. Despite having a less osmotic effect than high-osmolar contrast, these agents still had three times the osmolality of plasma (Claussen, 1992). Finally, iso-osmolar contrast agents were developed in the mid-1990s with an osmolality level similar to that of blood (290 mOsm/kg H_2O) and a dimeric structure, as opposed to monomeric in most high- and low-osmolar agents, which reduces the osmolality further (Mruk, 2016). Studies have shown that compared with high-osmolar contrast, the low-osmolar contrast is associated with a lower risk of AKI, especially in high-risk patients (Barrett & Carlisle, 1993; Goldfarb et al., 1993). In this context, however, recent studies have not been able to show any consistent benefit of iso-osmolar over low-osmolar contrast agents (Feldkamp et al., 2006; Giustino et al., 2016). Thus, the KDIGO AKI guidelines from 2012 recommend using either low- or iso-osmolar contrast agent (Kidney Disease Improving Global Outcomes: (KDIGO) Acute Kidney Injury Work Group, 2012).

The nephrotoxic effect of contrast media has mostly been examined in animal models (**Figure 9**). The contrast is believed to cause vasodilatation followed by an intense and long period of vasoconstriction (Morris et al., 1978). The contrast stimulates vasoconstriction mediated by an influx of extracellular calcium (Bakris & Burnett, 1985) and the release of vasoconstrictors, such as endothelin and adenosine (Clark et al., 1997). In addition, the hyperosmolar contrast agents reduce nitric oxide (NO) production, thereby inhibiting vasodilatation and disrupting autoregulation (Ribeiro et al., 2004).

The vasoconstriction reduces renal blood flow, mainly in the medulla (Heyman et al., 1988), and with the reperfusion that follows, it also leads to oxidative stress and release of free radicals—contributing to the kidney injury (Sandhu et al., 2002). Furthermore, the high osmotic load of the contrast medium has been shown to have a direct toxic effect on renal tubular cells (Moreau et al., 1980). The high-osmolar contrast agents are no longer used intra-arterially or intravenously. On the other hand, the reduction of osmolality in the modern contrast agents was achieved at the expense of increased viscosity (Jost et al., 2011). The high viscosity of the contrast causes an elevation of urine viscosity and leads to a decrease in GFR in rats (Seeliger et al., 2010). The number of studies that have investigated the effect of

contrast medium on renal blood flow in humans has been limited and they have given conflicting results (Tumlin et al., 2006). Hence, further human studies on the physiological effect of contrast agents are required, especially the contrast agents with low osmolality.

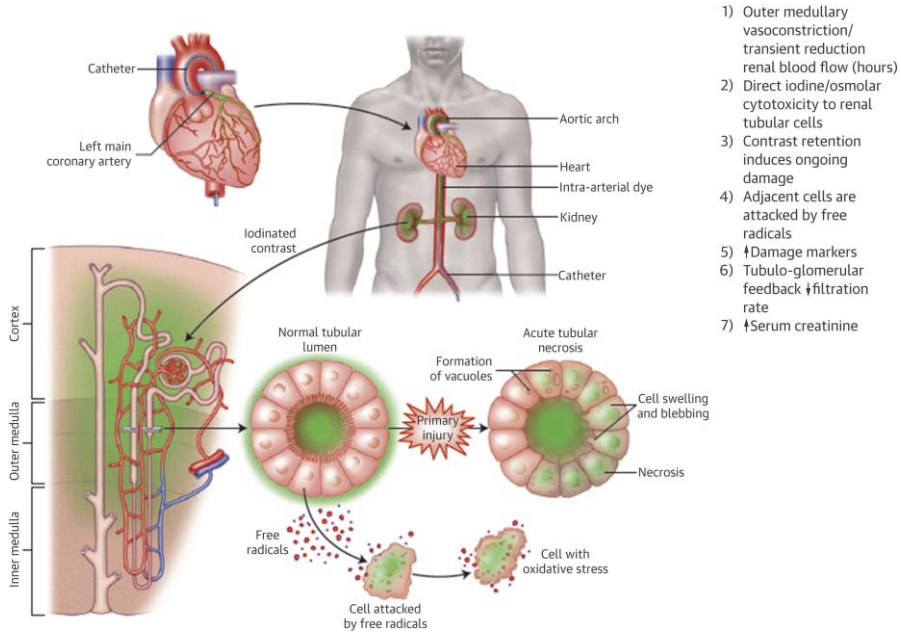

Figure 9. Pathogenesis of contrast-induced acute kidney injury. See text for details. Reproduced with permission of Elsevier, from (McCullough et al., 2016).

Other risk factors for AKI following CA have been identified, such as CKD, diabetes, CHF and shock (Mehran et al., 2004). Several risk scores have been developed to identify high-risk patients. Even so, their usefulness has been questioned, and to date none of them have been established as a tool for use in the clinical setting. In addition to identifying high-risk patients, many pharmacological and non-pharmacological therapies have been tried in an attempt to prevent and treat CI-AKI, for example volume expansion, acetyl-cysteine, statins, ascorbic acid and sodium bicarbonate (McCullough et al., 2016). However, none of these therapies have proven to be effective except for volume expansion with normal saline or sodium bicarbonate (Weisbord et al., 2018).

In recent years, the contribution of contrast agents to the development of AKI following CA has been debated, especially with the emergence of contrast agents with lower osmolarity. In a study by Smucker et al., AKI in

STEMI patients was investigated. The haemodynamic effect of the STEMI was the major cause of AKI, whereas the contrast dose was not significantly associated with the disorder (Schmucker et al., 2017). This is further supported by a recent randomised controlled study, where a so-called AVERT system was used to minimise the contrast doses in CA in patients with eGFR below 30 mL/min/1.73 m^2. The system significantly reduced the amount of contrast but did not have any effect on the development of AKI (Mehran et al., 2018). Thus, the importance of contrast medium in the development of AKI following CA remains uncertain. In addition, a study on more than 12,000 patients who underwent CT scanning at the Mayo Clinic revealed that intravenous contrast was not associated with AKI, even in patients with eGFR below 30 mL/min/1.73 m^2 (McDonald et al., 2014).

AKI following CA has been associated with adverse outcomes, both short- and long-term survival (James et al., 2013). However, in a recent meta-analysis and systematic review, it was concluded that the effect of AKI on survival could in part be explained by confounding comorbidities (James et al., 2013). Importantly, there has been a limited number of studies with long-term follow-up of kidney function in these patients, especially the development of CKD, since SCr measurements are often lacking in the long-term follow-up of patients. A study by James et al. showed that AKI following CA was associated with a sustained decline in kidney function 3 months after the procedure (James et al., 2010), and in a large Veterans Administration study, AKI following PCI was found to be an independent predictor of CKD with a median follow-up of 1.7 person-years (Brown et al., 2016).

1.3.1.2 AKI following open heart surgery

AKI is one of the most common complications following open heart surgery and has been the subject of several studies in recent years. The pathogenesis is multi-factorial, consisting both of underlying clinical characteristics and intraoperative factors. Characteristics that make patients more susceptible to AKI include advanced age, diabetes, CKD and the severity of the disease that leads to the open heart surgery (Coleman et al., 2011). The effect of drugs that are used before cardiac surgery on AKI has been studied and it is debated whether RAS blockers should be discontinued before surgery. Recommendations differ between guidelines, but in the current European Association of Cardiothoracic Surgery (EACTS) guidelines, discontinuation of these drugs is recommended 12–24 hours before surgery based on the half-life of the drugs (Sousa-Uva et al., 2018). Intraoperative factors also play a significant role, as well as the complexity and type of the

surgery, perioperative red blood cell (RBC) transfusion, intraoperative hypotension and requirement for inotropic support (O'Neal et al., 2016). Finally, the CPB machine that is used in most open heart surgeries plays an important role in the development of AKI and deserves special mention.

CPB is associated with significant haemodynamic changes. The maintenance of cardiovascular stability during CPB requires interaction between the CPB machine and patient factors such as systemic vascular resistance, venous compliance and the autoregulatory capacity of vascular beds (Rosner & Okusa, 2006). The aim is to maintain perfusion at a level that supports optimal cellular and organ function. Thus, any decrease in renal perfusion during CPB, depending on its severity and duration, can lead to significant cellular injury (Rosner & Okusa, 2006).

A loss of pulsatile blood flow within the renal arteries despite maintenance of mean flow and pressure stimulates the RAS and, together with vasopressin release, results in vasoconstriction. On the other hand, the vasoconstriction can lead to peripheral circulatory insufficiency and reduced visceral perfusion (Hornick & Taylor, 1997). Furthermore, in a study by Lannemyr et al., non-pulsatile CPB was found to impair renal oxygenation through vasoconstriction and haemodilution, both during and after CPB, with an increase in NAG, a marker for tubular injury (Lannemyr et al., 2017; Liangos et al., 2007).

Importantly, however, the role of CPB in the pathogenesis of AKI following cardiac surgery is not solely related to changes in haemodynamics. CPB can also induce systemic inflammatory response syndrome—a hyperdynamic state characterised by increased cardiac output and decreased systemic vascular resistance, and a requirement for vasopressors and fluid replacement (Cremer et al., 1996). This condition is thought to be driven by inflammatory mediators such as IL-6, IL-8 and TNF-α, and is associated with contact of blood with the artificial surface of the CPB machine, ischaemia-reperfusion injury, endotoxemia and non-pulsatile blood flow among other factors (Rosner & Okusa, 2006).

1.3.1.2.1 Coronary artery bypass grafting

The incidence of AKI following CABG, the most common type of open heart surgery, is generally between 12% and 20% (Brown et al., 2006; Li et al., 2011). The need for RRT following surgery is around 2–3% but it is 6% following emergent or salvage CABG (Axelsson et al., 2016). Patient-related risk factors for AKI include female sex, CKD and diabetes (Rosner & Okusa,

2006). Interestingly, despite the known role of CPB in development of AKI, studies on OPCAB, where the coronary bypass is performed on a beating heart, have only shown a mild reduction in the incidence of AKI and no change in rates of RRT compared with on-pump CABG in randomised controlled trials (Fudulu et al., 2016). This indicates that factors other than CPB contribute to the development of AKI following CABG.

1.3.1.2.2 Valvular replacement surgery

AKI is more common following valvular surgery than after CABG, with up to a 2.7-fold risk (Grayson et al., 2003). These operations are usually regarded as more complex than CABG, with longer CPB time and the patients being generally older (Johannesdottir et al., 2017; Viktorsson et al., 2016). In octogenarians, the incidence of AKI following valvular surgery was found to be 35% (Thongprayoon et al., 2017). Another study found an incidence of AKI of 30% following tricuspid valve surgery (Englberger et al., 2013). Despite the fact that SAVR is the most common valvular procedure and the second most common open heart surgery in western countries, there have been few studies that have focused on AKI following SAVR. However, in a Swedish study by Ryden et al., the incidence of AKI following SAVR was 17% (Ryden et al., 2015). On the other hand, studies comparing the incidence of AKI following SAVR and TAVI have shown discrepant results. In one of the larger studies, the PARTNER trial, the incidence of AKI and need for RRT were found to be comparable between the groups (Smith et al., 2011), whereas other studies have shown a lower risk of AKI following TAVI (Bagur et al., 2010; Kumar & Garg, 2018).

1.3.1.2.3 Surgery for acute type A aortic dissection

A limited number of studies have focused on AKI following ATAAD repair. Most current reports are based on single-centre analyses covering a small number of patients, where the incidence of AKI has most often been between 40% and 55% (Wang et al., 2018). Large multi-centre registries of AD, for example the International Registry of Acute Aortic Dissection (IRAD) and the German Registry for Acute Aortic Dissection Type A (GERAADA), have not yet reported on the incidence and outcomes of patients with AKI following ATAAD repair (Czerny et al., 2015; Yuan et al., 2017). The pathogenesis of AKI following ATAAD repair is often different from AKI after most other cardiac procedures, such as CABG and SAVR, which in most cases are non-urgent operations. In these surgeries, the risk of AKI is mostly dictated by

operative factors and the comorbidity of patients. In ATAAD, the underlying disease, the dissection itself can cause shock and the dissection can expand to the renal arteries, resulting in renal hypoperfusion with a subsequent decline in kidney function (Roh et al., 2012). In addition, ATAAD repair is a longer procedure and is more complex than most other cardiac surgeries.

1.3.1.2.4 Outcome of AKI following cardiac surgery

AKI has been associated with worse survival following cardiac surgery (Hobson et al., 2009), and even a mild elevation in SCr has been associated with a threefold risk of short-term mortality (Lassnigg et al., 2004). The focus in recent years has been on the effect of the duration of AKI and renal recovery on survival (Steinbruchel, 2000). However, there is no consensus regarding the definition of renal recovery.

The amount of data regarding the association between AKI and postoperative outcomes differs between the different types of cardiac surgery. The best evidence exists for AKI following CABG, with studies consistently showing that AKI is predictive of inferior short-term and long-term survival (Brown et al., 2006; Li et al., 2011). Ryden et al. found that following SAVR, stage 1 AKI had a 27% increased relative risk of death, which was increased more than twofold for stages 2 and 3 (Ryden et al., 2015). In a meta-analysis, AKI was found to be associated with more than a threefold risk of 30-day mortality following ATAAD surgery, but the number of patients in each study was limited (Wang et al., 2018). Furthermore, two smaller studies have indicated that AKI is also predictive of inferior long-term survival following ATAAD repair (Sasabuchi et al., 2016).

