Acute Kidney Injury Following Cardiac Surgery

- Incidence, Risk Factors, Association With Other Perioperative Complications, Survival, and Renal Recovery

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Thesis for the degree of Doctor of Philosophy

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Bráður nýrnaskaði eftir hjartaskurðaðgerðir

- tíðni, áhættuþættir, tengsl við aðra fylgikvilla við og eftir skurðaðgerð, lifun og langtímaáhrif á nýrnastarfsemi

Sólveig Helgadóttir

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Ágrip

Framfarir í skurðlækningum og gjörgæslu hafa leitt til bættrar meðferðar sjúklinga sem þjást af hjarta- og æðasjúkdómum. Í dag eru opnar hjartaaðgerðir algengar á Vesturlöndum og útlit er fyrir að þeim muni fjölga á komandi áratugum, samfara auknum fjölda aldraðra. Sjúklingar sem gangast undir opnar hjartaaðgerðir eru oft með flókin heilsufarsvandamál sem eykur tíðni fylgikvilla. Á meðal algengustu fylgikvilla eftir opnar hjartaaðgerðir eru hjartsláttaróregla, einkum gáttatif, og blæðingar. Bráður nýrnaskaði (BNS) er einnig algengur fylgikvilli eftir hjartaaðgerðir og tengist verri horfum sjúklinga eftir aðgerð. Skortur á gögnum um grunnstarfsemi nýrna hefur þó verið galli á mörgum fyrri rannsóknum sem auk þess hafa oft á tíðum skoðað mjög sérhæfða sjúklingahópa.

Árlega eru framkvæmdar um 250 opnar hjartaaðgerðir á Íslandi og eru um 2/3 þeirra kransæðahjáveituaðgerðir. Markmið þessarar doktorsritgerðar var að meta tíðni og áhættuþætti BNS eftir hjartaaðgerðir á Íslandi en skort hefur á slíkar rannsóknir fram til þessa. Auk þess voru könnuð tengsl BNS og annarra fylgikvilla eftir opnar hjartaaðgerðir. Loks var samband BNS og langtíma skerðingar á nýrnastarfsemi rannsakað, þar með talið þörf á nýrnaskilunarmeðferð, sem og langtímalifun. Að lokum var sérstaklega lagt mat á hvaða áhrif bati á nýrnastarfsemi hefur á horfur sjúklinga sem hljóta BNS.

Við rannsóknirnar var stuðst við gagnagrunna með ítarlegum upplýsingum um alla sjúklinga sem gengust undir hjartaaðgerð á Íslandi frá 2001-2015. Ber þar sérstaklega að nefna nákvæma skráningu á nýrnastarfsemi sjúklinga, bæði fyrir og eftir aðgerð, en þær upplýsingar eru forsenda til að geta lagt mat á tíðni og áhættuþætti BNS.

Rannsóknirnar leiddu í ljós að tíðni BNS eftir hjartaaðgerðir er heldur lægri hér á landi samanborið við nágrannalönd okkar. Líktog aðrar rannsóknir hafa sýnt er BNS tengdur undirliggjandi ástandi sjúklinga og voru aldur, skerðing á nýrnastarfsemi fyrir aðgerð, hærri áhættustigun fyrir aðgerð, umfangsmeiri skurðaðgerð og hærri líkamsþyngdarstuðull sjálfstæðir áhættuþættir.

Bráður nýrnaskaði tengdist verri horfum sjúklinga eftir aðgerð sem meðal annars endurspeglaðist í hærri tíðni ýmissa fylgikvilla. Gáttatif reyndist algengasti fylgikvillinn og greindist í nærri helmingi sjúklinga sem gengust

undir kransæðahjáveitu- eða ósæðarlokuskiptaaðgerð á Landspítala. Auk þess kom í ljós að tíðni gáttatifs var marktækt aukin hjá sjúklingum sem fengu BNS. Eins og fyrir BNS, reyndust hærri aldur, umfang aðgerðar og hærri áhættustigun fyrir aðgerð vera sjálfstæðir áhættuþættir fyrir greiningu gáttatifis.

Greining BNS tengdist einnig aukinni þörf á skammtíma nýrnaskilunarmeðferð og versnun á langtíma nýrnastarfsemi. Aukinheldur höfðu sjúklingar sem fengu BNS marktækt lakari lifun eftir aðgerð og reyndist langtímalifun í öfugu hlutfalli við alvarleika upphaflegs nýrnaskaða. Meirihluti sjúklinga virtist hinsvegar endurheimta nýrnastarfsemi eftir BNS í kjölfar aðgerðar. Bati á nýrnastarfsemi spáði ekki fyrir um eins árs lifun sjúklinga en hinsvegar lifðu sjúklingar sem náðu bata marktækt lengur en samanburðarhópur sem ekki náði bata.

Með því að notast við yfirgripsmikla og nákvæma gagnagrunna, sem ná til heillar þjóðar, reyndist unnt að meta tíðni BNS og gáttatifs eftir opnar hjartaaðgerðir á Íslandi um leið og lifun og forspárþættir lifunar eftir þessar aðgerðir voru kannaðir. Flestir sjúklingar sem hlutu BNS endurheimtu nýrnastarfsemi og fáir hlutu endastigs nýrnabilun. Samt sem áður virðist BNS tengjast verri útkomu eftir hjartaaðgerð og ljóst er að úrræði skortir þegar greining BNS liggur fyrir. Snemmbúin greining BNS og kortlagning áhættuþátta á þó vonandi eftir að auka skilning okkar á BNS og hvernig fyrirbyggja má sjúkdóminn og að bæta horfur þessa sjúklingahóps.

Lykilorð:

Bráður nýrnaskaði, bati á nýrnastarfsemi, gáttatif, langtímahorfur, tíðni

Abstract

In line with advances in surgery, perioperative care, and intensive care, the outcome in patients treated for cardiovascular disease has improved. Open-heart surgery is common in most western countries and, in line with the general ageing of populations, the frequency of these procedures is expected to increase in the coming decades. Patients who undergo cardiac surgery often have complex medical problems that predispose them to a range of surgical complications. Among the most common postoperative complications are arrhythmias, most often atrial fibrillation, and bleeding. Acute kidney injury (AKI) is also a common and often serious complication—as well as being a strong risk factor for worse postoperative outcome and increased mortality after surgery. However, many previous studies have suffered from a lack of data on baseline kidney function before AKI as well as selective patient cohorts.

Approximately 250 open-heart surgeries are performed annually in Iceland. However, there has been a lack of data on the incidence and risk factors for AKI following heart surgery. The aim of the studies in this thesis was to evaluate the incidence of AKI using internationally validated criteria. Furthermore, we wanted to examine the association between AKI and other postoperative complications, and also long-term outcome, mainly regarding kidney function and survival. In that context, we particularly examined the effect of recovery of renal function on long-term outcome.

Data were gathered from comprehensive nationwide databases that contained detailed information on all patients who underwent heart surgery in Iceland from 2001 through 2015. Information on kidney function, both pre- and postoperatively, was recorded in a thorough manner, as it is a prerequisite for reliable evaluation of AKI.

The studies showed that the incidence of AKI after cardiac surgery in Iceland was relatively low compared to neighboring countries. In line with previous studies, the preoperative condition of patients was shown to be associated with the incidence of AKI. Advanced age, reduced preoperative kidney function, higher preoperative risk assessment scores, a higher body mass index, and more complex surgery were found to be independent predictors of the development of AKI.

AKI was significantly associated with worse postoperative outcome, as reflected by higher rates of various postoperative complications when compared to patients with normal kidney function postoperatively. Atrial fibrillation, diagnosed in almost half of the patients, was the most common postoperative complication following surgical myocardial revascularization and aortic valve replacement in Iceland. Furthermore, the incidence of atrial fibrillation was higher in patients who sustained AKI than in those who did not. As in the case of AKI, the independent predictors of atrial fibrillation were advanced age, more complex surgery, and higher preoperative risk assessment scores.

The diagnosis of AKI was found to be associated with an increased need for renal replacement therapy and worse long-term kidney function. Also, AKI patients had significantly higher postoperative mortality and worse long-term survival, with survival being inversely correlated to the severity of AKI. Importantly, the majority of patients recovered their renal function after AKI. Although renal recovery was not a significant predictor of one-year survival, it was found to be associated with more favorable long-term survival.

By using extensive comprehensive nationwide databases, it was possible to determine the incidence of AKI after open-heart surgery in Iceland and to define risk factors. Most patients who sustained AKI recovered their renal function and the rate of progression to end-stage renal disease was low. Although AKI appears to be associated with a worse postoperative outcome in patients, early detection of AKI and gaining a better understanding of the risk factors remain important steps in reducing the morbidity and mortality of patients diagnosed with AKI. It is to be hoped that a better understanding of these factors will help to improve the long-term prognosis in this patient group, leading to increased rates of renal recovery and reduced costs of treatment.

Key words:

Acute kidney injury, incidence, long-term outcome, postoperative atrial fibrillation, renal recovery.

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Finally, I want to express my gratitude and love to my dear ones who passed away before the final steps of this long journey.