During the first few days after cardiac surgery, AKI can lead to volume overload and heart failure, and can cause arrhythmias through electrolyte disturbance. Hence, these patients can develop CRS type 3 where AKI leads to acute cardiac dysfunction (Ronco et al., 2010). When AKI occurs, there is an immediate release of cytokines such as TNF-α and IL-6, which can have a cardio-depressant effect and reduce LVEF. AKI also leads to hyperactivation of the sympathetic nervous system, which impairs myocardial activity and activation of the RAS, promoting vasoconstriction and increase in vascular resistance (Di Lullo, Bellasi, Russo, et al., 2017). The increased long-term mortality in patients who develop AKI following cardiac surgery results from an increased risk of cardiovascular death (Hansen et al., 2015). This can possibly be explained by the cardio-renal syndrome type 4, where CKD is a mediator. Hypertension, which is common in CKD, leads to left ventricular

hypertrophy and pressure overload. Hyperphosphatemia and secondary hyperparathyroidism lead to ossification of coronary arteries and valves, leading to CAD and valvular disease. Finally, chronic inflammation also contributes to the increased risk of cardiovascular disease in CKD (Di Lullo, Bellasi, Barbera, et al., 2017).

Even so, the number of studies that have assessed the development of CKD after AKI following cardiac surgery using SCr measurements has been very limited. A study on patients who underwent cardiac surgery at Veterans Affairs hospitals in the United States showed that the magnitude of SCr elevation was associated with an increased risk of CKD (Ishani et al., 2011). However, that study did not represent a general population. Finally, there is a paucity of studies on the development of CKD following both SAVR and ATAAD repair.

2 Aims

2.1 Study I

The aim of study I was to determine the incidence and risk factors of AKI following CA in a nationwide cohort, focusing on the role of iso-osmolar contrast dose. In addition, the aim was to evaluate the association between AKI and the short-term and long-term outcomes of these patients, including mortality and the onset or progression of CKD.

2.2 Study II

The aim of study II was to determine the incidence and risk factors of AKI following CABG and to study the association between AKI and postoperative outcomes, especially long-term survival and development of CKD. Furthermore, the aim was to evaluate the effect of other postoperative complications on the association between AKI and survival.

2.3 Study III

The aim of study III was to determine the incidence and risk factors of AKI following SAVR for AS in a population-based cohort. Another aim was to determine the short-term and long-term outcome of AKI patients.

2.4 Study IV

The aim of study IV was to determine the incidence and risk factors of AKI following ATAAD repair and to evaluate the association between AKI and short-term and long-term survival.

3 Materials and methods

In the following section, the materials and methods of the four studies will be described. The studies were all retrospective, and studies I–III were single-centre studies with nationwide implications while study IV was a multi-centre study from eight centres in four Nordic countries. Landspitali (the National University Hospital of Iceland, hereafter referred to as the University Hospital) is the only hospital in Iceland that performs cardiac surgery and CA. Furthermore, it serves all patients who require dialysis treatment.

All of the studies were approved by the Icelandic National Bioethics Committee and study IV was also approved by bioethics committees in Denmark, Finland and Sweden. Approvals for studies II and III were obtained from the Icelandic Data Protection Authority. The studies' methods are summarised in **Table 3**.

3.1 Study populations

3.1.1 Study I

This was a study of all CA procedures in Iceland from 1 January 2008 to 31 December 2015 (n = 13,974). Patients who were receiving dialysis treatment for ESRD before CA (n = 99) were excluded, as were cases who had a missing baseline SCr value (n = 172) and those who underwent open heart surgery within 3 days after the CA and had not met criteria for AKI before the surgery (n = 142). The remaining 13,561 procedures, 5,570 (41.0%) of which included PCI, performed on 10,553 patients were used for analysis.

3.1.2 Study II

A total of 1,754 patients underwent isolated CABG at the University Hospital from 1 January 2001 to 31 December 2013. Patients with missing baseline or postoperative SCr (n = 42) and those who were receiving dialysis treatment preoperatively (n = 2) were excluded, leaving 1,710 for analysis.

3.1.3 Study III

This was a study of adult patients who underwent SAVR for AS with or without concomitant CABG at the University Hospital from 1 January 2002 to 31 December 2011. In total, 436 SAVR operations were performed during the

study period. Thirty-one patients were excluded because of having a history of previous cardiac surgery, 27 were excluded because AS was not the indication for SAVR and 13 were excluded because of missing data, since their patient charts were not found. This left 365 patients for analysis.

3.1.4 Study IV

This was a multi-centre study that included 1,159 patients who underwent ATAAD surgery from 1 January 2005 to 31 December 2014 at eight centres—in Denmark (Aarhus University Hospital), Finland (Tampere University Hospital and Turku University Hospital), Iceland (the University Hospital) and Sweden (Karolinska University Hospital, Orebro University Hospital, Sahlgrenska University Hospital and Skåne University Hospital). Excluded were patients who died intraoperatively (n = 77), those who had a missing baseline or postoperative SCr (n = 136) and those who required RRT for ESRD preoperatively (n = 5), leaving 941 patients for further analysis.

3.2 Data collection

Data were obtained from electronic medical record systems, hospital databases and several registries, enabling identification of patients, documentation of patient- and procedure-related information and follow-up regarding survival and renal function.

3.2.1 The Swedish Coronary Angiography and Angioplasty Registry

The Swedish Coronary Angiography and Angioplasty Registry (SCAAR) is a registry used for CA and PCI in Sweden and Iceland (Jernberg et al., 2010). This registry, which was used to identify patients who underwent CA in study I, prospectively registers extensive patient- and procedure-related factors, including type of contrast and dose.

3.2.2 Serum Creatinine Database

In studies I and II, SCr measurements were obtained from a database that contains all SCr measurements performed in Iceland from 2008 to 2016 and at the University Hospital from 1998 to 2007. This permitted an accurate definition of baseline kidney function, identification of AKI episodes and follow-up of patient kidney function regarding development and progression of CKD.

Table 3. Summary of materials and methods in the four studies.

	Study I	Study II	Study III	Study IV
Study cohort	Patients undergoing CA in Iceland	CABG patients in Iceland	SAVR patients in Iceland	ATAAD repair patients in Iceland, Denmark, Sweden and Finland
Number of patients/procedures	10,553/13,561	1,710/1,710	365/365	941/941
Period	2008–2015	2001–2013	2002–2011	2005–2014
Main outcome measures	Incidence and risk factors of AKI, together with survival and incident/progression of CKD	Incidence and risk factors of AKI, together with survival and rate of CKD and ESRD	Incidence and risk factors of AKI, together with survival	Incidence and risk factors of AKI together with survival

AKI, acute kidney injury; ATAAD, acute type A aortic dissection; SAVR, surgical aortic valve replacement; CA, coronary angiography; CABG, coronary artery bypass; CKD, chronic kidney disease; ESRD, end-stage renal disease.

3.2.3 Electronic medical record systems and hospital databases

In study I, patients' International Classification of Diseases, 10th revision (ICD-10) diagnostic codes were retrieved from the University Hospital database and used to calculate a van Walraven-modified Elixhauser comorbidity index score for each patient (Elixhauser et al., 1998). In study I, laboratory results other than SCr were obtained from the clinical laboratories of the University Hospital. In studies II–IV, information on patient characteristics, medication, operative and postoperative information and laboratory results, including SCr measurements in studies III and IV, were manually obtained from the medical records.

3.2.4 The Icelandic End-Stage Renal Disease Registry

Information on long-term RRT for papers I–III was obtained from a centralised registry for RRT in Iceland, managed by the Division of Nephrology at Landspitali. Data regarding RRT in the ICU were obtained from ICU hospital charts for all four studies.

3.2.5 The National Prescription Drug Database

In study I, information on pre-procedural medication use up to six months prior to CA was obtained from the National Prescription Drug Database of the Directorate of Health in Iceland, which holds information on all drug prescriptions and dispensing in Iceland since 2003.

3.2.6 Statistics Iceland and other population registries

Information on all deaths in Iceland is reported to the Icelandic national population register at Statistics Iceland. The register uses a personal identification number, which is a unique number that every citizen is given. In addition, every foreign citizen who is admitted to a hospital in Iceland is assigned a personal identification number. Information on mortality was collected from Statistics Iceland in all studies but in addition, mortality information in study IV was obtained from centralised population registries in Denmark, Finland and Sweden.

3.3 Definitions

3.3.1 Acute kidney injury

In studies I and II, AKI was defined according to the SCr component of the KDIGO criteria for AKI (Kidney Disease Improving Global Outcomes: (KDIGO) Acute Kidney Injury Work Group, 2012). Stage 1 AKI was classified as an increase in SCr of ≥ 26.5 µmol/l above baseline within 48 hours or 1.5–

1.9 times baseline within 7 days, stage 2 AKI as SCr 2.0–2.9 times baseline within 7 days and stage 3 AKI as ≥ 3 times baseline within 7 days or an increase to ≥ 354 µmol/L with a rise in SCr of ≥ 26.5 µmol/L from baseline or initiation of RRT. In study I, patients who had no available SCr measurement within 7 days after the CA (n = 7,330) were assumed not to have developed AKI.

In studies III and IV, SCr measurements within 48 hours were not registered in the databases and AKI was therefore defined according to the SCr part of the RIFLE criteria, where AKI is defined as an increase in SCr of > 50% compared with baseline and is categorised into three stages: Risk (1.5–2.0 times baseline SCr), Injury (2.0–3.0 times baseline SCr) and Failure (> 3.0 times baseline SCr or postoperative SCr > 356.3 µmol/L with an acute rise of at least 44 µmol/L) (Bellomo et al., 2004). The eGFR part of the RIFLE criteria was not included in the definition of AKI and the urine output criteria were not included in any of the studies. In all four studies, SCr obtained closest to the surgery or CA was used as a baseline value.

3.3.2 Chronic kidney disease and renal recovery

The eGFR was calculated according to the CKD-EPI equation in studies I, II and IV, but the MDRD equation was used in study III to define and stage CKD according to the KDIGO classification system (Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group, 2013).

CKD-EPI equation

$GFR = 141 \times \min(SCr/\kappa, 1)^{\alpha} \times \max(SCr/\kappa, 1)^{-1.209} \times 0.993^{age} \times 1.018$ (if female) × 1.159 (if black) (Levey et al., 2009)

κ is 0.7 for females and 0.9 for males, α is −0.329 for females and −0.411 for males, min indicates the minimum of SCr/κ or 1 and max indicates the maximum of SCr/κ or 1.

MDRD equation

$GFR = 186 \times SCr^{-1.154} \times age^{-0.203} \times 1.212$ (if black) × 0.742 (if female) (Levey et al., 1999).

In study I, CKD was defined as eGFR < 60 mL/min/1.73^2 (CKD stages 3–5) for at least 3 months. The baseline CKD stage was the worst stage sustained over at least 90 days before CA. For patients who did not have adequate numbers of SCr measurements available before CA (n = 1,188), the baseline CKD stage was defined based on the SCr closest to the CA. Progression of pre-existing CKD was defined as eGFR corresponding to a higher CKD stage than baseline, sustained for at least 90 days. In studies, II–IV, CKD stages were determined based on an eGFR from a single SCr measurement.

3.3.3 Other definitions

3.3.3.1 Study I

Indications for CA were classified as cardiac arrest, STEMI, NSTEMI or unstable angina, stable angina or unspecified chest pain, or miscellaneous. Miscellaneous was primarily non-ischaemic heart disease and included diagnoses such as heart failure, valvular heart disease and arrhythmias. Anaemia was defined as haemoglobin level < 120 g/L in females and < 135 g/L in males, and hyponatraemia as serum sodium < 136 mmol/L. The Killip classification, which categorises the severity of heart failure in patients with acute MI, was used to define cardiogenic shock (Killip class IV) (Killip & Kimball, 1967).

3.3.3.2 Studies II and III

Clinical features were characterised according to the New York Heart Association (NYHA) and Canadian Cardiac Society (CCS) classification systems and the standard and logistic European System for Cardiac Operative Risk Evaluation (EuroSCORE) scores were calculated (Roques et al., 2003). The same definition of anaemia was used as in study I. Operative mortality was defined as death within 30 days of surgery. Postoperative complications were categorised as either major or minor. Major complications included stroke, mediastinitis, endocarditis (only in study III), MI (defined as isolated ST-segment changes or new left bundle branch block on electrocardiogram along with an elevation in CK-MB of ≥ 70 µg/L), reoperation, sternum dehiscence and acute respiratory distress syndrome (ARDS) or multiple organ failure (MOF). Minor complications included leg wound infection, urinary tract infection, pleural effusion requiring drainage, atrial fibrillation and pneumonia.

3.3.3.3 Study IV

Hypotensive shock on admission was defined as an initial systolic blood pressure measurement of < 90 mmHg (regardless of vasoactive agent usage). The extent of malperfusion was classified according to the Penn classification, which is defined as follows: Aa (no organ ischaemia), Ab (localised ischaemia), Ac (generalised ischaemia) and Abc (localised and generalised ischaemia together) (Augoustides et al., 2009). Postoperative complications were categorised as minor or major, as previously described for studies II and III, but postoperative coma was defined as coma lasting more than 24 hours and not attributable to sedation.

3.4 Statistical analysis

Data were processed using custom scripts in the JAVA programming language in study I and data collection was performed using a standardised Excel (Microsoft Corp., Redmond, WA, USA) data sheet in studies II–IV. All statistical analyses were performed in R (R Foundation for Statistical Computing, Vienna, Austria; version 3.1.1 in study II, version 3.1.2 in study III and version 3.3.3 in studies I and IV).

Descriptive statistics were reported as number (%), mean ± standard deviation, or median (range/interquartile range). In all the studies, continuous variables were compared between patients with and without AKI with a t-test or the Mann–Whitney U-test, based on the normality of the data. Categorical variables were compared using the chi-square test when the minimum expected number was > 5, but otherwise, Fisher's exact test was used. Trends in the incidence of AKI over time were estimated using Poisson regression.

3.4.1 Multivariable logistic regression

A similar approach was used to analyse predictors of AKI in all studies. Multivariable logistic regression models were used to assess patient- and procedure-related risk factors for AKI and were generated by using variables that yielded p-values < 0.1 (0.05 in study I) in a univariable analysis together with previously reported AKI risk factors as predictor variables. The models were modified manually with support of the stepwise backward and forward regressions in R until the best model was found. In studies I and IV, missing values for variables used in the final models were imputed with the random forest method from the missForest package in R. The goodness of fit of the models was tested using the Hosmer–Lemeshow test from the Resource selection package in R in all studies and collinearity of the variables in the final models was estimated by examining the variance inflation factor from the car package in R in studies I and IV.