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Contents

List of abbreviations

ADQI	Acute Dialysis Quality Initiative
AFib	atrial fibrillation
AKI	acute kidney injury
AKIN	Acute Kidney Injury Network
APACHE	acute physiology and chronic health evaluation
ARDS	acute respiratory distress syndrome
ARF	acute renal failure
AS	aortic stenosis
ASA	American Society of Anesthesiology physical status classification
ATN	acute tubular necrosis
AUC	area under the curve
AVR	aortic valve replacement
BMI	body mass index
CABG	coronary artery bypass grafting
CAD	coronary artery disease
CHF	congestive heart failure
CI	confidence interval
CKD	chronic kidney disease
CKD-EPI	Chronic Kidney Disease-Epidemiology Collaboration
CO	cardiac output
COPD	chronic obstructive pulmonary disease
CPB	cardiopulmonary bypass
CRRT	continuous renal replacement therapy
CRS	cardiorenal syndrome
CS-AKI	cardiac surgery-associated acute kidney injury
CVD	cardiovascular disease
DM	diabetes mellitus
ECG	electrocardiogram
eGFR	estimated glomerular filtration rate
ESKD	end-stage kidney disease
ESRD	end-stage renal disease
EuroSCORE	European System for Cardiac Operative Risk Evaluation
GFR	glomerular filtration rate
Hb	hemoglobin
HF	heart failure
HR	hazard ratio

HTN	hypertension
ICD-10	International Classification of Diseases, tenth revision
ICU	intensive care unit
IHD	ischemic heart disease
LVEF	left ventricular ejection fraction
KDIGO	Kidney Disease: Improving Global Outcomes
KDOQI	Kidney Disease Outcome Quality Initiative
MDRD	Modification of Diet in Renal Disease
MI	myocardial infarction
MOF	multiple organ failure
NSR	normal sinus rhythm
OPCAB	off-pump coronary artery bypass
OR	odds ratio
P	pressure
P_B	hydrostatic pressure in Bowman‘s capsule
P_C	hydrostatic pressure of the glomerular capillaries
PCI	percutaneous coronary intervention
POAF	postoperative atrial fibrillation
PPV	positive pressure ventilation
PSM	propensity score match
RBC	red blood cell
R_A	renal efferent arteriolar resistance
R_E	renal blood flow
RCT	randomized controlled trial
RenR	renal recovery
RIFLE	Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease
ROC	receiver operating characteristic
RRT	renal replacement therapy
SCr	serum creatinine
SD	standard deviation
SR	sinus rhythm
TAVI	transcatheter aortic valve insertion
TIA	transient ischemic attack
π_c	colloid osmotic pressure of glomerular capillaries

List of figures

List of tables

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–V):

I. Acute kidney injury in intensive care units according to RIFLE classification: a population-based study. Martin I Sigurdsson, Iris O Vesteinsdottir, Kristinn Sigvaldason, Solveig Helgadottir, Olafur S Indridason, and Gisli H Sigurdsson. Acta Anaesthesiol Scand 2012;56:1291-1297.

II. Renal recovery and long-term survival following acute kidney injury after coronary artery surgery: a nationwide study. Solveig Helgadottir, Martin I. Sigurdsson, Runolfur Palsson, Dadi Helgason Gisli H. Sigurdsson, and Tomas Gudbjartsson. Acta Anaesthesiol Scand 2016;doi:10.1111/aas/12758.

III. Acute kidney injury and outcome following aortic valve replacement for aortic stenosis. Dadi Helgason, Solveig Helgadottir, Sindri A. Viktorsson, Andri W. Orrason, Inga L Ingvarsdottir, Arnar Geirsson, and Tomas Gudbjartsson. Interact CardioVasc Thorac Surg 2016; doi:10.1093/icvts/ivw117.

IV. Renal recovery following postoperative acute kidney injury – evaluation of definitions, clinical risk factors, and survival. Solveig Helgadottir (equally contributing first authors), Thorir E. Long (equally contributing first authors), Dadi Helgason, Gisli H. Sigurdsson, Runolfur Palsson, Olafur S Indridason, Tomas Gudbjartsson, and Martin I. Sigurdsson. Manuscript.

V. Atrial fibrillation following cardiac surgery: risk analysis and long-term survival. Solveig Helgadottir, Martin I. Sigurdsson, Inga L. Ingvarsdottir, David O. Arnar, and Tomas Gudbjartsson. J Cardiothorac Surg 2012 Sept 19;7:87.

In addition, some unpublished data has been presented.

Declaration of contribution

The doctoral student, Solveig Helgadottir, planned the research work for Papers II, IV, and V, of which she is the first author. She also applied for the appropriate ethical and research approval and performed the statistical analyses in cooperation with the co-authors. She participated in planning and writing of the manuscripts of Papers I and III in cooperation with the co-authors. She wrote this thesis under the guidance of her supervisor and doctoral committee.

1 Introduction

Acute kidney injury (AKI) is a complex condition that is seen in diverse settings. The term covers a broad range of renal dysfunction, ranging from a slight decrease in kidney function to extensive renal injury. The aim of this thesis is to provide some insight into AKI after cardiac surgery, with emphasis on AKI following either coronary artery bypass grafting (CABG) surgery or aortic valve replacement (AVR). Normal anatomy and kidney function will be explained briefly before any further discussion on the mechanisms underlying AKI. Then the importance of baseline and postoperative kidney function will be examined and the effect of recovery of renal function following AKI assessed. Lastly, postoperative atrial fibrillation (POAF), the most common complication of open-heart surgery, and its relationship to AKI, will be examined.

1.1 The kidneys

The kidneys are a pair of bean-shaped, retroperitoneal organs that play an important role in various homeostatic mechanisms that are essential for survival (Figure 1). They serve in regulating fluid, pH, and electrolyte balance, filter and eliminate waste products of metabolism from the circulation, aid in the regulation of blood pressure via the renin-angiotensin-aldosterone system, and are important producers of hormones (Hall & Guyton, 2011; Wein et al., 2012).

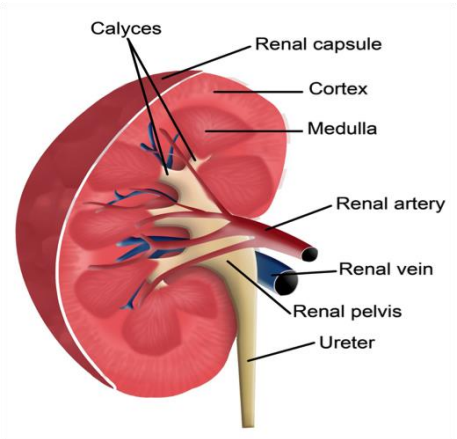

Figure 1. Anatomy of the kidney.

Each kidney normally has around 800,000 to 1.5 million nephrons, the kidney's urine-producing functional units (Brenner, 2005). The nephron consists of an initial filtering component (the renal corpuscle) and an associated tubule. The renal corpuscle is made up of the glomerulus, a network of capillaries that receives blood from the afferent renal arteriole and is responsible for ultrafiltration of blood. The glomerulus is covered by a simple layer of squamous epithelium, called the Bowman's capsule (Figure 2) (Wein et al., 2012).

The kidneys usually weigh around 115-170 g in an adult human and make up only 1–2% of the total body mass (Wein et al., 2012). However, every minute, between 20% and 25% of the total cardiac output passes through the kidneys and is filtered by them (Janson & Tischler, 2012). In the glomeruli, primary urine is produced at an approximate rate of 125 mL/min, amounting to roughly 180 L on a daily basis (Hall & Guyton, 2011). The tubuli serve to further modify the initial corpuscular filtrate before it progresses to the collecting system of the kidneys and is excreted from the body in the form of urine.

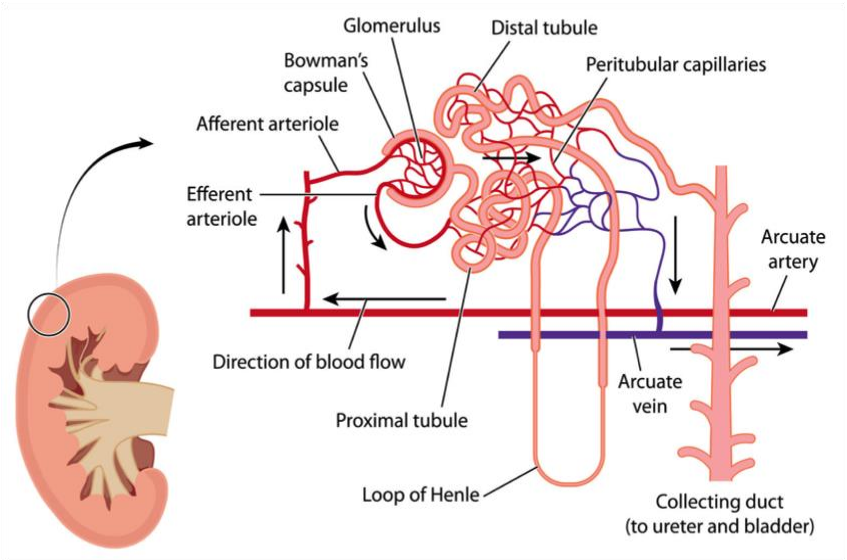

Figure 2. The nephron.

Glomerular filtration rate (GFR) is the term used to describe the rate of flow of filtered fluid through the kidney, and it is measured in mL/min. Glomerular filtration is a passive process governed by Starling forces that force fluid to filter along a pressure gradient. GFR depends on the filtration coefficient (K_F) and the balance between factors driving and opposing

filtration (Figure 3) (Brenner, 2005). The main factor that drives filtration is the hydrostatic pressure inside the glomerular capillaries (P_c), whereas the hydrostatic pressure in the Bowman's capsule (P_B) and the mean colloid osmotic pressure of the glomerular capillaries (π_c) oppose filtration (Guyton & Hall, 2006). Thus, GFR can be expressed by the following equation:

$$GFR = K_F \times ((P_c - P_B) - \pi_c)$$

Physiologically, GFR is primarily modified through changes in pressure inside the glomerular capillaries, which is in turn dependent on renal afferent arteriolar resistance (R_A) and efferent arteriolar resistance (R_E), as well as on systemic arterial pressure. It should, however, be noted that due to an autoregulation of GFR and the renal blood flow, the pressure in the afferent arterioles in the glomerulus remains constant over a wide range of systemic arterial pressure (Guyton & Hall, 2006).

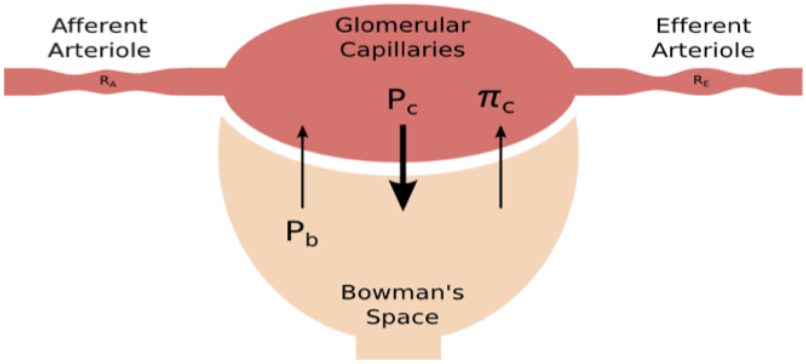

Figure 3. Factors governing glomerular filtration rate. Modified from http://pathwaymedicine.org/glomerular-filtration-rate.