The final risk models in studies I, III and IV included both patient- and procedure-related variables. In study II, models including patient- and procedure-related variables were constructed separately. In studies I and IV, models that only included patient-related factors available before the procedure were also constructed. When assessing the association between contrast dose and AKI in paper I, the contrast dose was analysed both as a continuous variable and a categorical variable, with categories based on the logit risk of AKI: < 80 mL, 80–150 mL and > 150 mL (**Appendix Figure A1**).

3.4.2 Survival and development of chronic kidney disease

In all studies, the overall long-term survival (all-cause mortality) of patients with and without AKI was estimated using the Kaplan–Meier method and log-rank test. In studies I and IV, landmark analysis was performed where patients who died within 30 days of the procedure were excluded from the analysis, but in study III a similar analysis was done by excluding patients who died within 7 days of surgery. Multivariable logistic regression was used to find predictors of operative mortality in studies II and III.

3.4.2.1 Propensity score matching

In study I, each AKI patient was assigned two control patients without AKI, using propensity score matching (PSM) with the nearest neighbor method, using the MatchIt package in R. Patients who died within 30 days of the procedure were excluded before the matching. Difference in survival in the PSM analysis was evaluated using stratified log-rank test. The following variables were used for matching based on known or presumed association with the outcome: age, sex, body mass index (BMI), history of smoking, baseline CKD stage, diabetes, CHF, chronic obstructive pulmonary disease (COPD), malignancy, a history of IHD, new-onset ACS, treatment with statins, anaemia and hyponatraemia. The quality of the matching was assessed by standardised mean difference for each variable. Since more than one set of controls met the criteria for best possible matching, a median p-value from stratified log-rank tests of 100 pairings was used.

To assess whether AKI was associated with an increased risk of development of incident CKD or progression of a pre-existing CKD, the same PSM method was used as described above. The following variables were used in the matching: age, sex, BMI > 30kg/m^2, history of smoking, COPD, CHF, diabetes and IHD.

3.4.2.2 Cox proportional hazard analysis

Multivariable Cox analyses were used to identify predictors of survival in studies II, III and IV, to find predictors of CKD in study II and to find predictors of incident CKD or progression of prior CKD in study I. In all studies, the cox.zph function in R was used to test the assumption of proportional hazards.

4 Results

4.1 Study I – AKI following coronary angiography

4.1.1 Incidence of AKI

AKI occurred in 231 of 13,561 cases (1.7%); with 175 (1.3%), 22 (0.2%) and 34 (0.3%) being at KDIGO stages 1, 2 and 3, respectively. The incidence of AKI was 17.0 per 1,000 CAs (99% CI: 14.3–20.1) and did not change significantly from 2008 to 2015, ranging from 10.0 to 23.8 per 1,000 CAs ($p = 0.37$). The majority of the cases (78.7%) met AKI criteria in the first 3 days following CA. When cases without any available post-procedural SCr were excluded, the incidence of AKI was 37.1 per 1,000 CAs (99% CI: 21.4–68.5) and when only PCI cases were included the incidence was 25.5 per 1,000 CAs (95% CI: 20.4–31.4). A comparison of patients with and without post-procedural SCr being available is given in the **Appendix**, **Table A1**. Compared with patients with available post-procedural SCr, patients without any post-procedural SCr were generally younger, with a lower CKD stage and a lower proportion had ACS as an indication for CA.

4.1.2 Baseline characteristics

A comparison of characteristics of patients with and without AKI is shown in **Table 4**. Briefly, patients who subsequently developed AKI were significantly older; were more likely to have a history of diabetes, CABG, COPD and CHF; their Elixhauser comorbidity score was higher; their baseline kidney function was also worse; and they were less likely to be smokers compared with patients without AKI. Before the CA, a higher proportion of patients with AKI were taking RAS blockers (54.1% vs. 44.6%; $p = 0.005$), loop diuretics (29.0% vs. 11.7%; $p < 0.001$) and diabetes medication, including insulin (10.8% vs. 3.6%; $p < 0.001$), but a lower proportion were taking statins (46.3% vs. 61.7%; $p < 0.001$) compared with patients without AKI. When pre-procedural laboratory results of the groups were compared, a higher proportion of patients with AKI had anaemia (45.6% vs. 20.2%; $p < 0.001$), hyponatraemia (17.7% vs. 4.3%; $p < 0.001$), white blood cell count over 10×10^9/L (55.3% vs. 13.7%; $p < 0.001$), troponin T elevation (85.3 vs. 32.7%; $p < 0.001$) and their serum glucose was significantly higher (9.8 ± 5.2 mmol/L vs. 6.6 ± 2.7 mmol/L; $p < 0.001$).

Table 4. Comparison of characteristics of patients with (n = 231) and patients without acute kidney injury (n = 13,330) following coronary angiography.

	AKI	No AKI	p-value
Age	70.2 ± 11.8	65.0 ± 10.9	< 0.001
Female sex	71 (30.7)	3,980 (29.9)	0.83
BMI > 30 kg/m^2	73 (32.4)	3,810 (28.8)	0.25
History of smoking	142 (61.5)	9,309 (69.8)	0.008
Diabetes	63 (27.3)	1,869 (14.0)	< 0.001
Hypertension	160 (69.3)	8,725 (65.5)	0.26
Ischaemic heart disease	105 (45.5)	5,766 (43.3)	0.55
History of PCI	41 (17.7)	3,212 (24.1)	0.03
History of CABG	35 (15.2)	1,174 (8.8)	0.001
Malignancy	24 (10.4)	1,043 (7.8)	0.19
CHF	41 (17.7)	793 (5.9)	< 0.001
COPD	27 (11.7)	479 (3.6)	< 0.001
Liver disease	1 (0.4)	128 (1.0)	0.73
Elixhauser Comorbidity Index score	66 (28.6)	1,876 (14.1)	< 0.001
eGFR, mL/min/1.73 m^{2a}			< 0.001
> 60	120 (51.9)	11,024 (82.7)	
45–60	43 (18.6)	1,611 (12.1)	
30–45	44 (19.0)	584 (4.4)	
15–30	18 (7.8)	96 (0.7)	
< 15	6 (2.6)	15 (0.1)	
Indication for CA:			
Cardiac arrest	28 (12.1)	160 (1.2)	< 0.001
STEMI	83 (35.5)	1,046 (7.8)	< 0.001
NSTEMI/UA	84 (36.4)	4,513 (33.9)	0.47
SA/UCP	9 (3.9)	6,030 (45.2)	< 0.001
Miscellaneous	28 (12.1)	1,581 (11.9)	0.98
Cardiogenic shock	33 (14.3)	178 (1.3)	< 0.001

Data are presented as number (%) or mean ± SD. AKI, acute kidney injury; BMI, body mass index; CABG, coronary artery bypass grafting; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; NSTEMI, non-ST-elevation myocardial infarction; PCI, percutaneous coronary intervention; STEMI, ST-elevation myocardial infarction; SA, stable angina; UA, unstable angina; UCP, unspecified chest pain.
[a]For more than 90 days before coronary angiography.

4.1.3 Intra-procedural information

During the CA, patients who later developed AKI received a significantly higher dose of intra-arterial contrast (160 mL [range: 37–627] vs. 100 [range: 10–880] mL; p < 0.001), femoral access was used more often (64.5% vs. 51.2%, p < 0.001), PCI was performed more often (61.5 vs. 40.7%; p <

0.001) than in patients without AKI and a higher proportion of patients with AKI were diagnosed with multi-vessel disease (more than one coronary artery affected, 61.0% vs. 35.7%; p < 0.001).

4.1.4 Risk factors for AKI

A multivariable analysis of risk factors for AKI is presented in **Table 5**. Higher baseline CKD stage, troponin T elevation, hyperglycaemia, WBC elevation, hyponatraemia and anaemia were independently associated with AKI. Compared with patients with stable angina or unspecified chest pain, patients with cardiac arrest, STEMI and NSTEMI or unstable angina had a greater risk of AKI and so did patients in the miscellaneous group. Furthermore, the contrast dose was found to be an independent risk factor for AKI (per 100 mL, odds ratio [OR] = 1.6, 95% CI: 1.3–1.9; p < 0.001). However, when CA with PCI was performed, the odds of AKI were lower in the adjusted model (OR = 0.6, 95% CI: 0.4–0.9). When only pre-procedural factors were analysed, pre-procedural treatment with RAS blockers was a significant risk factor for AKI (OR = 1.4, 95% CI: 1.0–1.9).

4.1.4.1 The association between contrast dose and AKI

There was a significant interaction between contrast dose and pre-procedural eGFR (p < 0.001). To examine the interaction between contrast dose and eGFR further, the cohort was divided into three subgroups according to baseline eGFR. Higher contrast dose increased the risk of AKI in all subgroups when assessed as a continuous variable (per 100 mL), but only in cases with eGFR < 45 mL/min/1.73 m^2 as a categorical variable (dose over 150 mL, OR = 5.3, 95% CI: 2.1–14.2; p < 0.001) (**Figure 10**).

Table 5. Multivariable analysis of patient- and procedure-related risk factors for acute kidney injury following coronary angiography.

	OR (95% CI)	p-value
Age, per 10 years	1.1 (1.0–1.3)	0.10
eGFR, compared with > 60 mL/min/1.73 m^2:		
45–60 mL/min/1.73 m^2[a]	1.7 (1.7–2.5)	0.01
30–45 mL/min/1.73 m^2[a]	3.8 (2.4–5.8)	< 0.001
< 30 mL/min/1.73 m^2[a]	8.6 (4.7–15.0)	< 0.001
Elixhauser Comorbidity Index score > 0	1.8 (1.3–2.5)	< 0.001
Renin-angiotensin system blockers	1.3 (1.0–1.8)	0.07
TNT elevation	2.7 (1.8–4.2)	< 0.001
Glucose, per mmol/L	1.1 (1.0–1.1)	< 0.001
WBCs > 10 × 10^9/L	2.8 (2.0–3.8)	< 0.001
Hyponatraemia[b]	1.7 (1.1–2.6)	0.008
Anaemia[c]	1.7 (1.3–2.4)	< 0.001
Cardiogenic shock[d]	2.4 (1.5–3.7)	< 0.001
Indication (compared with stable angina/unspecified chest pain):		
Cardiac arrest	14.4 (6.2–36.0)	< 0.001
STEMI	11.7 (5.6–27.0)	< 0.001
NSTEMI / UA	4.9 (2.5–10.9)	< 0.001
Miscellaneous	6.4 (3.0–14.8)	< 0.001
Contrast dose, per 100 mL	1.6 (1.3–1.9)	< 0.001
PCI	0.6 (0.4–0.9)	0.01

Hosmer–Lemeshow goodness-of-fit test: $X^2 = 4.0$, p = 0.85, C statistic = 0.905.
CI, confidence interval; eGFR, estimated glomerular filtration rate; NSTEMI, non-ST-elevation myocardial infarction; OR, odds ratio; PCI, percutaneous coronary intervention; STEMI, ST-elevation mocardial infarction; TNT, troponin T; UA, unstable angina; WBCs, white blood cells.
[a]For more than 90 days before coronary angiography.
[b]Defined as serum sodium < 136 mmol/L.
[c]Defined as haemoglobin level < 120 mg/dL in females and < 135 mg/dL in males.
[d]Defined as Killip class IV.

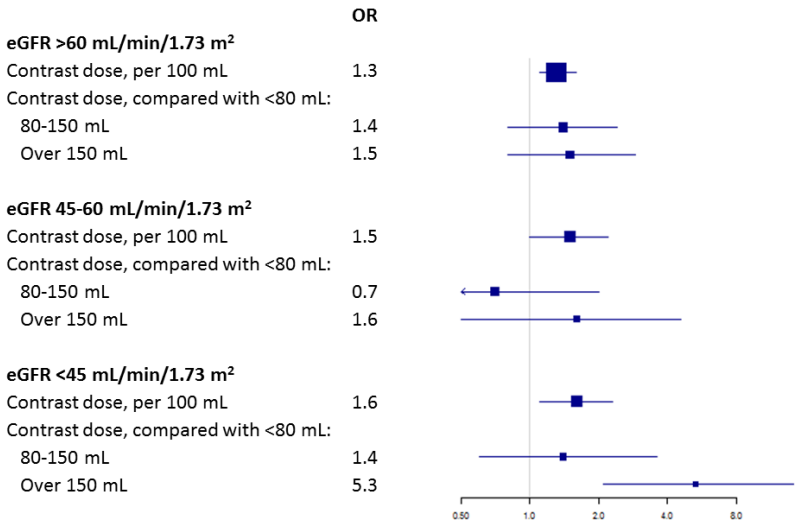

Figure 10. The association between contrast dose and AKI following coronary angiography according to baseline kidney function.
Factors used in adjusted models for CKD subgroups: age, Elixhauser Comorbidity Index score > 0, troponin T elevation and coronary intervention.
AKI, acute kidney injury; CI, confidence interval; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; OR, odds ratio.

4.1.5 Survival

Median follow-up time for the survival analysis was 4.2 years (range: 0.0–8.4 years). Thirty-day survival was 77.1% (178 of 231 patients) in the AKI group as compared with 98.9% (13,184 of 13,330 patients) in the non-AKI group ($p < 0.001$). The 1-year survival was 77.5%, 40.9% and 39.5% in patients with AKI stages 1, 2 and 3, respectively, as compared with 97.1% for the group without AKI ($p < 0.001$). When patients who died within 30 days of CA were excluded, the long-term survival of AKI cases remained worse than that of a propensity score-matched control group ($p = 0.006$) (**Figure 11**).