The condition that arises when the kidneys become incapable of maintaining GFR, and even of excreting nitrogenous waste, regulating electrolytes and intravascular volume, and in assisting in maintenance of the acid-base balance, is termed renal failure. Renal failure may be acute or chronic. Before any further explanation of the complex condition of renal failure, another key topic will be covered in the following sections, namely how renal function is assessed in clinical practice.

1.2 Assessment of renal function

Renal function can be estimated in several ways. For instance, urine output (diuresis), routinely monitored in patients in intensive care units (ICUs), is an indirect marker of renal function. Diuresis is, however, affected by several other mechanisms, e.g. the normal physiological response of increased

vasopressin secretion due to volume depletion and administration of diuretics. Diureses can therefore be an unreliable marker of renal function in the setting of AKI (Bellomo et al., 2004).

The most accurate method of determining GFR, and thereby assessing renal function, is by performing repeated blood measurements of intravenously administered exogenous filtration markers (e.g. inulin, iothalamate, or iohexol), which, however, is economically and temporally impractical in clinical practice (Stevens & Levey, 2005, 2009).

In the clinical setting, the most widely used method of estimation of GFR (eGFR) is measurement of serum levels of the endogenous filtration marker creatinine (SCr) (Brenner, 2005). Creatinine is an amino acid compound derived from the conversion of creatine to phosphocreatinine in skeletal muscle and subsequent metabolism in the liver. It is mainly excreted through glomerular filtration and secreted in an unchanged form (Miller, 2003; Taylor, 1989). Measurement of SCr permits estimation of creatinine clearance, which in turn has an inverse correlation with GFR (Stevens & Levey, 2005). The normal range of eGFR is 90–130 mL/min/1.73 m^2, but around the fifth decade of life it begins to decrease (by approximately 10 mL/min/1.73 m^2 per decade) (Brenner, 2005; Feehally et al., 2007). However, estimation of GFR by measurement of SCr has several important limitations (Bagshaw & Gibney, 2008; Shemesh et al., 1985; Waikar et al., 2009):

i. Release of creatinine varies with age, sex, exercise, diet, and muscle mass.
ii. Up to 10–40% of creatinine is secreted by the proximal tubular cells of the kidneys, leading to overestimation of GFR, especially in states of renal dysfunction.
iii. SCr values become abnormal only when there is a more than a 50% reduction in GFR.
iv. SCr is a functional marker rather than an injury marker. Thus, it does not reflect kidney injury in the early stages, it may take up to 24 hours to rise following abrupt damage to the kidneys, and it has low predictive value regarding injury. Furthermore, critical illness itself may also cause large fluctuations in SCr due to factors such as deranged volume status and catabolic metabolism.

The search for biomarkers that are more sensitive in the recognition of AKI is ongoing, but none are currently well enough established to replace creatinine as a biomarker of renal function (de Geus et al., 2012; Dedeoglu et al., 2013; Susantitaphong et al., 2013b). In the meantime, to overcome some

of the obstacles in using SCr and to increase the accuracy of GFR and creatine clearance estimations in clinical practice, equations adding demographic and clinical data to SCr values have been formulated. It should, however, be emphasized that all these equations are based on SCr, which, as already mentioned, has various limitations—especially in the AKI setting (Waikar et al., 2009).

1.3 Estimation of GFR

Despite efforts to correct for differences regarding age, sex, race, and body mass, it can be difficult to produce a single equation that can accurately predict creatine clearance and GFR in all clinical settings. The following three formulas have been in most extensive use:

i. **The Cockcroft-Gault formula** was published in 1973, and provides estimated creatinine clearance values, which in turn provide an estimation of GFR. It is still widely used, but recommended drug doses are commonly based on Cockcroft-Gault values (Cockcroft & Gault, 1976). The equation was developed based on 249 males with steady-state SCr, and women were assigned an adjustment factor of 0.85, based on a theoretically lower muscle mass (by 15%). Lean body weight is included in the numerator of the formula to adjust for muscle mass. That may, however, adversely affect the performance of the formula in patients where weight change is not a result of changes in muscle mass (e.g. pregnancy, obesity, and edematous states) (Coresh & Stevens, 2006). Furthermore, due to tubular secretion of creatinine, the formula will lead to overestimation of GFR (Botev et al., 2009). Since publication of the formula, SCr measurement has been standardized. However, samples from the original study are no longer available for measurement and there is no version of the equation with standardized creatinine values.

ii. **The Modification in Diet and Renal Disease (MDRD) formula** for estimation of GFR was published in 1999, and has been extensively validated in populations between the ages of 18 and 70 with chronic kidney disease (CKD) (eGFR < 60 mL/min/1.73 m^2) (Levey et al., 1999). The equation has, however, been criticized for the fact that the study that it was based on was conducted on a population that was not representative of the general population—but rather a population with reduced kidney function (with a mean measured GFR of 40 mL/min/1.73 m^2). The MDRD equation thus overestimates eGFR at values < 30 mL/min/1.73 m^2, but underestimates eGFR at

values from 30 to 90 mL/min/1.73 m^2 (Levey et al., 1999; Stevens et al., 2006).

iii. **The Chronic Kidney Disease-Epidemiology Collaboration (CKD-EPI) formula** for estimation of GFR was developed in 2009 and uses the same premises as the MDRD formula, but is more accurate in patients with eGFR > 60 mL/min/1.73 m^2 (Levey et al., 2009).

1.4 Acute renal failure

Acute renal failure (ARF) involves an abrupt loss of kidney function (Webb & Dobb, 2007). It can have various causes, e.g. renal tissue damage, reduced renal blood flow, urinary tract obstruction, or exposure to nephrotoxins (Brenner, 2005).

At the turn of the 21st century, inter-study comparison of research on the subject of ARF suffered from a lack of consensus diagnostic criteria (Eknoyan, 2002). Indeed, at the time, over 35 different definitions of ARF were reported, leading to wide variations in reported ARF rates (Chertow et al., 1997; Kellum et al., 2002). In ARF, the decrease in renal function occurs abruptly, usually within hours or days, and results in imbalance in fluid and electrolyte states (Webb & Dobb, 2007). Many cases of ARF are reversible due to the kidney's unique ability to recover from almost complete loss of function. So for a long time, ARF, in its less severe form was considered to be a relatively minor event with little clinical impact. However, there is mounting evidence to indicate that even a slight rise in SCr can negatively affect patient outcome, be it morbidity, short-term complications, or long-term mortality (Chertow et al., 1998; Lassnigg et al., 2004; Mangano et al., 1998). Changes in SCr could simply coincide with unmeasured variables that lead to increased mortality, but even after controlling for other clinical variables, a consistent linear relationship between reduced kidney function and worse outcome has been observed. Consequently, research has undergone much change in recent years—with the term AKI largely replacing the term ARF.

1.5 Acute kidney injury

Acute kidney injury is defined as a sudden and sustained decrease in kidney function that develops within seven days and leads to a rapid reduction in GFR (Webb & Dobb, 2007). Decreases in GFR stem from a decline in the number of nephrons, a decline in single nephron GFR, or both, and reflect various etiologies, including specific renal disease and extra-renal pathology (Brenner, 2005). This may result in extensive derangement of normal homeostasis, e.g. acid-base disturbances, electrolyte imbalance, retention of nitrogenous waste products, and fluid overload, and it has also been shown

to hasten progression of CKD and impair innate immunity (De Waele et al., 2008; Rossaint et al., 2011; Thakar et al., 2003).

As mentioned, AKI is a known complication in various clinical settings and it may develop as a consequence of complex interactions between an insult and subsequent activation of pro-inflammatory and coagulatory responses. However, AKI may occur with only minimal histological signs of tissue damage (Kosaka et al., 2016).

AKI is a large and costly problem for patients and healthcare systems (Chertow et al., 2005). In a recent meta-analysis involving 312 studies and almost 50 million hospitalized patients worldwide, AKI was diagnosed in one in five adults and in one in three children (Susantitaphong et al., 2013a). The most common underlying causes for hospital-diagnosed AKI are sepsis and cardiac surgery (Susantitaphong et al., 2013a; Zakeri et al., 2005; Zarbock et al., 2014). One concern is the fact that studies have indicated that the incidence of AKI is rising, and the same holds true for incidence of AKI requiring dialysis (Hsu, 2010; Hsu et al., 2013).

1.5.1 Defining AKI – the RIFLE, AKIN, and KDIGO criteria

The use of varying definitions of AKI and the heterogeneity of different patient populations has led to large differences in reported AKI rates in previously published studies (Kaufman et al., 1991; Metcalfe et al., 2002). This in turn has made studies of the epidemiology and outcome of AKI unnecessarily complex (Gottlieb et al., 2002). In an effort to provide evidence-based guidelines, several interdisciplinary groups have proposed standardized criteria for the diagnoses and staging of AKI in the last decade. In the coming chapters, the three most frequently used criteria will be discussed further: the RIFLE, AKIN, and KDIGO criteria (see List of abbreviations).

1.5.1.1 The RIFLE criteria

The RIFLE criteria, shown in Table I, were published in 2004 (Bellomo et al., 2004). The criteria are multi-level and consist of three graded levels of kidney injury (Risk, Injury, and Failure) and outcome measures (Loss of kidney function and End-stage kidney disease). They are based on a sudden increase in SCr and decrease in GFR or urine output (known or presumed to have developed over seven days or less) compared to baseline levels. Since they were published, various studies of different populations have shown the criteria to be useful in determining the incidence of AKI as well as being predictive of complications and perioperative mortality (Hoste et al., 2006; Kuitunen et al., 2006).

Table I: The RIFLE criteria for acute kidney injury (Bellomo et al., 2004).

Stage	SCr criteria	Urine output criteria
Risk	1.5-fold increase in SCr or decrease in eGFR of > 25% from baseline	< 0.5 mL/kg/h for > 6 h
Injury	2-fold increase in SCr or decrease in eGFR of > 50% from baseline	< 0.5 mL/kg/h for > 12 h
Failure	3-fold increase in SCr, decrease in eGFR of > 75% from baseline, SCr ≥ 354 µmol/L or acute rise in SCr ≥ 44 µmol/L	< 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)	

eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease; SCr, serum creatinine.