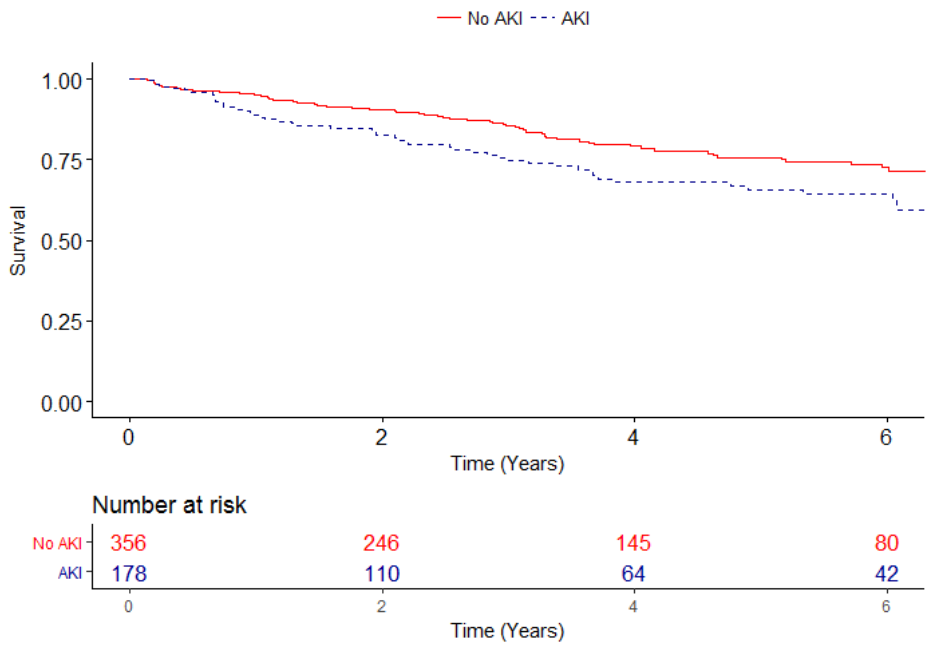

Figure 11. Survival of AKI patients following coronary angiography compared with that of a propensity score-matched control group (patients who died within 30 days excluded); $p = 0.006$.
AKI, acute kidney injury.

4.1.6 Incident chronic kidney disease or progression of pre-existing chronic kidney disease

During a median follow-up of 3.3 years (range: 0.1–8.4 years), 2,569 (20.8%) patients developed new-onset CKD and 1,041 (8.4%) had progression of pre-existing CKD. In multivariable Cox analysis, AKI increased the risk of both new-onset CKD (HR = 3.7, 95% CI: 2.7–5.0) and the progression of pre-existing CKD (HR = 2.0, 95% CI: 1.5–2.6). In the PSM analysis, AKI patients were more likely to develop incident CKD or worsening of prior CKD (61.1% vs. 39.5%; p < 0.001) (**Figure 12**).

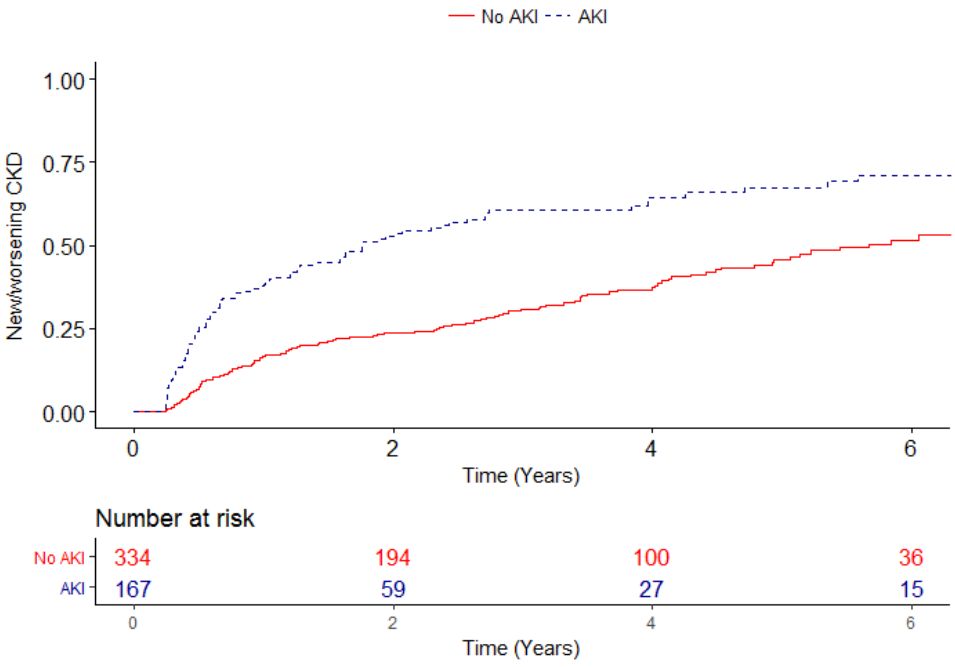

Figure 12. Incident CKD or progression of pre-existing CKD in AKI patients following coronary angiography compared with that of a propensity score-matched control group (p < 0.001).
AKI, acute kidney injury; CKD, chronic kidney disease.

4.2 Study II – AKI following coronary artery bypass grafting

4.2.1 Incidence of AKI

AKI occurred in 184 of 1,710 patients (10.8%) following CABG: 121 patients (7%) had stage 1 AKI, 27 (2%) had stage 2 AKI and 36 (2%) had stage 3 AKI. A decrease in incidence was seen from 2001 to 2013, with an incidence rate ratio of 0.95 annually ($p = 0.01$).

4.2.2 Baseline characteristics

Patients with AKI were on average older and more likely to have diabetes, a history of MI and pre-existing CKD. Furthermore, their preoperative haemoglobin was generally lower, they had higher NYHA score and EuroSCORE, and were more likely to require emergency surgery than patients who did not develop AKI (**Table 6**).

4.2.3 Perioperative course

During surgery, patients with AKI had longer CPB time (104 ± 50 min vs. 89 ± 31 min; $p < 0.001$) than patients without AKI, but the cross-clamp time (50 ± 23 min vs. 47 ± 17 min; $p = 0.25$) and the proportion of OPCAB surgery (20% vs. 21%; $p = 0.63$) were similar between the groups. Perioperatively, patients who developed AKI were transfused with more units of RBCs (6 ± 7 vs. 2 ± 3) than patients who did not, and they bled on average approximately 400 mL more during the first 24 postoperative hours (1,341 ± 2,478 mL vs. 942 ± 636 mL; $p = 0.002$).

Table 6. Baseline characteristics of patients with (n = 184) and patients without (n = 1,526) acute kidney injury following coronary artery bypass grafting.

	AKI	No AKI	p-value
Age, years	69 ± 10	66 ± 9	< 0.001
BMI, kg/m^2	29 ± 5	28 ± 4	0.057
Diabetes	45 (25)	225 (15)	0.001
Statin use	144 (81)	1139 (78)	0.39
History of myocardial infarction	52 (29)	331(22)	0.048
Preoperative CCS score			0.023
0	0 (0)	11 (1)	
1	6 (3)	77 (5)	
2	22 (12)	302 (20)	
3	61 (33)	487 (32)	
4	94 (51)	629 (42)	
Preoperative LVEF, %	55 ± 12	55 ± 10	0.87
Preoperative NYHA score			0.003
0	10 (7)	175 (14)	
1	8 (5)	90 (7)	
2	27 (18)	336 (27)	
3	62 (42)	411 (33)	
4	40 (27)	249 (20)	
Preoperative SCr, µmol/L	95 ± 39	90 ± 25	0.42
Preoperative eGFR, mL/min/1.73 m^2	72 ± 23	83 ± 18	< 0.001
Preoperative eGFR, mL/min/1.73 m^2			< 0.001
> 60	124 (67)	1350 (88)	
45–59	32 (17)	122 (8)	
30–44	19 (10)	43 (3)	
15–29	8 (4)	9 (1)	
< 15	1 (1)	2 (0)	
COPD	14 (8)	106 (7)	0.65
Preoperative haemoglobin, g/L	135 ± 16	142 ± 14	< 0.001
Emergency surgery	19 (10)	61 (4)	< 0.001
Preoperative myocardial infarction	61 (33)	405 (27)	0.066
Preoperative heart failure	38 (21)	193 (13)	0.004
EuroSCORE	6 ± 4	5 ± 3	< 0.001

Data are presented as number (%) or mean ± standard deviation.
AKI, acute kidney injury; BMI, body mass index; CABG, coronary artery bypass grafting; CCS, Canadian Cardiovascular Society; EuroSCORE, European System for Cardiac Operative Risk Evaluation; IHD, ischaemic heart disease; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; SCr, serum creatinine.

Table 7. Short-term complications of patients with (n = 184) and patients without (n = 1,526) acute kidney injury following coronary artery bypass grafting.

	AKI	No AKI	p-value
Major complication	39 (21)	144 (10)	< 0.001
Stroke	1 (1)	8 (1)	1
Mediastinitis	2 (1)	15 (1)	0.7
Myocardial infarction[a]	16 (9)	66 (4)	0.016
Reoperation due to bleeding	23 (13)	95 (6)	0.003
Sternum dehiscence	5 (3)	21 (1)	0.19
ARDS or MOF	18 (10)	35 (2)	< 0.001
Minor complication	111 (60)	723 (48)	0.001
Atrial fibrillation	97 (53)	574 (38)	0.001
Leg wound infection	20 (11)	159 (10)	0.8
Urinary tract infection	9 (5)	50 (3)	0.28
Pleural effusion	31 (17)	160 (11)	0.013
Pneumonia	19 (10)	94 (6)	0.04
ICU stay, days	3 ± 6	2 ± 3	< 0.001
30-day mortality	16 (9)	24 (2)	< 0.001

Data are presented as number (%) or mean ± standard deviation.
AKI, acute kidney injury; ARDS, acute respiratory distress syndrome; CABG, coronary artery bypass grafting; ICU, intensive care unit; MOF, multiple organ failure.
[a]Defined as isolated ST-segment changes or a new left bundle branch block on electrocardiogram along with an elevation in creatine kinase MB of ≥ 70 µg/L).

4.2.4 Short-term complications and operative mortality

Postoperatively, 19 patients with AKI (10%) required RRT. A comparison of short-term complications of patients with and without AKI is given in **Table 7**. The rate of major complications was higher in patients with AKI than in those without AKI, including perioperative MI and they more often required reoperation for excessive bleeding. AKI patients were also more likely to experience minor complications such as new-onset postoperative atrial fibrillation and pleural effusion that required drainage. Furthermore, their operative mortality was 9%, as compared with 2% in patients without AKI, and they stayed on average one day longer in the ICU.

4.2.5 Risk factors for AKI

In multivariable analysis, BMI (OR = 1.04, 95% CI: 1.00–1.08), diabetes (OR = 1.66, 95% CI: 1.11–2.47), preoperative eGFR (OR = 0.97, 95% CI: 0.96–0.98), EuroSCORE (OR = 1.11, 95% CI: 1.06–1.16) and perioperative RBC transfusions (OR = 1.23, 95% CI: 1.16–1.31) were found to be independent risk factors for AKI.

4.2.6 Development of chronic kidney disease

Following surgery, 33% of AKI patients developed CKD as compared with 19% of those without AKI ($p < 0.001$). In multivariable analysis, AKI was found to be an independent risk factor for the development of CKD (HR = 2.08, 95% CI: 1.49–2.90), but not ESRD (HR = 2.74, 95% CI: 0.28–26.46), over a follow-up period of 62 ± 47 months.

4.2.7 Survival

Survival was inversely related to the severity of AKI, the 10-year survival of patients without AKI being 76%, with survival of AKI stages 1, 2 and 3 being 63%, 56% and 49%, respectively. When the stages of AKI were analysed further, only stage 3 AKI patients had significantly lower unadjusted survival than patients without AKI ($p < 0.001$).

To study the effect of other major complications on the association between AKI and survival, patients were categorised into four groups: (1) patients with AKI and other major complications; (2) patients with AKI but with no major complications; (3) patients without AKI but with major complications; and (4) patients without AKI and with no major complications (**Figure 13**). Patients with major complications had worse survival, but there was a significant difference in long-term survival between AKI patients without major complications and patients without AKI and with no major complications in unadjusted analysis ($p < 0.001$). After adjustment for age, EuroSCORE and diabetes, patients with AKI and other major complications (OR = 30.3, 95% CI: 9.1–105.8) and patients without AKI but with other major complications (OR = 11.6, 95% CI: 4.2–34.9) had an increased risk of 30-day mortality compared with those without AKI and without any major complications, while the risk in patients with AKI but with no other major complications did not reach statistical significance (OR = 3.4, 95% CI: 0.8–13.3). In a Cox model for survival analysis of all four groups, the proportional hazards assumption was not met and therefore Cox models including only patients with no major complications were constructed. When the follow-up time was limited to 5

years, AKI with no major complications was not associated with inferior survival compared with patients without AKI and with no major complications (**Table 8**), but when the entire follow-up time was included, then AKI proved to be a significant predictor of worse survival (**Table 9**).

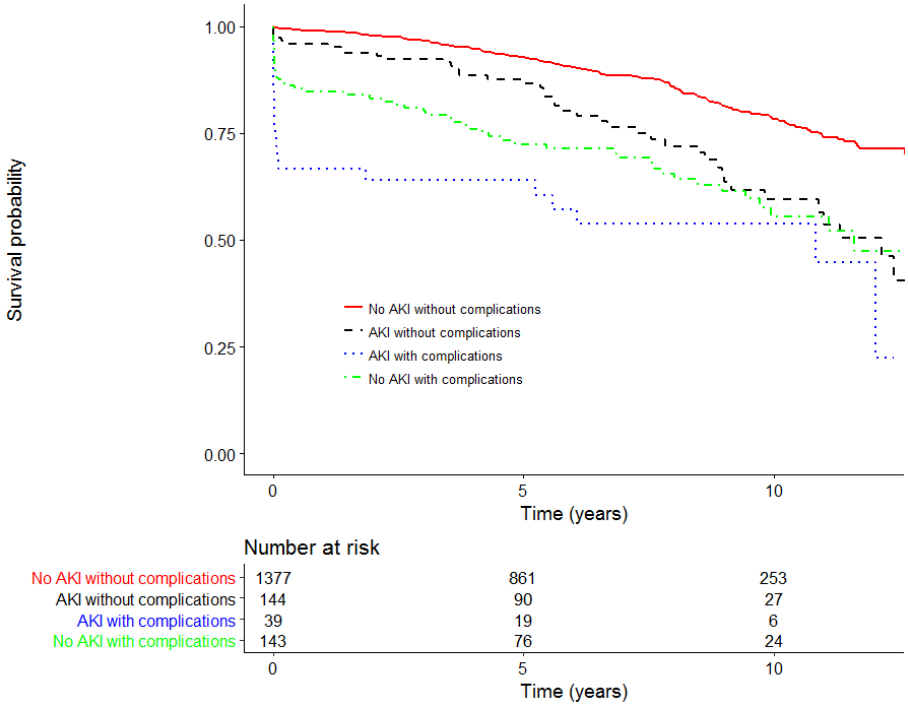

Figure 13. Long-term survival of patients with and patients without AKI following coronary artery bypass grafting, categorised on the basis of whether or not they developed other major complications.
AKI, acute kidney injury.

Table 8. Multivariable Cox analysis for predictors of 5-year survival in patients with no major complications.

	HR (95% CI)	p-value
Age	1.0 (1.0–1.0)	0.37
BMI > 30 kg/m^2	0.8 (0.5–1.3)	0.40
Diabetes	1.9 (1.2–3.0)	0.008
Preoperative eGFR < 60 mL/min/1.73 m^2	1.1 (0.6–1.9)	0.79
History of heart failure	1.8 (1.1–3.0)	0.020
Hypertension	0.9 (0.6–1.4)	0.72
EuroSCORE	1.2 (1.1–1.3)	< 0.001
AKI without major complications	1.4 (0.8–2.4)	0.25

AKI, acute kidney injury; BMI, body mass index; CI, confidence interval; eGFR, estimated glomerular filtration rate; EuroSCORE, European System for Cardiac Operative Risk Evaluation; HR, hazard ratio.

Table 9. Multivariable Cox analysis for predictors of long-term survival in patients with no major complications.

	HR (95% CI)	p-value
Age	1.0 (1.0–1.0)	0.032
BMI > 30 kg/m^2	0.9 (0.7–1.2)	0.57
Diabetes	1.8 (1.3–2.5)	< 0.001
Preoperative eGFR < 60 mL/min/1.73 m^2	1.2 (0.8–1.8)	0.33
History of heart failure	1.5 (1.1–2.1)	0.016
Hypertension	0.9 (0.7–1.2)	0.59
EuroSCORE	1.2 (1.1–1.2)	< 0.001
AKI without major complications	1.6 (1.1–2.2)	0.015

AKI, acute kidney injury; BMI, body mass index; CI, confidence interval; eGFR, estimated glomerular filtration rate; EuroSCORE, European System for Cardiac Operative Risk Evaluation; HR, hazard ratio.

4.3 Study III – AKI following aortic valve replacement

4.3.1 Incidence

AKI, as defined by the RIFLE criteria, occurred in 82 patients (22.5%) following SAVR, where 40 patients (11.0%), 28 patients (7.7%) and 14 patients (3.8%) were classified as Risk, Injury and Failure, respectively. The incidence ranged from 10% to 36% but did not change significantly over the study period ($p = 0.44$).

4.3.2 Baseline characteristics and perioperative data

Baseline characteristics and perioperative data of patients with and without AKI are compared in **Table 10**. Patients with AKI were four years older on average; were more likely to be female; had a significantly higher BMI; more often had CKD, a history of diabetes and MI; and had a lower preoperative haemoglobin value than patients without AKI. Preoperatively, AKI patients were more likely to have severe heart failure symptoms according to the NYHA classification. Patients who developed AKI had longer CPB and cross-clamp times during surgery and more often required intra-aortic balloon pump (IABP). While a stentless biological valve was the most common prosthesis implanted in patients, both with and without AKI, there were no significant differences in valve types between the groups. Although patients who underwent SAVR with concomitant CABG had longer CPB time than those who underwent isolated SAVR (181 min vs. 136 min; $p < 0.001$), there was no difference in the incidence of AKI between the groups. Patients who developed postoperative AKI received on average eight more units of RBCs perioperatively than those without AKI and their blood loss at 24 hours after surgery was on average 260 mL more than in patients who did not experience AKI (**Table 10**).

4.3.3 Risk factors for AKI

In multivariable analysis, transfusion of RBCs (OR = 1.64, 95% CI: 1.33–2.07, per 5 units), a prolonged CPB time (OR = 1.10, 95% CI: 1.04–1.16, per 10 min) and obesity (BMI > 30 kg/m^2) (OR = 2.71, 95% CI: 1.41–5.22) were found to be independent predictors of AKI (**Table 11**).

Table 10. Comparison of patient characteristics and perioperative data for patients with (n = 82) and patients without (n = 283) acute kidney injury following surgical aortic valve replacement.

Factor	AKI	No AKI	p-value
Male sex	42 (51.2)	188 (66.4)	0.017
Age, years	74.2 ± 7.7	70.3 ± 10.0	< 0.001
BMI, kg/m^2	29.1 ± 5.9	27.2 ± 3.9	0.010
Diabetes mellitus	20 (24.4)	34 (12.0)	0.010
Hypertension	65 (79.2)	189 (66.8)	0.043
Dyslipidemia	38 (45.8)	117 (41.5)	0.51
History of smoking	44 (53.7)	189 (66.8)	0.041
History of myocardial infarction	19 (23.1)	29 (10.3)	0.005
Chronic heart failure	29 (35.4)	49 (17.4)	0.001
Preoperative eGFR < 60 mL/min/1.73 m^2	37 (45.1)	72 (25.4)	0.001
Preoperative SCr, µmol/L	97.9 ± 27.3	93.4 ± 44.1	0.25
Preoperative Hb, g/L	131.9 ± 15.1	138.6 ± 13.2	< 0.001
Preoperative anaemia[a]	29 (35.4)	65 (23.8)	0.034
NYHA III/IV	61 (74.4)	159 (56.2)	0.005
Logistic EuroSCORE	14.1 ± 15.4	8.3 ± 10.2	0.001
LVEF, %	55 ± 9	57 ± 8.6	0.15
Acute surgery	1 (1.2)	4 (1.4)	0.86
Urgent surgery	17 (20.7)	23 (8.1)	0.003
IABP	15 (18.3)	8 (2.8)	< 0.001
CABG	49 (59.8)	150 (53.0)	0.34
Cross-clamp time, min	135 ± 40	111 ± 31	< 0.001
CPB time, min	191 ± 58	151 ± 46	< 0.001
Stented biological valve	28 (34.1)	86 (30.4)	0.61
Stentless biological valve	46 (56.1)	138 (48.8)	0.30
Mechanical valve	8 (9.8)	59 (20.8)	0.034
Lowest intraoperative temperature, °C	34.5 ± 1.0	34.6 ± 0.9	0.20
Bleeding in the first 24 hours, mL	1,320 ± 1,064	1,060 ± 771	0.041
Transfusions of RBCs, units	13.4 ± 11.1	5.5 ± 5.6	< 0.001

Data are number (%) or mean ± standard deviation. AKI, acute kidney injury; BMI, body mass index; CABG, coronary artery bypass grafting; CPB, cardiopulmonary bypass; EuroSCORE; European System for Cardiac Operative Risk Evaluation; IABP, intra-aortic balloon pump; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; RBCs, red blood cells; SAVR, surgical aortic valve replacement. [a]Defined as Hg < 120 g/L in females and < 135 g/L in males.

Table 11. Multivariable analysis of risk factors for acute kidney injury after surgical aortic valve replacement (n = 365).

Factor	OR (95% CI)	p-value
RBC transfusions, per 5 units	1.64 (1.33–2.07)	< 0.001
CPB time, per 10 min	1.10 (1.04–1.16)	0.002
Obesity (BMI > 30 kg/m^2)	2.71 (1.41–5.22)	0.003
Perioperative treatment with IABP	2.43 (0.81–7.53)	0.11
Preoperative anaemia[a]	1.11 (0.58–2.16)	0.76
History of hypertension	1.74 (0.90–3.53)	0.11
Female	1.56 (0.85–2.87)	0.15
Preoperative eGFR < 60 mL/min/1.73 m^2	1.30 (0.69–2.42)	0.42
Age, per year	1.03 (1.00–1.08)	0.10

Hosmer–Lemeshow goodness-of-fit test: $X^2 = 6.17$, p = 0.63.
AKI, acute kidney injury; BMI, body mass index; CBP, cardiopulmonary bypass; CI, confidence interval; IABP, intra-aortic balloon pump; OR, odds ratio; RBC, red blood cell; SAVR, aortic valve replacement.
[a]Defined as Hg < 120 g/L in females and < 135 g/L in males.

4.3.4 Postoperative complications

Patients who developed AKI were more likely than patients without AKI to develop other complications following surgery, including major complications such as bleeding requiring reoperation, MI, sternal dehiscence and ARDS or MOF. Furthermore, a higher proportion of AKI patients had minor complications, including pneumonia, urinary tract infection and pleural effusion that required drainage, but the rate of new-onset atrial fibrillation was similar in both groups (**Table 12**).

Fifteen patients (4.1%) required transient RRT following the SAVR. Fourteen of these patients received continuous RRT in the ICU. Three patients (0.8%) needed RRT for more than four weeks after surgery, including one patient who developed ESRD (0.27%).

Table 12. Short-term outcome of patients with (n = 82) and patients without (n = 283) acute kidney injury following surgical aortic valve replacement.

Factor	AKI	No AKI	p-value
Major complications	53 (64.6)	63 (22.3)	< 0.001
Myocardial infarction[a]	24 (29.3)	25 (8.8)	< 0.001
Sternal dehiscence	4 (4.9)	3 (1.1)	0.048
Stroke	2 (2.4)	6 (2.1)	1.00
Deep sternal infection	1 (1.2)	3 (1.1)	1.00
Reoperation for bleeding	23 (28.0)	31 (11.0)	< 0.001
ARDS or MOF	34 (41.0)	4 (1.4)	< 0.001
Minor complications	69 (84.1)	171 (60.4)	< 0.001
Superficial wound	11 (13.4)	19 (6.7)	0.086
Atrial fibrillation	46 (78.0)	144 (65.2)	0.086
Pleural effusion	24 (29.3)	25 (8.8)	< 0.001
Pneumonia	24 (29.3)	16 (5.7)	< 0.001
Urinary tract infection	28 (34.1)	11 (3.9)	< 0.001
TIA	2 (2.4)	5 (1.8)	0.66
ICU stay, days	6 (1–80)	1 (0–15)	< 0.001
Surgical ward, days	13 (0–127)	9 (0–41)	< 0.001
30-day mortality	15 (18.1)	6 (2.1)	< 0.001

Data are number (%) or median (range).
ARDS, acute respiratory distress syndrome; MOF, multiple organ failure; TIA, transient ischaemic attack; ICU, intensive care unit.
[a]Defined as isolated ST-segment changes or a new left bundle branch block on electrocardiogram along with an elevation in creatine kinase MB of ≥ 70 µg/L.

4.3.5 Survival

Thirty-day mortality was 18% in patients with AKI as compared with 2% in those without AKI ($p < 0.001$). It was 10%, 32% and 14% in the Risk, Injury and Failure groups, respectively.

In multivariable analysis, AKI proved to be an independent predictor of operative mortality (OR = 5.89, 95% CI: 1.99–18.91) after adjustment for EuroSCORE, CPB time and number of RBC transfusions. Patients who developed AKI had significantly lower unadjusted 5-year survival than non-AKI patients: 66% vs. 87% ($p < 0.001$) (**Figure 14**), with the 5-year survival being 70.6%, 60.5% and 63.5% in the Risk, Injury and Failure groups, respectively. In multivariable Cox analysis, AKI was not found to be a significant predictor of long-term survival (HR = 1.44, 95% CI: 0.86–2.42). The association between AKI and survival remained insignificant when patients who died within seven days of surgery were excluded from the analysis (HR = 1.72, 95% CI: 0.99–2.99).

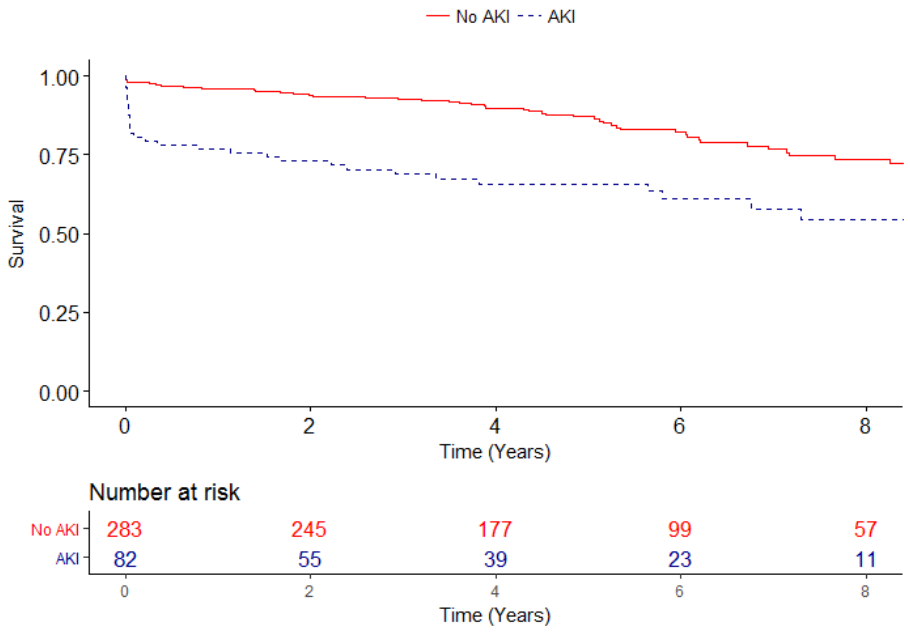

Figure 14. Overall survival of patients with and patients without AKI following surgical aortic valve replacement ($p < 0.001$).
AKI, acute kidney injury.