A major point of criticism of the RIFLE criteria is the requirement for baseline SCr values, which are often missing in the clinical setting. The criteria recommend assuming baseline GFR to be 75 mL/min/m^2 when there is no history of CKD, and calculation of SCr by using the MDRD equation. However, studies have shown this to be too rough an approximation in many cases (Bagshaw et al., 2009; Pickering & Endre, 2010).

1.5.1.2 The AKIN criteria

The Acute Kidney Injury Network later modified the original RIFLE criteria, in an effort to increase both sensitivity and specificity (Table II) (Mehta et al., 2007). The AKIN criteria differ from the RIFLE criteria mainly regarding the time component and the fact that not outcome measures are described. While the RIFLE criteria are defined as change within seven days, the AKIN criteria propose using 48 hours (Mehta et al., 2007). The AKIN criteria also include less severe kidney dysfunction in the diagnosis of AKI, and do not use GFR as a marker, as GFR has been shown to be unreliable in the setting of AKI. Lastly, the AKIN criteria propose that the diagnoses of AKI should only be made after optimization of fluid balance and exclusion of urinary tract obstructions. However, studies have failed to reliably show superior prognostic value of the AKIN criteria over the original RIFLE criteria (Englberger et al., 2011; Ostermann & Chang, 2011).

Table II: The AKIN criteria for acute kidney injury (Mehta et al., 2007).

Stage	SCr criteria	Urine output criteria
1	Increase in SCr of ≥ 26.4 µmol/L in ≤ 48 h or 1.5- to 2-fold increase in baseline SCr	< 0.5 mL/kg/h for > 6 h
2	Increase in SCr to > 2- to 3-fold from baseline SCr	< 0.5 mL/kg/h for > 12 h
3	Increase in SCr to > 3-fold from baseline or baseline SCr ≥ 354 µmol/L with an acute increase of ≥ 44 µmol/L in ≤ 48 h	< 0.3 mL/kg/h for > 24 h or anuria for > 12 h

eGFR, glomerular filtration rate; SCr, serum creatinine.

1.5.1.3 The KDIGO criteria

Efforts have been made to further homogenize and improve the definition of AKI—with the KDIGO definition, combining the RIFLE and AKIN criteria, as a recent example (Table III) (Khwaja, 2012). The three classifications of AKI mentioned above have been compared in several studies, but no conclusive evidence of superiority of one system over the others has yet emerged (Bastin et al., 2013; Joannidis et al., 2009; Luo et al., 2014).

Table III: The KDIGO criteria for acute kidney injury (Khwaja, 2012).

Stage	SCr criteria	Urine output criteria
1	SCr ≥ 1.5–1.99 times baseline in ≤ 7 days *or* ≥ 26.5 µmol/L increase occuring in ≤ 48 h	< 0.5 mL/kg/h for 6–12 h
2	SCr 2.0–2.99 times baseline in ≤ 7 days	< 0.5 mL/kg/h for ≥ 12 h
3	SCr ≥ 3.0 times baseline in ≤ 7 days *or* SCr ≥ 354 µmol/L with either rise of ≥ 26.5 µmol/L in ≤ 48 h or SCr ≥ 1.5 times from baseline ≤ 7 days *or* initiation of renal replacement therapy *or* in patients < 18 years a decrease in eGFR to < 35 mL/min per 1.73 m^2	< 0.3 mL/kg/h for ≥ 24 h *or* anuria for ≥12 h

eGFR, estimated glomerular filtration rate; h, hour; SCr, serum creatinine.

1.5.2 Ascertainment of baseline SCr

Although standardized definitions of AKI, based on changes in SCr and urine output, have facilitated epidemiological studies, some controversy remains regarding the diagnosis of AKI. All the aforementioned criteria are based on relative deviance from baseline SCr, and they can be significantly affected by the choice of reference SCr. An important hurdle is choosing a suitable baseline SCr, i.e. one that accurately reflects kidney function in the steady state, prior to onset of AKI (Siew & Matheny, 2015). Studies have indicated that in patients for whom data on SCr is missing, the eGFR 75 approach, suggested in the RIFLE criteria, is likely to provide too rough an estimation of baseline kidney function in a study cohort (Bagshaw et al., 2009; Pickering & Endre, 2010). Knowledge of actual kidney function is preferable, and pre-hospital SCr values may be useful in determining baseline SCr (Siew & Matheny, 2015).

1.5.3 The pathophysiology and etiology of AKI

To aid in diagnosis and management, the causes of AKI have been divided into three main categories (Brenner, 2005):

i. **Pre-renal:** This accounts for approximately 55% of cases. It represents a physiological response to renal hypoperfusion (e.g. hypovolemia or low cardiac output) and—by definition—is reversible upon correction of renal blood flow, as no induction of ischemic injury to renal parenchyma has taken place.
ii. **Intrinsic:** This comprises approximately 40% of cases, and it may be a complication of diverse diseases of the renal parenchyma. Most intrinsic injury is triggered by renal ischemia or nephrotoxins (such as radio-contrast or aminoglycosides). As such, intrinsic injury has been shown to go hand in hand with major cardiovascular surgery, trauma, hemorrhage, or sepsis.
iii. **Post-renal:** This represents about 5% of cases and is caused by urinary tract obstruction, usually distally in the ureter or urethra.

It has, however, been pointed out that this may be an oversimplification for underlying pathological mechanisms that frequently overlap, as evident in cases where hypoperfusion of renal tissue (pre-renal) may cause sufficient harm to lead to ischemic cellular injury and acute tubular necrosis (intrinsic) (Case et al., 2013). A schematic representation of postoperative AKI is shown in Figure 4. It highlights some of the complex interplay of various factors that affect the process.

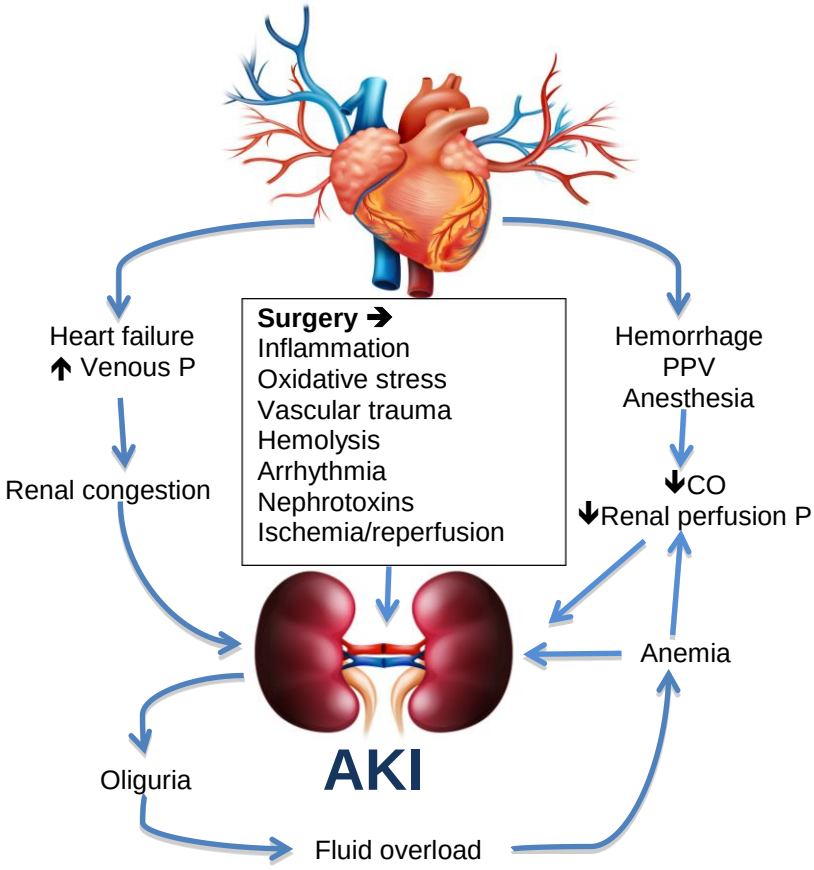

Figure 4. A schematic representation of factors that contribute to AKI in the perioperative period (Brenner, 2005; Legrand & Payen, 2013). AKI, acute kidney injury; CO, cardiac output; P, pressure; PPV, positive pressure ventilation.

1.5.4 Risk factors for AKI

Risk factors for AKI can be divided into patient- or exposure-specific. Individual clinical factors known to increase a patient's susceptibility include advanced age, diabetes mellitus, and congestive heart failure (CHF) (Long et al., 2016). As already mentioned, sepsis and cardiac surgery are the leading extrinsic causes of AKI (Susantitaphong et al., 2013a). Other reported risk factors include trauma, exposure to nephrotoxic drugs (e.g. radio-contrast and aminoglycosides), and burns (Bagshaw et al., 2008; Rewa & Bagshaw, 2014). Lastly, pre-existing kidney disease is an established risk factor for the development of AKI, and the risk has been found to be proportional to the

respective stage of CKD (Hsu et al., 2008; Khosla et al., 2009).

1.6 Postoperative AKI

Postoperative AKI is believed to account for approximately 20–50% of hospital-acquired AKI, and is a result of complex pathophysiological mechanisms (Carmichael & Carmichael, 2003). According to a large prospective multicenter study that examined ARF in almost 30,000 ICU patients, 41% of ARF cases were defined as postoperative (Uchino et al., 2005). Cardiovascular surgical procedures were by far the most common surgical causes of postoperative AKI, comprising more than twice as many cases as the second most common surgical procedure, i.e. gastrointestinal surgery (56.4% vs. 27.8%). In contrast to cardiac surgery, considerably less emphasis has been placed on AKI following non-cardiac surgical procedures, perhaps due to a significantly lower incidence of AKI (Long et al., 2016). Nevertheless, there is some evidence that AKI may complicate up to one-third of all major non-cardiac surgeries (Bihorac et al., 2009)..