4.4 Study IV – AKI following acute type A aortic dissection repair

4.4.1 Incidence

Altogether, 382 patients (40.6%) developed AKI postoperatively, with 138 (14.7%), 100 (10.6%) and 144 (15.3%) within the Risk, Injury and Failure categories, respectively. The annual incidence of AKI did not change significantly during the period 2005–2014, ranging from 30.1% to 46.6% (p = 0.11).

4.4.2 Baseline characteristics

Baseline characteristics of patients with and without AKI are shown in **Table 13**. Patients who developed postoperative AKI were significantly older and had a higher BMI, a lower preoperative eGFR and were more likely to have a history of hypertension. Patients with AKI were also more frequently on antihypertensive treatment, including RAS blockers, and on anticoagulation before surgery.

Sudden chest pain was the most common clinical presentation in patients with and patients without AKI. Upon arrival at the hospital, patients who subsequently developed AKI were more likely to present with dissection involving both the ascending and the descending aorta and more often presented with cardiac tamponade. Patients with AKI were more likely than patients without AKI to have malperfusion syndrome, including renal hypoperfusion, and also had a more severe Penn class. There was no significant difference between initial systolic blood pressure measurements between the groups and the proportion of patients with hypotensive shock upon arrival was similar (**Table 14**)**.**

Time from onset of symptoms to surgery was shorter in patients with AKI, but the time from diagnosis to surgery was similar between the groups. Patients with AKI had a longer duration of CPB, and longer aortic cross-clamp and hypothermic circulatory arrest (HCA) times (**Table 15**). The median number of RBC units transfused perioperatively to patients who subsequently developed AKI was significantly higher than in patients who did not experience AKI (**Table 15**)**.**

Table 13. Baseline characteristics of patients with (n = 382) and patients without (n = 559) acute kidney injury following acute type A aortic dissection repair.

Factor	AKI	No AKI	p-value
Age	63.1 ± 10.6	60.3 ± 12.7	< 0.001
Male sex	268 (70.2)	363 (64.9)	0.11
BMI kg/m^2	27.6 ± 5.1	26.1 ± 4.5	< 0.001
History of smoking	129 (35.1)	181 (34.5)	0.91
History of hypertension	224 (58.6)	267 (47.8)	0.001
Diabetes	10 (2.6)	10 (1.8)	0.53
Hyperlipidemia	47 (12.4)	64 (11.5)	0.75
Preoperative eGFR (mL/min/1.73 m^2)	71.9 ± 24.4	74.9 ± 21.9	0.05
Preoperative eGFR (mL/min/1.73 m^2):			0.29
> 60	264 (69.1)	407 (72.8)	
45–60	71 (18.6)	102 (18.2)	
30–45	34 (8.9)	40 (7.2)	
< 30	13 (3.4)	10 (1.8)	
Stroke	17 (4.4)	21 (3.8)	0.71
COPD	23 (6.1)	30 (5.4)	0.77
Coronary artery disease	20 (5.3)	16 (2.9)	0.089
TAA	40 (10.5)	53 (9.5)	0.69
Bicuspid valve	23 (6.1)	35 (6.3)	1.00
Connective tissue disease	12 (3.2)	34 (6.1)	0.059
Aspirin	111 (29.3)	146 (26.4)	0.37
Warfarin	40 (10.6)	28 (5.1)	0.002
Antihypertensives	187 (50.5)	227 (41.4)	0.008
RAS blockers	75 (26.3)	82 (18.2)	0.012

Data presented are number (%) or mean ± standard deviation.

AKI, acute kidney injury; ATAAD, acute type A aortic dissection; BMI, body mass index; eGFR, estimated glomerular filtration rate; COPD, chronic obstructive pulmonary disease; RAS, renin-angiotensin system; TAA, thoracic aortic aneurysm.

Table 14. Clinical presentation of patients with (n = 382) and patients without (n = 559) acute kidney injury following acute type A aortic dissection repair.

	AKI	No AKI	p-value
Sudden pain	315 (83.1)	483 (86.7)	0.15
Hypotensive shock	78 (22.2)	116 (21.6)	0.90
Systolic blood pressure	124.4 ± 39.1	123.4 ± 36.4	0.72
Diastolic blood pressure	71.8 ± 22.8	69.8 ± 21.1	0.27
Preoperative cardiac arrest	21 (5.5)	16 (2.9)	0.060
Cardiac tamponade	73 (19.6)	71 (12.9)	0.008
Descending aorta involved	299 (79.1)	400 (71.7)	0.013
Penn class[a]:			< 0.001
Aa	200 (52.9)	391 (70.5)	
Ab	107 (28.3)	99 (17.8)	
Ac	49 (13.0)	47 (8.5)	
Abc	22 (5.8)	18 (3.2)	
Intramural haematoma	26 (7.0)	50 (9.0)	0.53
Malperfusion syndrome (any):	132 (34.8)	117 (21.1)	< 0.001
Cardiac malperfusion	30 (8.9)	33 (6.8)	0.33
Cerebral malperfusion	31 (9.2)	41 (8.5)	0.83
Renal malperfusion	29 (8.6)	13 (2.7)	< 0.001
Gastrointestinal malperfusion	13 (3.9)	12 (2.5)	0.35
Peripheral malperfusion	27 (8.0)	33 (6.8)	0.60
Spinal malperfusion	12 (3.6)	10 (2.1)	0.27

Data presented are number (%) or mean ± standard deviation. AKI, acute kidney injury; ATAAD, acute type A aortic dissection.

[a]Aa, no organ ischaemia; Ab, localised ischaemia; Ac, generalised ischaemia; Abc, localised and generalised ischaemia together.

4.4.3 Risk factors for AKI

In a risk model that included both patient-related and perioperative factors, age (per 10 years, OR = 1.3, 95% CI: 1.1–1.5), BMI > 30 kg/m^2 (OR = 2.4, 95% CI: 1.6–3.5), malperfusion (Penn classes Ab, Ac, or Abc, OR = 1.7, 95% CI: 1.2–2.3), CPB time (per 10 minutes, OR = 1.04, 95% CI: 1.01–1.06) and RBC transfusion (OR = 1.1 for each unit transfused, 95% CI: 1.1–1.1) were found to be independent risk factors for AKI.

Table 15. Intraoperative data on patients with (n = 382) and patients without (n = 559) acute kidney injury following acute type A aortic dissection repair.

	AKI	No AKI	p-value
Proximal surgical technique:			0.38
Supracoronary graft	277 (72.5)	405 (72.6)	
Supracoronary graft + aortic valve replacement	14 (3.7)	16 (2.9)	
Bentall procedure	91 (23.8)	137 (24.5)	
Distal surgical technique:			0.32
Ascending aorta	265 (69.7)	416 (75.2)	
Hemiarch procedure	85 (22.4)	108 (19.5)	
Arch procedure	28 (7.4)	26 (4.7)	
Time from first symptoms to surgery, hours	6 (4–10)	7 (5–19)	0.002
Time from diagnosis to surgery, hours	3 (2–3.5)	3 (2–4)	0.061
Operative time (skin to skin, minutes)	405 ± 146	334 ± 96	< 0.001
CPB time, minutes	223 ± 85	190 ± 59	< 0.001
Cross-clamp time, minutes	112 ± 62	101 ± 48	0.008
HCA time, minutes	31 ± 20	28 ± 14	0.036
Lowest temperature, °C	21.3 ± 4.8	21.0 ± 4.9	0.38
Moderate hypothermia[a]	174 (49.8)	199 (39.7)	0.004
Deep hypothermia[b]	162 (46.4)	273 (54.5)	0.025
Re-sternotomy	20 (6.0)	5 (1.1)	< 0.001
RBC transfusion, units	9 (4–17)	4 (2–8)	< 0.001

Data presented are number (%), mean ± standard deviation, or median (interquartile range).
AKI, acute kidney injury; ATAAD, acute type A aortic dissection; CPB, cardiopulmonary bypass; HCA, hypothermic circulatory arrest; RBC, red blood cell.
[a] 20–32°C
[b] < 20°C.

4.4.4 Early postoperative complications

Fifty-nine percent of patients with AKI experienced another major complication, as compared with 33% of patients without AKI (p < 0.001) (**Table 16**). Furthermore, 105 patients with AKI (28%) required RRT, either continuous RRT (n = 70), intermittent haemodialysis (n = 17), or both (n = 18). Four patients who did not meet the criteria for AKI within the first seven postoperative days ultimately required RRT during their hospital admission.

Table 16. Postoperative outcomes in patients with (n = 382) and patients without (n = 559) acute kidney injury following acute type A aortic dissection repair.

Factor	AKI	No AKI	p-value
Any major complication	224 (59.1)	186 (33.4)	< 0.001
Reoperation for bleeding	108 (28.3)	85 (15.3)	< 0.001
Other reoperation	23 (6.0)	17 (3.1)	0.042
Perioperative myocardial infarction[a]	40 (10.5)	22 (4.0)	< 0.001
Stroke (n = 934)	105 (27.7)	88 (15.9)	< 0.001
Deep sternal wound infection	12 (3.2)	10 (1.8)	0.26
Respiratory failure[b]	75 (19.7)	14 (2.5)	< 0.001
Dialysis	105 (27.5)	4 (0.7)	< 0.001
Coma[c]	63 (18.5)	28 (5.6)	< 0.001
Pneumonia	101 (26.6)	62 (11.2)	< 0.001
Sepsis	64 (16.8)	37 (6.7)	< 0.001
Acute limb ischaemia	22 (5.8)	16 (2.9)	0.041
Tamponade	74 (19.4)	69 (12.4)	0.005
New-onset atrial fibrillation	180 (48.0)	207 (37.4)	0.002
Ventilatory support > 48 h	209 (55.9)	108 (19.6)	< 0.001
Length of ICU stay, days	7 (1–134)	4(0–28)	< 0.001
30-day mortality	65 (17.0%)	37 (6.6%)	< 0.001

Data presented are number (%) or median (range).
AKI, acute kidney injury; ATAAD, acute type A aortic dissection; ICU, intensive care unit.
[a]Defined as creatine kinase MB ≥ 70 µg/L and new Q wave or left bundle branch block on EKG.
[b]Defined as respiratory failure requiring a tracheostomy.
[c]Defined as coma lasting more than 24 hours and not attributable to sedation.

4.4.5 Survival

Thirty-day mortality was 17.0% (65 of 382) in the AKI group as compared with 6.6% (37 of 558) in the non-AKI group ($p < 0.001$). Long-term survival was worse in the AKI group than in the non-AKI group, including one-year survival (76.5% vs. 91.5%), three-year survival (72.9% vs. 86.8%) and five-year survival (69.4% vs. 83.6 %; $p < 0.001$). In landmark analysis, when patients who died within 30 days were excluded from the survival analysis, the patients with AKI still had inferior long-term survival (**Figure 15**). Furthermore, after adjustment for age, sex, preoperative eGFR, history of hypertension and preoperative treatment with RAS blockers, AKI proved to be an independent predictor of all-cause mortality in 30-day survivors (HR = 2.0, 95% CI: 1.3–3.0) together with advanced age (per 10 years, HR = 1.9, 95% CI: 1.5–2.3). Treatment with RAS blockers before surgery was associated with more favourable long-term survival (HR = 0.4, 95% CI: 0.2–0.7).

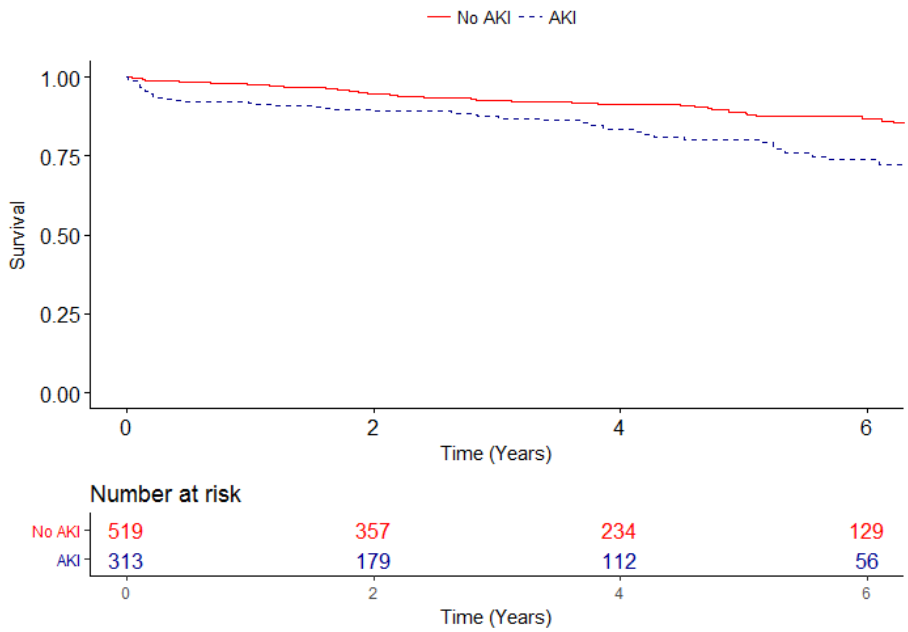

Figure 15. Long-term survival of patients with and patients without AKI following surgery for acute type A aortic dissection. Patients who died within 30 days were excluded (n = 839; p = 0.006).
AKI, acute kidney injury.