1.6.1 AKI following cardiac surgery

Patients who undergo cardiac surgery are faced with a unique combination of possible renal stressors, related to both the surgery itself and, in some cases, the cardiopulmonary bypass (CPB) (Rosner & Okusa, 2006). Reported rates of AKI following open-heart surgery vary widely, depending on factors such as the patient population and the type and extensivness of surgery, but most are within the range of 15–60% (Machado et al., 2009; Roh et al., 2012; Rosner & Okusa, 2006). The incidence of cardiac surgery-associated AKI (CS-AKI) is lowest after CABG, followed by valvular surgery, and it is highest after combined CABG and valvular procedures (Rosner et al., 2008).

Multiple risk factors for AKI following cardiac surgery have been reported but among the most prominent are: emergency surgery, chronic kidney disease, and female gender (Bagshaw et al., 2008; Chertow et al., 1997; Mangano et al., 1998; Rosner & Okusa, 2006). Advanced age and diabetes have also been shown to be risk factors for AKI—a fact that has increasing implications considering constantly ageing patient populations and the growing incidence of diabetes (Wild et al., 2004).

The pathophysiology of CS-AKI is complex and is believed to be multifactorial (Rosner & Okusa, 2006). It has, however, been proposed that the occurrence of CS-AKI may be explained by six different but

synergistically acting mechanisms: endogenous and exogenous toxins, metabolic mechanisms, neurohormonal activation, ischemia-reperfusion, oxidative stress, and inflammation (Bellomo et al., 2008).

The latter two pathways are one of the reasons that lipid-lowering statins have been suggested as a possible prophylactic treatment for AKI, due to their anti-inflammatory and anti-oxidative properties (Morgan et al., 2009). This also holds true for another well-known complication of cardiac surgery, POAF (Liakopoulos et al., 2009). However, this possible pleiotropic effect of statin therapy has been disputed, and a recent randomized study examining the effects of treatment with rosuvastatin in patients undergoing cardiac surgery indicated no effect on rates of POAF. Also, rates of AKI were higher in the treatment group (Zheng et al., 2016).

1.7 AKI in the ICU setting

Most studies on the overall incidence of AKI in the ICU have found rates in the 40–70% range, with mortality as high as 80% (Case et al., 2013; Hoste & Kellum, 2006). Furthermore, the incidence of AKI in the ICU setting has been on the rise worldwide (Bagshaw et al., 2007; Case et al., 2013). This trend appears not only to be due to the fact that older patients with more comorbidities and higher risk of AKI are being admitted to ICUs, as the incidence of AKI also seems to be on the rise in the less severely ill patients. However, studies have shown that acute physiology and chronic health evaluation (APACHE) scores and simplified acute physiology scores have not changed in line with changes in incidence (Bagshaw et al., 2007; Lameire et al., 2006). It has therefore been speculated that the increase in incidence of AKI may be due to the more rigorous diagnostic interventions in later years (Lameire et al., 2006). The highest incidence has been seen in patients with sepsis, but the incidence of AKI is generally lower in surgical patients than in medical patients in the ICU (Case et al., 2013). Even so, and reassuringly, recent studies have indicated that mortality in patients with AKI has decreased (Bagshaw et al., 2007; Waikar et al., 2006). This may stem from various factors such as the overall improvement in ICU treatment, a reduction in the use of nephrotoxic agents, and increased awareness of AKI (Waikar et al., 2006).

1.8 Prevention and treatment of AKI

Despite our improved knowledge of the pathophysiology of AKI, and advances in surgical techniques together with improved ICU management

(including dialysis therapies), effective therapeutic interventions for AKI have yet to emerge. Furthermore, randomized studies on various pharmacological agents and renal replacement therapy (RRT) have not shown any conclusive effect in reducing mortality (Bagshaw et al., 2013; Jo et al., 2007; Schneider et al., 2013). Emphasis is therefore placed on prevention. Although no single preventive measure reaches the highest levels of evidence, current recommendations are that one of the key targets for amelioration of AKI should be strict maintenance of hemodynamic stability (Prowle et al., 2014). Optimally, the goal should be to ensure that there is adequate renal perfusion and oxygen delivery to the kidneys, without fluid overload, as several studies have shown that overhydration increases the likelihood of adverse events and possibly contributes to AKI (Payen et al., 2008; Prowle et al., 2014; Stein et al., 2012). What is more, restrictive fluid management has been associated with reduced incidence of intra-abdominal hypertension (IAH), a well-defined risk factor for the development of postoperative AKI, especially following abdominal surgery (Dalfino et al., 2008).

1.8.1 Renal replacement therapy

When preventive measures fail and patients progress to end-stage renal disease (ESRD), RRT ensues. RRT may be indicated in patients with symptomatic CKD (e.g. electrolyte disturbances) (Lameire & Van Biesen, 2010) or in patients with AKI (Ronco et al., 2015). In AKI, the most common indications are acidemia, electrolyte abnormalities, fluid overload that is unresponsive to diuretic treatment, complications of uremia, and—in rare cases—intoxication with dialyzable substances (Ronco et al., 2015).

RRT includes conventional dialysis (both hemodialysis and peritoneal dialysis), hemofiltration and hemodiafiltration, and also kidney transplantation (Ronco et al., 2015). The first three treatment modalities take on the blood filtration role of the kidneys, but they lack other aspects of kidney function and are not curative (de Francisco & Pinera, 2006). They can be performed using arteriovenous or venovenous modes, either in a continuous manner (so-called continuous renal replacement therapy (CRRT)) or intermittently (Ronco et al., 2015) (Figure 5). In the ICU setting, patients are often selected for CRRT rather than intermittent hemodialysis, as they have lower MAP and are deemed too hemodynamically unstable to tolerate intermittent dialysis (Ronco et al., 2015).

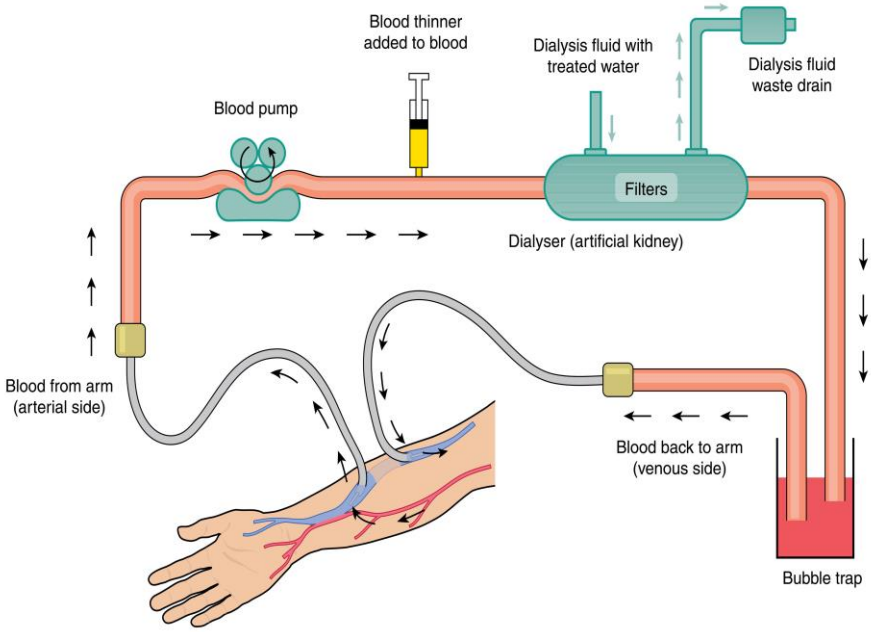

Figure 5. A schematic overview of extracorporeal hemodialysis.

1.9 Recovery of renal function

There are more and more studies examining how patients who survive critical illness fare later on (Goldstein, 2014; Palevsky et al., 2005). An estimated 8–22% of critically ill patients suffer an AKI episode from which they fail to completely recover, which may even necessitate ongoing intermittant renal dialysis after discharge (Bell et al., 2007; Uchino et al., 2005).

Animal studies have indicated that there is a causal relationship between AKI and CKD (Basile et al., 2001). Furthermore, a growing number of studies in humans also point to an association between AKI and progression of—or to—CKD (Amdur et al., 2009; Hsu et al., 2009; Ishani et al., 2011; Waikar & Winkelmayer, 2009). Following AKI, incomplete regeneration of the tubulointerstitial epithelium, characterized by fibrosis and persistent inflammation, may occur and correlate with loss of kidney function. However, the condition may remain subclinical for prolonged periods (Gueler et al., 2004).

Importantly, several studies on the long-term effect of AKI have suggested that early recovery of kidney function may be associated with better clinical

outcome after AKI (National Kidney, 2012; Rosner & Okusa, 2006). Furthermore, recovery of renal function following AKI has been shown to be an independent determinant of morbidity and mortality in patients (Bagshaw, 2006; Pannu et al., 2013; Swaminathan et al., 2010). Factors that affect the long-term prognosis after AKI are not completely understood, but the process leading to development of CKD may be at least partially modifiable, e.g. by tighter regulation of blood pressure and diabetes (Murugan & Kellum, 2011).

No agreed-upon criteria exist for the definition of recovery of renal function following an episode of AKI, making comparison of studies on the subject cumbersome. The majority of previously employed definitions fall into one of three categories:

i. Freedom from dialysis (Bagshaw et al., 2005; Schiffl & Fischer, 2008).

ii. Absolute cut-off values of follow-up eGFR (Cantarovich et al., 2004; Macedo et al., 2012).

iii. Relative changes in SCr or eGFR (Macedo et al., 2008; Pannu et al., 2013).

These definitions of renal recovery (RenR) vary widely, are based on functional improvement, and do not take into consideration the complex structural effect of acute injury on the renal tissue (Srisawat et al., 2010). This is an important point, as complete functional RenR may be noted even in the setting of residual structural damage, which in turn can have implications for progression to CKD (Gueler et al., 2004; Hsu et al., 2009). Furthermore, current definitions of RenR lack a relationship with the time course of recovery of renal function, and insufficiently define optimal length of follow-up of patients' renal function following AKI. The RIFLE criteria propose a cut-off of 3 months after AKI prior to diagnosis of CKD in patients who do not have recovered renal function (Bellomo et al., 2004). However, some studies have revealed that the RenR process may go on for up to 18 months (Macedo et al., 2012).

RenR, defined as liberation from dialysis, only covers those with the most severe forms of AKI. However, milder forms of AKI have also been shown to affect morbidity and mortality (Zakeri et al., 2005). Thus, definitions have emerged that outline absolute and relative changes in eGFR and SCr. However, a disadvantage of basing definitions of RenR on SCr and/or eGFR is the non-linear relationship between SCr and GFR (Figure 6). Another problem with definitions based on SCr might also be the confounding factor

of decreased muscle mass during severe illness (Srisawat et al., 2010). In addition, cut-off levels for criteria of renal recovery may in fact be over baseline in patients with advanced CKD, limiting the usefulness of the definition in that patient group (Macedo et al., 2012). On the other hand, the disadvantage of basing definitions of RenR on relative changes in SCr or eGFR is the dependency on availability of baseline SCr.

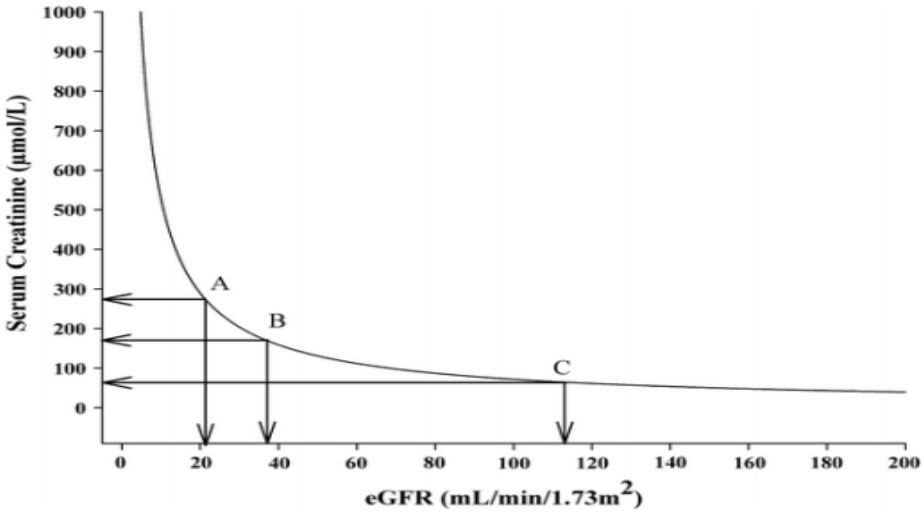

Figure 6. The relationship of the estimated glomerular filtration rate (eGFR) to serum creatinine (SCr). The graph shows how a substantial decline in eGFR only leads to slight elevations in SCr on the flat part of the curve, meaning that a substantial decrease in eGFR may lead to a very subtle increase in SCr. However, on the steep part of the curve a very slight decrease in eGFR leads to a significant increase in SCr (Damman et al., 2012).

The Acute Dialysis Quality Initiative (ADQI) Group sought to provide a consensus definition of AKI recovery, and suggested that complete RenR should be defined as a return of SCr to below the definition of RIFLE-R, or within 50% of baseline SCr. Furthermore, partial RenR was defined as freedom from RRT, but not to within 50% of baseline SCr (Bellomo et al., 2004).

A 2008 study with 5-year follow-up provided important insight into the course of AKI after critical illness. In the study, only 57% achieved full renal recovery (defined as eGFR within 10% of baseline) before hospital discharge (Schiffl & Fischer, 2008). The study also confirmed the poorer survival of patients diagnosed with AKI, even during long-term follow-up. This was most evident in patients with more extensive comorbidities and in those who did not achieve full recovery of kidney function. Furthermore, the study showed that if patients failed to reach normal renal function 6–12 months after the index insult, no further improvement could be expected. Importantly, around

10% of the group that had only partially recovered renal function had a further decline in renal function during subsequent long-term follow-up. Lastly, the study highlighted that a further kidney insult in a patient recovering from AKI leads to a reduced likelihood of complete RenR (Schiffl & Fischer, 2008). Similarly, other studies have shown that more than one episode of AKI is an independent predictor of poorer survival (Guerin et al., 2000). This further drives home the message of the importance of scrupulous follow-up in this patient population, both during hospitalization and after discharge.

Research on factors that affect RenR is in progress. Loss of autoregulation of renal blood flow and hypotension have been singled out as key factors in delayed RenR (Conger & Hammond, 1992). Fluid overload has also been shown to negatively affect renal recovery (Bouchard et al., 2009; Heung et al., 2012). Furthermore, it has been shown that the degree of recovery from AKI requiring dialysis is associated with the initial dialysis modality used (Sun et al., 2014). This is in line with the results of several other studies, with higher rates of RenR in patients treated with CRRT as compared to intermittent hemodialysis (Bell et al., 2007; Lin et al., 2009; Uchino et al., 2007). However, the effect of factors such as inflammation and oxygen delivery to the kidneys on renal recovery has yet to be fully determined (Srisawat et al., 2010).

1.10 Chronic kidney disease

During the acute phase of kidney injury, mechanisms such as hyperfiltration and hypertrophy may aid in ensuring the kidney‘s ability to secrete waste products. In the long run, however, they are believed to factor in as causes of progressive renal dysfunction due to propagation of increased glomerular capillary pressures, ultimately leading to glomerulosclerosis, destruction of renal parenchyma, and CKD (Helal et al., 2012; Wald et al., 2009). Whatever the underlying cause of CKD, patients usually experience progressive kidney dysfunction when the loss of functional nephrons reaches a certain threshold, as irreversible sclerosis occurs in the remaining, strained functional units of the kidneys (Hsu et al., 2009). Subsequently, the rate of progression depends on factors such as age, underlying etiology, and successful treatment of exacerbating factors (Gullion et al., 2006). There are many components that may exacerbate the process, i.e. systemic hypertension, hyperlipidemia, obesity, nephrotoxic substances (e.g. non-steroidal anti-inflammatory drugs, and various antibiotics), sub-optimally treated diabetes mellitus (DM), and smoking (Bash et al., 2009; Brenner, 2005; Chang et al., 2016; Thakar et al., 2011). In a recent study, a validated risk calculator was reported, which is applicable to adult populations and based upon routine laboratory tests and baseline characteristics. The study showed that lower eGFR, albuminuria, young age, and male sex were indicative of higher risk of progression to end-

stage kidney disease, the final stage of CKD. Furthermore, the results suggested that lower albumin, calcium, and bicarbonate levels and higher phosphate levels were predictive of elevated risk of disease progression (Tangri et al., 2011).

However, the term CKD covers a wide range of kidney dysfunction, and in 2002 the National Kidney Foundation's Kidney Disease Outcome Quality Initiative (KDOQI) presented guidelines for classification of CKD ("KDOQI Clinical Practice Guideline for Diabetes and CKD: 2012 Update," 2012). They defined CKD as deranged kidney function and albuminuria with or without a decreased GFR, persisting for over three months. Furthermore, they divided CKD into stages based on the degree of the decrease in GFR (Table IV).

Table IV: The KDOQI classification of chronic kidney disease ("KDOQI Clinical Practice Guideline for Diabetes and CKD: 2012 Update," 2012).

Stage	GFR	Description
1	≥ 90	Kidney damage (albuminuria) with normal GFR
2	60–89	Kidney damage (albuminuria) with mild reduction of GFR
3	30–59	Moderate reduction of GFR
4	15–20	Severe reduction of GFR
5	< 15	Kidney failure

GFR, glomerular filtration rate.

Importantly, studies have consistently shown a relationship between CKD and the development of vascular disease, be it coronary artery disease or peripheral vascular disease (Coresh et al., 2003; Gullion et al., 2006). Rates of hospitalization in patients with CKD are elevated compared to the general population, especially due to infections and cardiovascular diseases (Bash et al., 2009; Foley et al., 2005). Furthermore, all-cause mortality rates increase as kidney function decreases and mortality rates are up to six times higher in patients with stage-5 CKD compared to the general population (Go et al., 2004). Interestingly, the leading cause of death in this group of patients is cardiovascular disease (CVD) (Neovius et al., 2014; Perazella & Khan, 2006; Tonelli et al., 2006).

1.11 Cardiorenal syndrome

The heart and kidneys cooperate in maintaining hemodynamic stability and organ perfusion, and are connected through interdependent relationships, e.g. neuronal and hormonal control (Brenner, 2005). A number of bidirectional interactions exist between the heart and kidney functions e.g.

regulation of electrolytes and fluid status (Ronco et al., 2008). The term cardiorenal syndrome (CRS) has been used to define the relationship in cases of dysfunction as: “a disorder of the heart and kidneys whereby acute or chronic dysfunction in one organ may induce acute or chronic dysfunction in the other” (Ronco & Ronco, 2012). CRS has been divided into five types (Ronco & Ronco, 2012) (Table V).

Table V: Cardiorenal syndrome.

Type	Initial dysfunction	Result	Example
1	Acute heart dysfunction	Acute kidney injury or dysfunction	Cardiogenic shock, acute decompensated heart failure
2	Chronic heart dysfunction	Progressive kidney dysfunction	Chronic heart failure
3	Acute kidney dysfunction	Acute cardiac dysfunction (e.g. arrhythmia or heart failure)	Acute kidney injury
4	Chronic kidney disease	Cardiac dysfunction or hypertrophy and/or higher risk of adverse cardiovascular events	Chronic glomerular disease
5	Systemic condition	Heart and kidney dysfunction	Diabetes mellitus, sepsis, hypertension

It has since been argued that this might be too simplistic a definition, but the consensus remains that a pathophysiological condition may occur in which the combination of heart and kidney dysfunction can amplify organ dysfunction through induction of pathological mechanisms affecting both organ systems (Braam et al., 2014). In line with this are studies showing increased risk of major cardiovascular events in patients who experience postoperative AKI, especially in the setting of pre-existing heart or kidney dysfunction (Hansen et al., 2015; Ryden et al., 2014).

1.12 Cardiovascular disease

CVD is the sole leading cause of death globally (Laslett et al., 2012; Mortality & Causes of Death, 2015). Furthermore, although age-standardized mortality rates for CVD fell by 22% from 1990 to 2013, the total number of deaths attributed to CVD are expected to rise from the current 17.3 million to 23.6 million in 2030, mainly due to ageing of the world population (Laslett et al., 2012; Mortality & Causes of Death, 2015). However, in the past few years and decades, advances have been made in the treatment of CVD that range from public health measures to reduce the incidence of known risk factors (e.g. smoking and hypertension), medical treatments such as the use of

statins, percutaneous coronary intervention (PCI), and—not least—advances in surgical procedures.