5 Discussion

The studies presented in this thesis underscore the fact that AKI is a serious complication following various cardiovascular procedures. As might be expected, the incidence and severity of AKI are dependent on the complexity of the procedure and the severity of the underlying disease, with the incidence ranging from 1.7% following CA to 41% following ATAAD repair. Furthermore, the development of post-procedural AKI was found to be affected by patient-related factors, including advanced age, obesity and malperfusion as well as procedure-related factors such as the length of CPB and the number of RBC transfusions. In addition, intra-arterial contrast appears to increase the risk of AKI in patients with pre-procedural advanced CKD when administered in high doses. Finally, AKI is associated with other postoperative complications, less favourable short-term and long-term survival, and the development and progression of CKD.

5.1 Definition of AKI

In studies I and II, the KDIGO criteria were used to define AKI, but in studies III and IV the RIFLE criteria were used. When studies III and IV were designed and data collection started, the RIFLE criteria were chosen to define AKI. As for study III, the KDIGO criteria had not been published and the RIFLE criteria were chosen over the AKIN criteria. SCr measurements within 48 hours, which are used in the KDIGO definition of AKI, were therefore not registered in the datasets used in studies III and IV. The KDIGO criteria and the RIFLE criteria differ in sensitivity, since the former include a minor elevation in SCr of > 26.5 µmol/L, which has been associated with increased mortality (Lassnigg et al., 2004). Thus, the use of the RIFLE criteria in studies III and IV may possibly have led to underestimation of the incidence of AKI compared with studies I and II. This is because patients with the mildest form of AKI according to the KDIGO criteria are not defined as AKI patients in the RIFLE criteria unless an SCr elevation of > 26.5 µmol/L is equal to an elevation of > 50% of baseline SCr. Even so, both criteria have been widely used and validated, and are good predictors of short-term mortality (Bastin et al., 2013; Fujii et al., 2014; Luo et al., 2014).

Importantly, the urine output criteria of RIFLE and KDIGO were not used in any of the studies, leading to underestimation of the incidence of AKI in all studies. Despite the fact that more AKI patients would have been identified by

including the urine output criteria, they do not predict adverse outcome as strongly as the SCr criteria (Md Ralib et al., 2013).

5.2 Incidence

The incidence of AKI was 1.7%, 10.8%, 22.5% and 40.6% following CA, CABG, SAVR and ATAAD repair, respectively. The wide range of incidence between procedures can be explained by differences in the extent and complexity of the procedures, ranging from minimally invasive CA and PCI to complex surgery, such as repair of the proximal aorta in ATAAD. Notably, the severity of the patients' pre-procedural condition varies, ranging from a stable condition to a life-threatening state. Patients undergoing elective CA are usually stable, while those with STEMI may suffer from cardiogenic shock. CABG is most often performed in stable patients—with only 5% of surgeries in the present study being emergency operations, and SAVR is almost always performed as an elective procedure. On the other side of the spectrum, ATAAD repair is almost always performed on patients who are in a critical condition and are haemodynamically unstable. Although the incidence of AKI following SAVR and ATAAD repair is higher than following CABG, the incidence is underestimated due to the use of the less sensitive RIFLE criteria.

5.2.1 Incidence of AKI following coronary angiography

The incidence of AKI following CA was 1.7%. This is low compared with previously reported rates, which have ranged from 2% to 25% (Solomon & Dauerman, 2010). Different criteria have been used to define AKI following CA, but in study I the sensitive KDIGO criteria were chosen in order to minimise underestimation of AKI (Kidney Disease Improving Global Outcomes: (KDIGO) Acute Kidney Injury Work Group, 2012). In study I, both elective angiography and emergency procedures were included, in contrast to several other studies which have only included patients with ACS or procedures in which PCI was performed (Chong et al., 2010). This may have contributed to the relatively low incidence of AKI in study I. When only PCI procedures were analysed, the incidence was 2.5%—as opposed to 7% in a study by Amin et al. that included more than 1.3 million patients (Amin et al., 2017). Furthermore, the assumption that patients with missing post-procedural SCr did not develop AKI may have led to underestimation of the true incidence of AKI. When all cases without post-procedural SCr were excluded, the incidence of AKI was 3.7%, which, although undoubtedly being an overestimation of the true incidence, would still be considered low

compared with studies involving similar cohorts (James et al., 2011). Compared with patients who underwent CA in Sweden, more CAs were performed in Iceland per capita in 2007. Furthermore, in Iceland more patients had stable angina as an indication for CA whereas NSTEMI and STEMI were more common in Sweden (Gudnason et al., 2013). This suggests that the low incidence of AKI in study I can be partially explained by the fact that the CA cohort in Iceland was composed of patients with less severe CAD than in some other cohorts.

5.2.2 Incidence of AKI following coronary artery bypass grafting

As in study I, the incidence of AKI following CABG was in the lower range of the reported incidence in comparable studies, despite the use of the sensitive KDIGO criteria to define AKI. Furthermore, the incidence of AKI decreased significantly over the study period. In a study by Brown et al., 12% of patients had a > 50% increase in SCr following CABG (Brown et al., 2006). In addition, a population-based study on patients undergoing CABG in Sweden found an incidence of 13% and Li et al. reported an incidence of 20%, both studies using the AKIN criteria and only including patients undergoing non-emergency CABG as opposed to both elective and emergency CABG in study II (Li et al., 2011; Ryden et al., 2014). Interestingly, some previous studies have found a higher incidence of AKI, even as high as 42% (Machado et al., 2014). The reason for the low AKI incidence in study II is unclear, but the inclusion of all CABG surgeries in Iceland limits referral bias. In addition, the patients in our study were younger than in some other studies. The incidence of diabetes, a risk factor for AKI identified in the current cohort, was low compared with other studies, which could in part explain the low incidence of AKI (Machado et al., 2014; Ryden et al., 2014).

5.2.3 Incidence of AKI following surgical aortic valve replacement

There have been very few studies focusing on AKI following SAVR in the literature. In a study carried out in Sweden (Ryden et al., 2015), the incidence of AKI was 17% as compared with 22.5% in study III, despite the use of the KDIGO criteria in the Swedish study rather than the less sensitive RIFLE criteria in study III. This difference could be reflected by the differences in the cohorts since study III included both isolated SAVR and SAVR with concomitant CABG, which showed a trend toward a higher incidence of AKI, but the Swedish study only included isolated SAVR. In a recently published study using the National In-patient Sample database, the incidence of AKI

following isolated SAVR in a nationally representative cohort was 15.4%, as compared with 18.7% in patients who underwent TAVI. In PSM analysis of that study, SAVR was found to be associated with an increased risk of AKI (Kumar & Garg, 2018).

5.2.4 Incidence of AKI following acute type A aortic dissection repair

Following ATAAD, the incidence of AKI was 41%, which is similar to that in previous reports where the incidence has generally been in the 40–55% range (Wang et al., 2018). Higher incidence rates have been reported, such as in a study by Zhao et al. that included obese patients undergoing ATAAD repair, where the incidence was 67% (Zhao et al., 2015). The variability in the reported incidence can be explained by the small cohort size and differences in the composition of the cohorts. On the other hand, study IV was a multi-centre study with a larger cohort than most previous studies.

5.3 Risk factors for AKI

Several risk factors were identified in the four studies. Variability in the procedural techniques (ranging from noninvasive CA using contrast medium to complex open surgeries using CPB) and patient cohorts together with variability in the pathogenesis of AKI could explain the differences in the risk of AKI between the studies. Moreover, the differences in the availability of patient- and procedure-related factors between studies probably contributed to the variability observed. For example, in study I, detailed information on pre-procedural blood tests and information on patient drug dispensing from a centralised database were available, allowing more thorough risk assessment than in the other studies. Even so, there were certain similarities in risk factors, especially in the studies on open heart surgery.

5.3.1 Patient-related factors

5.3.1.1 Pre-procedural chronic kidney disease

Reduced pre-procedural kidney function was a significant risk factor for AKI in studies I and II, but not in studies III and IV. A study by Long et al. showed that patients with CKD are more likely to develop the mildest form of AKI according to the KDIGO criteria (elevation of more than 26.5 μmol/L). This mild form is not included in the RIFLE criteria that were used in studies III and IV, which could therefore explain this difference to some extent (Long et al., 2018). In addition, baseline CKD stage was determined based on at least two

SCr measurements over a minimum of a 90-day period for the majority of patients in study I, while eGFR was calculated from a single baseline SCr in the other studies. Single measurements do not adequately reflect the true baseline kidney function of these patients. This could explain why CKD, which is among the most important risk factors for postoperative AKI in the literature, was not significantly associated with AKI in all the studies. This particularly applies to patients with ATAAD, for whom the preoperative admission SCr was used as a baseline value since older SCr values were not available for many patients— despite a study by Wang et al. showing that 23% of ATAAD patients had already developed AKI on admission (Wang et al., 2016).

5.3.1.2 Obesity

Obesity was a risk factor for AKI in studies II, III and IV. Obesity has previously been shown to be a risk factor for several postoperative complications, including AKI (O'Sullivan et al., 2015). This can partly be explained by an increased risk of perioperative hypotension and insufficient volume resuscitation in this patient group (Kelz et al., 2013). Furthermore, adipose tissue has been shown to produce pro-inflammatory mediators, which could increase the risk of AKI (Obin & Greenberg, 2006). The increased risk of postoperative complications in obese patients should be taken into account when treatment options are considered.

5.3.1.3 Malperfusion

In study IV, Penn classes Ab, Ac and Abc were predictors of AKI. This classification has been shown to predict hospital mortality and other short-term adverse outcomes after ATAAD repair (Augoustides et al., 2009). Malperfusion increases the risk of AKI by affecting the systemic circulation, for example in cardiac malperfusion, while the dissection itself can also extend to the renal arteries, causing renal hypoperfusion resulting in kidney injury. It is noteworthy that hypotensive shock on admission, based on a single systolic blood pressure measurement of < 90 mmHg, was not associated with AKI in this cohort. The Penn classification, which is based on an assessment of the patient's condition from the time of admission to the surgery, can be considered a more accurate reflection of the circulatory and haemodynamic status than a single blood pressure measurement. In study I, cardiogenic shock and STEMI were predictors of AKI with a similar effect as cardiac malperfusion in patients with ATAAD. AKI was also more common in patients requiring emergency CABG, but these patients are often haemodynamically unstable before surgery (Axelsson et al., 2016).

5.3.1.4 Other

In study I, pre-procedural hyperglycaemia was independently associated with an increased risk of AKI. Interestingly, hyperglycaemia was a stronger predictor of AKI than diabetes but previous studies have shown hyperglycaemia in non-diabetic patients to be a predictor of AKI (Shacham et al., 2015). Hyponatraemia was also linked with AKI in study I. Hyponatraemia is associated with several conditions that can increase the risk of AKI, such as hypovolemia and low cardiac output states (Spasovski et al., 2014). Elevation in white blood cells was a risk factor for AKI, a finding that has also been reported in patients with sepsis (Bagshaw et al., 2008).

When only pre-procedural factors were included in a risk model for AKI following CA, treatment with a RAS blocker was found to be an independent risk factor for AKI. There are conflicting data on the effect of continuation of RAS blockers on AKI following CA. Some randomised controlled trials have shown an increased risk of AKI when RAS blocker treatment is continued (Bainey et al., 2015; Rim et al., 2012). However, the KDIGO guidelines concluded that there is currently insufficient evidence to recommend discontinuation of these medications prior to CA (Kidney Disease Improving Global Outcomes: (KDIGO) Acute Kidney Injury Work Group, 2012).

5.3.2 Intraoperative factors

5.3.2.1 Contrast dose

In study I, contrast dose was shown to be a relatively weak but statistically significant risk factor for AKI overall (OR = 1.6 per 100 mL). However, patients with CKD stages 3B–5 who received more than 150 mL had a substantially increased risk of developing AKI (a fivefold risk compared with patients who received < 80 mL). Contrast dose has been associated with an increased risk of AKI ever since the use of contrast media began in the middle of the last century. Thus, a search for the upper limit of a “safe“ contrast dose has been ongoing for years. Laskey et al. reported an increased risk of AKI when the ratio of contrast dose and creatinine clearance exceeded 3.7 (Laskey et al., 2007). Furthermore, a study by Brown et al. defined a maximum allowable contrast dose as being 5 mL × body weight (kg)/baseline SCr (mg/dL) (Brown et al., 2010) and a review by Keaney et al. concluded that the grams of iodine- to-GFR ratio should not exceed 1 (Keaney et al., 2013). These recommendations may not be useful in daily practice and have not been validated in other studies.

Recent studies examining contrast exposure during noninvasive and invasive imaging tests using intravenous or intra-arterial contrast, such as CT and CA, have suggested that the contrast dose required does not affect the risk of AKI (McDonald et al., 2013; Schmucker et al., 2017). Unlike studies on patients undergoing CT scans, who receive a narrow range of contrast dose, the current work enabled estimation of a dose-response relationship. The analysis was, however, limited by the fact that few cases developed AKI (n = 231). Although only a mild risk factor, the possible role of contrast in the pathogenesis of AKI should always be considered when assessing the risk of an imaging study in patients with advanced CKD, but it should not prevent a potentially diagnostic procedure in patients with serious conditions.

5.3.2.2 Cardiopulmonary bypass

CPB time was a significant risk factor for AKI in studies III and IV, which is consistent with numerous previous studies (O'Neal et al., 2016). The use of CPB may contribute to the development of AKI both through haemodynamic changes associated with non-pulsatile flow and through stimulation of an inflammatory response. Although CPB is potentially a modifiable factor, it also serves as a marker for the complexity of the surgery. Most studies comparing OPCAB and CABG have shown a slightly lower risk of AKI following OPCAB (Fudulu et al., 2016). However, due to inferior long-term outcome when compared with conventional CABG, OPCAB is now less frequently performed (Johannesdottir et al., 2017; Takagi & Umemoto, 2014).

5.3.2.3 Red blood cell transfusion

The number of RBC units transfused was independently associated with AKI in studies II–IV. RBC transfusion is an indirect marker of anaemia, bleeding and complexity of surgery, whereas increased bleeding is a known risk factor for AKI (Stone et al., 2012) and anaemia was a risk factor for AKI in study I. Importantly, the association between AKI and transfusions remained significant in study II after patients who required reoperation due to bleeding had been excluded.