Generally, heart surgery is performed using CPB and the heart is arrested with potassium-rich cardioplegia. This allows the procedure to be performed on an empty and motionless heart. Then, during the operation, the CPB technique uses an extracorporeal circuit to filter and oxygenate blood before it is re-circulated into the systemic circulation (Figure 7) (Machin & Allsager, 2006).

Figure 7. Cardiothoracic surgery performed at Landspitali University Hospital. In the surgical wound are circuits of the cardiopulmonary bypass, emptying the heart of desaturated blood, circulating and oxygenating it extracorporally before re-circulation of it to the patient. Photograph courtesy of Ragnar Th. Sigurdsson.

The first open-heart operation using CPB was performed in 1953 (Stoney, 2009). Since then, advances in surgical techniques, anesthesiology and CBP technique, perioperative care, and ICU treatment have led to an era in which increasingly complicated cardiac procedures can be conducted. Ever older patients with more comorbidities are undergoing cardiac surgery (Horan et al., 2006), and the list of possible perioperative complications is extensive and includes death, bleeding, infections, and stroke. However, among the most common complications are heart arrhythmias, most often POAF, and AKI (Glance et al., 2007; Sigurjonsson et al., 2012).

Coronary artery revascularization, first performed in 1960, is now one of the most commonly conducted open-heart surgeries, although the number of surgeries performed has decreased following advances in the field of PCI (Hannan et al., 2005). However, the large randomized SYNTAX trial, comparing PCI and CABG in patients with advanced CAD, showed that one-year rates of major adverse cardiac and cerebrovascular events were 5.4%

lower in surgical patients (12.4% vs. 17.8%, p = 0.002) (Serruys et al., 2009). In line with these results and those from further studies on the subject, CABG remains the standard of care for three-vessel or left main stem coronary disease (Mohr et al., 2013; So, 2002) Other indications supporting myocardial revascularization surgery include debilitating angina, concomitant diabetes (Farkouh et al., 2012), occlusions not reachable by PCI, left main stem stenosis, poor left ventricular function (but with viable myocardium), ongoing ischemia in the setting of a non-ST-segment elevation myocardial infarction unresponsive to medical therapy, and total occlusion of a coronary artery (Task Force et al., 2013). Emergency surgery may also be performed in the setting of an ST-segment elevation myocardial infarction where PCI is impossible or has failed (Hillis et al., 2011).

Myocardial revascularization surgery is generally performed with the help of CPB. However, CABG can also be performed on a beating heart (off-pump, OPCAB), thereby circumventing the need for CPB and associated complications such as disturbances in the fibrinolytic system, activation of the systemic inflammatory response, non-pulsatile blood flow, and hypotension (Machin & Allsager, 2006; Sniecinski & Chandler, 2011). Since the advent of OPCAB surgery, several studies have sought to compare the off- and on-pump techniques. Initial non-randomized studies indicated that the rates of various complications were lower following OPCAB (Gold et al., 2004). However, the largest randomized studies comparing OPCAB and conventional CABG, the ROOBY and CORONARY studies, have failed to show a significant change with regard to the incidence of AKI, POAF, stroke, myocardial infarction (MI), or perioperative death—further highlighting the complex association between CPB and AKI (Lamy et al., 2012; Lamy et al., 2013; Shroyer et al., 2009).

After CABG, AVR is the second most common open-heart procedure in most western countries ("Annual report SWEDEHEART 2012," 2014). AVR is most often conducted in patients with aortic stenosis (AS), usually secondary to degeneration of a tricuspid valve or calcification of a congenital bicuspid aortic valve. AS increases with age (Rajamannan et al., 2011) and its incidence has been reported to be 0.2% in patients aged between 50 and 59, 1.3% in those between 60 and 69 years, 3.9% in those between 70 and 79 years, and 9.8% in the age group 80–89 years (Eveborn et al., 2013). By convention, AVR is conducted via a sternotomy using CPB and the diseased valve is replaced by a biological or mechanical prosthesis (Figure 8). Biological aortic valves may also be inserted using percutaneous techniques via femoral arteries, or with minimally invasive techniques through the apex of the left ventricle, which is called transcatheter aortic valve insertion (TAVI). Once in place, the prosthetic valve is expanded, pushing the leaflets of the old valve out of the way and taking their place (Dworakowski et al., 2010).

Both TAVI and AVR, and especially AVR, are considered to be effective therapies for severe AS, but the procedures have different complication profiles. In general, TAVI patients are at greater risk of postoperative paravalvular leakage, aortic regurgitation, and major vascular events, whereas surgical AVR patients are at greater risk of major bleeding, AKI, and new-onset POAF (Kodali et al., 2012; Mack et al., 2015; Thyregod et al., 2015).

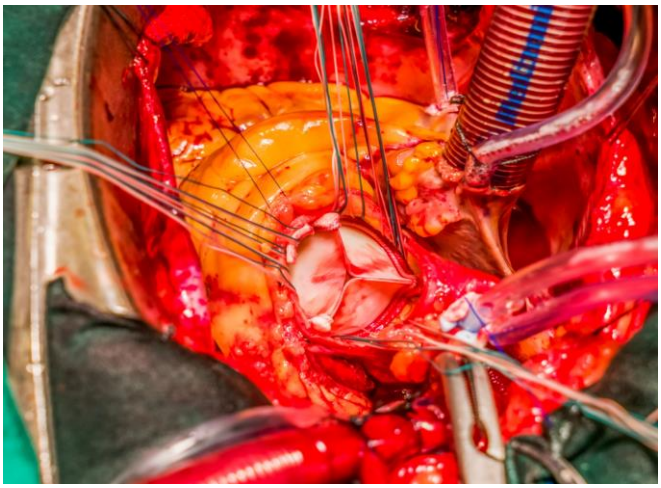

Figure 8. Aortic valve surgery. The prosthetic valve is being sewn in place after removal of the diseased native valve. Photograph courtesy of Ragnar Th. Sigurdsson.

1.13 Postoperative atrial fibrillation following cardiac surgery

Arrhythmia is one of the most common complications of cardiac surgery and may negatively affect morbidity, length of hospital stay, and 30-day mortality (Almassi et al., 1997; Villareal et al., 2004). In the postoperative period, POAF is the most common arrhythmia, with the majority of studies reporting rates of 20–40% following CABG, 40–50% after valvular surgery, and up to 60% following combined valvular and CABG surgery (Echahidi et al., 2008; Kowey et al., 2001; Maisel et al., 2001). POAF may present with obvious clinical symptoms such as increased heart rate, hypotension, or even MI, and is most commonly confirmed using 12-lead electrocardiogram (ECG) or continuous telemetry.

POAF is most often detected on the second to third postoperative days and is frequently self-limiting and short-lived. Up to 80% of patients convert to sinus rhythm (SR) within 24 h, and six weeks after initial diagnosis 98% of patients have converted to SR (Aranki et al., 1996). Note that since the rate of POAF increases with age, POAF can be expected to be an increasing

problem in the large and growing population of elderly patients undergoing cardiac surgery (Amar et al., 2002).

While POAF after cardiac surgery can be transient and without any consequences, it may lead to serious complications such as hemodynamic instability, cardiac failure, AKI, and stroke—and also to substantial economic costs (Ahlsson et al., 2009; Almassi et al., 1997; Steinberg, 2004). Furthermore, recent studies have indicated that POAF may play an even greater role in long-term mortality than previously believed, warranting more aggressive preventive and therapeutic measures (Phan et al., 2015). In a recent prospective, propensity score-matched (PSM) study, the effect of POAF following cardiac surgery on long-term survival was studied and was found to be in line with these observations. After close matching, based on patient comorbidity, extended POAF (lasting more than two days) was found to be associated with worse long-term survival (HR 1.97; 95% CI: 1.37–2.80) (Sigurdsson et al., 2016).

1.13.1 Risk factors for POAF

As in the case of AKI, the pathophysiology of POAF is complex, incompletely understood, and multifactorial. Also, as in the case of AKI, inflammatory mechanisms—peaking on postoperative days 2 to 3—have also been implicated as predisposing to the development of POAF (Chung et al., 2001; Shlipak et al., 2003). What is more, a self reinforcing relationship between kidney dysfunction and POAF may be initiated by the pro-inflammatory effect of surgery (Fried et al., 2004). Pro-inflammatory cytokines have been shown to affect the expression and function of intracellular ion channels and electrical stability and conductance of current in the atrial myocyte membranes, predisposing to POAF (Friedrichs et al., 2011; Soliman et al., 2010). Furthermore, the clearance of pro-inflammatory cytokines is reduced when there is significant renal dysfunction, further compounding the harmful effect of inflammation on heart function (Ak et al., 2005; Fried et al., 2004).

Several perioperative factors have been reported as possible risk factors for POAF, both patient- and surgery-related (Peretto et al., 2014). Age has shown a consistent relationship with increased risk of POAF, which is believed to stem from both structural and electrophysiological changes in cardiovascular tissue with increasing age (Spach & Dolber, 1986; Zaman et al., 2000). Other reported risk factors include a previous history of cardiac disease (e.g. CAD, CHF, valvular heart disease, and cardiomyopathy), chronic obstructive pulmonary disease (COPD), obesity, increased perioperative ischemia, and postoperative infection (Ak et al., 2005; Aranki et al., 1996; Steinberg, 2004; Zacharias et al., 2005). Other risk factors that have been found to independently increase the risk of POAF in patients with AKI are age, low preoperative eGFR and hemoglobin, and nadir hematocrit

during CPB (Ng et al., 2016). Interestingly, these factors have also been associated with an increased risk of postoperative AKI (Hsu et al., 2008; Karkouti, 2012; Murphy et al., 2015).