In study III, the association between transfusions and AKI could partially be explained by a more frequent occurrence of preoperative anaemia in patients with AKI compared with patients without AKI. Even so, RBC transfusions remained an independent risk factor for AKI when preoperative anaemia, intraoperative and postoperative bleeding, and reoperation for bleeding were included in the risk model. When blood is stored, RBCs undergo morphological changes that are associated with multiple biochemical

and biomechanical changes known as the storage lesion (Ho et al., 2003). These changes instigate a pro-inflammatory state and oxidative stress, which may increase the risk of AKI (Tinmouth et al., 2006). However, a newly published meta-analysis of randomised controlled trials comparing restrictive and liberal RBC transfusion strategies showed non-inferiority of restrictive strategies with respect to the study's endpoints, including renal failure (Shehata et al., 2019). The 2017 EACTS/EACTA (European Association of Cardiothoracic Anaesthesiology) guidelines on patient blood management for adult cardiac surgery emphasise that the clinical condition of patients and the optimisation of the balance between oxygen delivery and extraction in the tissues should be taken account of rather than using a fixed threshold for the level of haemoglobin (Pagano et al., 2018).

5.4 Survival of patients with AKI

5.4.1 Short-term mortality

AKI was associated with an increased risk of 30-day mortality in all four studies, the difference being twelvefold, fivefold, ninefold and threefold compared with patients without AKI in studies I, II, III, and IV, respectively. The association of AKI with short-term survival has been reported previously by several investigators (Chertow et al., 1998; James et al., 2013; Wang et al., 2018). This relationship is thought to be partially explained by confounding comorbidity (James et al., 2013). The impact of other perioperative complications on the association between AKI and short-term mortality has not been thoroughly described before. In study II, patients who developed AKI and other major complications were at markedly increased risk of dying within 30 days compared with patients without AKI and with no major complications. However, patients with AKI who did not have major complications did not have a significantly increased mortality risk in multivariable analysis. These findings do not necessarily preclude an effect of AKI on short-term mortality since AKI can by itself increase the risk of other complications and therefore enhance the risk of mortality.

Indeed, not all AKI episodes result in reduced urine output, volume overload, or electrolyte disturbances, but AKI can cause a cardio-depressant effect by promoting the release of cytokines (Di Lullo, Bellasi, Russo, et al., 2017). This could possibly lead to an increased risk of short-term mortality.

5.4.2 Long-term survival

Patients who developed AKI following CA or surgery had worse long-term survival than patients without AKI in all four studies. The difference in survival could be partially explained by the worse short-term survival of patients with AKI, so short-term mortality was excluded to analyse the association between AKI and long-term survival. Patients who experienced AKI following CA had worse survival than propensity score-matched non-AKI patients, even after excluding those who died within 30 days of the procedure. This finding is in line with the results of a systematic review and meta-analysis from 2013 that included 39 studies, which, despite heterogeneity of the cohorts, consistently found an increased risk of death in those with AKI (James et al., 2013). However, the authors of the meta-analysis concluded that the association between AKI and mortality was strongly confounded by baseline characteristics and comorbidities. Other major complications were not included in that analysis.

In the CABG cohort, patients with AKI and with no other major complications were not at increased risk of dying over the first five years of follow-up compared with patients without AKI and other major complications. However, increased risk of mortality in the AKI group became apparent with extended follow-up. The delayed effect of AKI on survival could possibly be explained by the association of AKI with CKD, with the latter being associated with increased risk of cardiovascular mortality (Liyanage et al., 2015).

AKI following SAVR was not a significant predictor of long-term survival in study III, even though other complications were not included in the analysis. These findings differ from the results of previous studies (Kumar & Garg, 2018; Ryden et al., 2015). The hazard ratios showed a trend toward worse survival in patients with AKI and the discrepant results could possibly be explained by the limited number of patients in study III.

In the case of patients undergoing ATAAD repair, AKI was a strong predictor of inferior survival, even when patients who died within 30 days were excluded. Although studies on ATAAD repair with long-term follow-up of patients are scarce, two small studies from Japan have described similar findings (Ko et al., 2015; Sasabuchi et al., 2016).

The difference between the cohorts must be considered when interpreting the results of the four studies, regarding both baseline characteristics and the severity of the underlying disease. In addition, the procedures differ regarding complexity and length. These differences could influence the pathogenesis of AKI and therefore have a variable effect on the outcome of patients.

5.5 Development or progression of chronic kidney disease

Long-term follow-up of post-procedural kidney function was included in studies I and II. In study I, the definition of new-onset CKD or progression of pre-existing CKD was based on at least two SCr measurements 90 or more days apart. In study II, new-onset CKD was defined according to a single SCr measurement at least 90 days from the AKI episode.

In study I, AKI was associated with increased odds of incident CKD and also progression of CKD. Furthermore, AKI patients were more likely to develop CKD stage 5 and require RRT. AKI has been shown—both in animal and human observational studies—to be associated with CKD (Basile et al., 2001; Coca et al., 2012). In addition, AKI has been identified as a risk factor for the development of ESRD following CA (James et al., 2011), but only a few studies have included follow-up regarding development or progression of CKD following AKI after CA. James et al. showed that AKI following CA was associated with a decline in kidney function at 3 months after the procedure (James et al., 2010), and in a large Veterans' Administration study, AKI was found to be a risk factor for the development of CKD following PCI (Brown et al., 2016).

One-third of patients with AKI developed CKD during the follow-up period in study II. In multivariable analysis, AKI was found to be an independent risk factor for incident CKD, but no significant association was seen between AKI and the progression to ESRD. A study on patients undergoing cardiac surgery at Veterans' Affairs hospitals in the United States showed that the magnitude of postoperative SCr elevation was associated with increased risk of both incident CKD and progression of pre-existing CKD (Ishani et al., 2011). In contrast to the current results, AKI was associated with ESRD in a study by Ryden et al. (Ryden et al., 2014). The different findings could be explained by the fact that only five patients (0.3%) developed ESRD in the Icelandic CABG cohort, limiting the statistical power of the analysis.

5.6 Strengths and limitations

All four studies had several strengths and contribute to the literature on AKI following cardiac procedures in various ways. Study I included detailed patient- and procedure-related factors that enabled detailed risk analysis—most importantly, assessment of the role of contrast medium in the development of AKI. Studies I and II included all SCr measurements performed in Iceland over many years, which allowed precise estimation of baseline kidney function and a thorough follow-up of kidney function, features

that have been lacking in most other studies. In addition, there were accurate follow-up data available for patients who developed ESRD and required RRT in studies I–III, using a centralised ESRD registry in Iceland.

In an era of emerging novel treatment options, it is important to study the outcome of conventional therapy, as was done in study III where AKI following SAVR was examined. Although the incidence of AKI following TAVI has been compared with SAVR, there is very limited information on risk factors for AKI following SVAR and the outcome of these patients. This lack of clinical studies was highlighted in a recent review on AKI following SAVR (Najjar et al., 2015). Since no study had focused on AKI following SAVR when this review article was published, only general studies of AKI following cardiac surgery were included and used to draw conclusions about the effect of SAVR on AKI. Study III, however, indicates that AKI is more prevalent following SAVR than, for example, CABG.

Study IV is an important addition to the knowledge base regarding the outcome of ATAAD repairs, as previous work has mostly been limited to a relatively small number of patients and a short period of follow-up. Study IV demonstrated the association between AKI and the long-term survival of these patients.

The studies also had certain limitations. Firstly, they were all retrospective, precluding causal inference from the association pattern. In order to minimise bias, multivariable analyses were carried out to control for confounding in the estimation of risk factors for AKI and in the assessment of its association with outcomes, together with propensity score matching. Another limitation was the lack of SCr values that resulted in the use of different AKI criteria between studies. Although similar, the KDIGO and the RIFLE criteria differ with respect to sensitivity, making the comparison of AKI incidence between the studies in this thesis inaccurate. In study I, post-procedural SCr was not measured in a large proportion of cases, as this is not routinely done at the University Hospital following uncomplicated CA in otherwise healthy individuals. Nevertheless, patients with missing values were included in the analysis and assumed not to have developed AKI. This approach was believed to yield an incidence of AKI that was closer to the true situation than if those patients had been excluded from the analysis. Furthermore, the definition of AKI included only the SCr component of the criteria because data on urine output were not available. This could lead to underestimation of AKI but does not affect the comparison with studies performed elsewhere, since they generally share this limitation. A further limitation of studies III and IV was the inability to assess long-term follow-up of kidney function due to the lack of SCr measurements.

6 Conclusion and future studies

AKI is a common complication following CA and cardiac surgery, and is highly associated with patient outcomes. The incidence is dependent on the complexity of the procedure and the severity of the underlying disease. Although the surgical procedures differ, they share a number of risk factors for AKI, namely age, obesity, CPB and RBC transfusions. The risk of AKI associated with the dose of contrast medium used for CA appears to be mainly confined to patients with advanced CKD who receive large amounts of contrast. AKI is associated with adverse outcomes, including short- and long-term survival. However, the association can be partly explained by other complications of cardiac procedures. AKI is also associated with increased risk of new-onset CKD or progression of a pre-existing CKD.

The results presented in the four papers that form the backbone of this thesis highlight the importance of intensive peri-procedural management of patients who are at increased risk of developing AKI. It is important to treat conditions associated with AKI—for example, hypotensive states such as hypovolemia and malperfusion—perioperatively. Nephrotoxic drugs should be avoided and RAS blockers should possibly be temporarily discontinued. During CA, the amount of contrast should be limited, especially in patients with advanced CKD, and when possible, the time of CPB used in cardiac surgery should also be reduced. When AKI is detected, aggressive treatment of AKI and other associated complications should be implemented. Last but not least, close follow-up of AKI patients after hospital discharge is warranted during the first months after the AKI episode.

Future studies should focus on identifying and defining additional modifiable risk factors for postoperative AKI and factors that increase the likelihood of achieving good recovery of kidney function following an AKI episode. Risk factors that have not been prominent in previously published risk models for AKI following CA, which were identified in study I, including hyponatraemia, hyperglycaemia and leukocytosis, deserve attention in future studies. Moreover, the aim of future work should include assessment of modifiable risk factors for premature death or development of CKD. In patients with ATAAD, a remaining dissection of the renal arteries may persist and lead to the development of CKD, but no previous or current studies have adequately explored the long-term kidney function of these patients.

Studies on novel biomarkers that can be used to diagnose AKI earlier than with SCr are important. Earlier detection of the AKI episode could facilitate timely initiation of appropriate treatment and hopefully prevent further injury. It is also important to study the underlying causes of AKI to facilitate more specific treatment, as most epidemiological studies of AKI have not differentiated the causes of the condition.

In spite of the increased awareness of AKI and improvements in the perioperative care of patients undergoing cardiac procedures, the outcome of patients remains unacceptable. Ideally, the results of future studies should enable clinicians to identify all patients who are at increased risk of developing AKI and provide a biomarker that allows accurate diagnosis of the condition early in the course. Furthermore, patients who are at risk of not achieving recovery of their kidney function should be identified and closely followed, with the aim of preventing the development of progressive CKD.

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Original publications

Paper I

Paper II

Paper III

Paper IV

Appendix

Supplementary table

Table A1. Comparison of patients with and patients without SCr in the first week following coronary angiography.

	Post-procedural SCr available (n = 6,231)	Post-procedural SCr unavailable (n = 7,330)	p-value
Age, years	65.7 ± 11.6	64.6 ± 10.4	< 0.001
eGFR, mL/min/1.73 m^{2a}			< 0.001
> 60	4,899 (78.6)	6,245 (85.2)	
45–60	829 (13.3)	825 (11.3)	
30–45	390 (6.3)	238 (3.2)	
15–30	97 (1.5)	17 (0.2)	
< 15	16 (0.3)	5 (0.1)	
Elixhauser Comorbidity Index score	0.7 ± 2.1	0.6 ± 2.0	0.04
Indication for CA:			
Cardiac arrest	165 (2.7)	23 (0.3)	< 0.001
STEMI	1,037 (16.6)	91 (1.2)	< 0.001
NSTEMI/AP	2,873(46.1)	1,724 (23.5)	< 0.001
SA/UCP	1,547 (24.7)	4,492 (61.3)	< 0.001
Miscellaneous	609 (9.8)	1,000 (13.7)	< 0.001
Contrast dose, mL	160 ± 84	104 ± 64	< 0.001

Data are presented as number (%) or mean ± SD. CA, coronary angiography; eGFR, estimated glomerular filtration rate; NSTEMI, non-ST-elevation myocardial infarction; SA, stable angina; SCr, serum creatinine; STEMI, ST-elevation myocardial infarction; UA, unstable angina; UCP, unspecified chest pain.

[a]For > 90 days before coronary angiography.

Supplementary figure

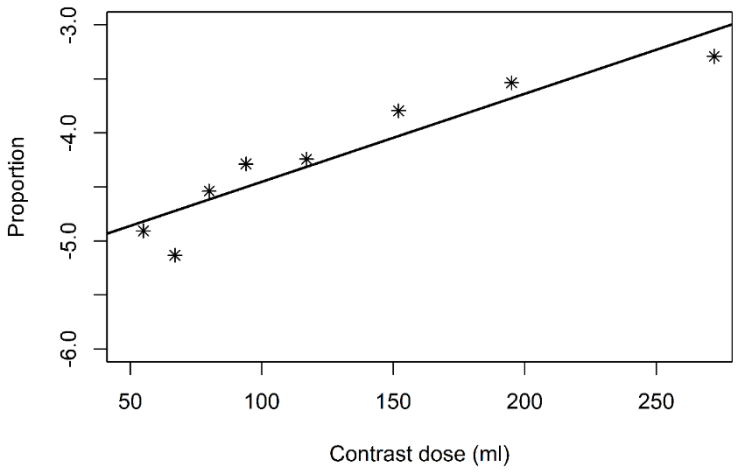

Figure A1. Logit of acute kidney injury – contrast dose.