1.13.2 Treatment of POAF

Management of POAF includes general measures, such as correction of underlying factors predisposing to arrhythmia, e.g. electrolyte and fluid deficits, specific pharmacological treatments (e.g. β-blockers and amiodarone), and non-pharmacological treatment (e.g. atrial pacing). However, all these treatments have variable efficacy and may adversely affect hemodynamic stability (Nair, 2010; Singhal & Kejriwal, 2010; Van Gelder et al., 2002; Wyse, 2011; Zimmer et al., 2003). Thus, identification of patients with several risk factors and at high risk of POAF after cardiac surgery is crucial for selection of those who might benefit from prophylactic therapy. β-blocker administration, the most used pharmacological prophylaxis, has been shown to significantly reduce the rate of POAF (Arsenault et al., 2013; Crystal et al., 2004). The European Society for Cardiothoracic Surgery therefore recommends it as the first choice in all patients who undergo open-heart surgery (Dunning et al., 2006). Amiodarone has also been shown to reduce the incidence of POAF, and to have an efficacy similar to that of β-blockers (Mitchell et al., 2005).

1.13.3 Cardiovascular disease in Iceland

One-third of all deaths in Iceland are attributable to CVD (Aspelund et al., 2010). Despite a 70% decrease in the incidence of MI in Iceland from 1981 to 2006, it remains the leading single cause of death, which is in line with other high-income nations (Aspelund et al., 2010). Moreover, the incidence of severe AS in Iceland is expected to increase greatly in coming decades, as evidenced in a recent study from Iceland where a random cohort of patients was evaluated with both computed tomography of the heart and echocardiography (Danielsen et al., 2014). As in other western countries, the largest increase is predicted to be in the population of patients who are 70 years old or more. Many of these patients can be expected to require treatment, both medical and surgical, thereby placing great strain on healthcare systems (Danielsen et al., 2014).

The first open-heart surgery using CPB, a form of CABG surgery, was conducted in Iceland on June 14, 1986 (Arnorsson, 2013) (Figure 9). Before that, Icelandic patients in need of open-heart surgery that required CPB had to be sent overseas for treatment. The number of surgeries has steadily increased since then and, to date, approximately 7,000 open-heart surgeries have been performed in Iceland (Guðbjartsson, 2016). Landspitali University

Hospital is the only center in Iceland where open cardiac surgery is performed, and currently four senior surgeons perform around 200–250 operations annually. In Iceland CABG still accounts for approximately two-thirds of the operations, and this ratio has been fairly stable in the last ten years (Sigurjonsson et al., 2012).

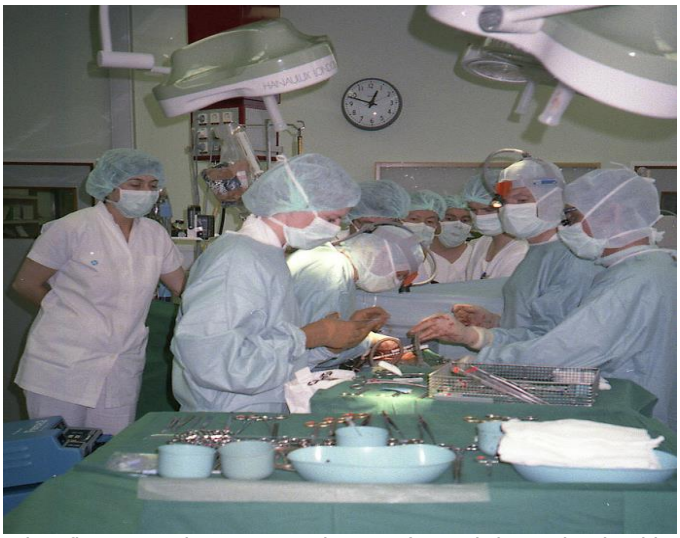

Figure 9. The first open-heart operation performed in Iceland with the aid of cardiopulmonary bypass technique. Photograph courtesy of Rannveig Þorvarðardóttir.

The first AVR in Iceland was performed in September 1987 (Arnorsson, 2013). By far the most common indication for AVR in Iceland is AS, followed by aortic valve regurgitation and endocarditis-related aortic valve disease (Ingvarsdottir et al., 2011) (Figure 10).

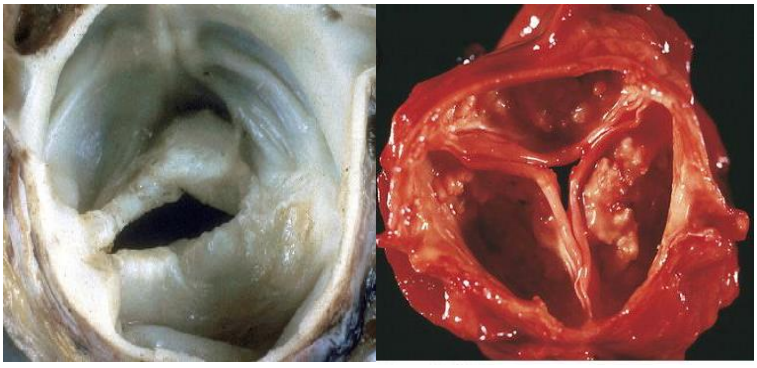

Figure 10. Aortic stenosis in a bicuspid aortic valve (left) and a tricuspid aortic valve (right). Modified from http://www.mo-media.com/pathology/bicvpic.jpg and http://www.visualphotos.com/image/1x6067829/heart_valve_disease_aortic_stenosis.

Other open-heart procedures performed at the university hospital include mitral valve repair and replacement, aortic and tricuspid valve repair, thoracic aorta aneurysm repair, anti-arrhythmia procedures (MAZE), and surgery for congenital heart disease. For over a decade the outcome of most of the open-heart procedures conducted in Iceland has been extensively studied. Briefly, the results indicate a long-term outcome comparable to that in neighboring nations (Ingvarsdottir et al., 2011; Melvinsdottir et al., 2016; Oddsson et al., 2012; Ragnarsson et al., 2012; Sigurdsson et al., 2012; Sigurjonsson et al., 2012; Smarason et al., 2009; Steingrimsson et al., 2008; Viktorsson et al., 2011). The mortality rate is in the lower range, as is the rate of deep sternal wound infections (Steingrimsson et al., 2012). However, postoperative bleeding and the need for reoperation for bleeding is relatively high (Smarason et al., 2009) and patients remain at risk of other serious complications such as heart failure, AKI, and arrhythmias.

2 Aims

2.1 Study I

In this study, the goal was to determine the incidence of AKI in the ICU after meticulous identification of baseline SCr to overcome potential shortcomings of the RIFLE criteria.

2.2 Study II

We aimed to determine the incidence and the risk factors for AKI after myocardial revascularization surgery in a whole nation. Special emphasis was placed on the part that AKI, and subsequent recovery of renal function, plays in the postoperative prognosis—chiefly long-term kidney function and survival.

2.3 Study III

In this study, we evaluated the incidence and risk factors for AKI following aortic valve replacement on the indication of aortic stenosis. We also sought to study the short-term and long-term outcome in patients, including survival.

2.4 Study IV

This retrospective, population-based study was designed to evaluate different criteria for renal recovery, regarding the effect of recovery on long-term survival. We sought to examine factors affecting renal recovery following AKI after CABG and/or AVR, and also the relationship between AKI, recovery of renal function, and long-term survival.

2.5 Study V

The main aim was to evaluate risk factors for postoperative atrial fibrillation following myocardial revascularization surgery and AVR, in a whole nation, and to develop a model that might help in the preoperative identification of patients at highest risk of postoperative atrial fibrillation. In addition, we studied short-term postoperative complications, 30-day mortality, and long-term survival.

3 Materials and methods

An overview of the materials and methods of studies I–V is given in Table VI. All the studies were single-center, nationwide, and retrospective in design, and they were performed on patients treated and operated at Landspitali University Hospital in Reykjavik. All the necessary study approvals were obtained from the Icelandic National Bioethics Committee and the Icelandic Data Protection Authority.

3.1 Registers

Several registers were used to identify and follow up patients, in an effort to minimize the amount of missing data.

3.1.1 Centralized registers

At Landspitali University Hospital, all patients who undergo surgery are registered in the institution‘s centralized electrical medical record system, called SAGA. Furthermore, patients who undergo open-heart surgery in Iceland are registered in a customized cardiac surgery database at the university hospital, the only institution performing cardiac surgery in Iceland. Relevant clinical information is continually registered in this database with the aim of quality control and further development of care of patients who undergo heart surgery. Individual patient information was obtained from patient charts, centralized laboratory databases, and surgical and anesthesiology reports. To ensure identification of all patients, the database was checked regularly against the hospital‘s electronic record system to confirm a 100% match. Lastly, in study IV, data on all patients ≥ 18 years of age who were admitted to ICUs in Iceland were collected from individual patient charts and registered.

3.1.2 The National Patient Register

The National Patient Register has been in use in Iceland since 2010. It has information on every patient‘s unique identification number, sex, age, place of residence, dates of admission to hospitals around the country, diagnoses according to the International Classification of Diseases, tenth revision (ICD-10) codes, procedures, and electronic prescriptions for drugs.

Table VI: Overview of materials and methods.

	Study I	Study II	Study III	Study IV	Study V
Population	ICU patients ≥ 18 years old	CABG patients	AVR patients operated for AS ± CABG	CABG ± AVR patients ≥ 18 years old	CABG ± AVR patients operated for AS
Nr. of patients	1,012	1,710	365	1,834	744
Period	2007	2001–2013	2001–2011	2007–2015	2002–2006
Statistical analysis	Multivariate logistic regression, Kaplan-Meier survival analysis, and Cox hazard regression analysis	Logistic and Poisson regression, Kaplan-Meier survival analysis, and multivariate Cox hazard regression analysis	Logistic regression, Kaplan-Meier survival analysis, and multivariate Cox hazard regression analysis	Receiver operator analysis, logistic and Cox hazard regression analysis, propensity score matching, and Kaplan-Meier survival analysis	Logistic regression, Kaplan-Meier survival analysis, receiver operator analysis, and multivariate Cox hazard regression analysis
Outcome measures	Incidence of AKI, risk factors, survival, and rate of ESRD	Incidence of AKI, renal recovery, and long-term survival	Incidence of AKI, and short-term and long-term complications, including survival	Definition of renal recovery, risk factors for non-recovery, and long-term survival	Incidence of POAF, short-term complications, and short-term and long-term survival

AKI, acute kidney injury; AS, aortic stenosis; AVR, aortic valve replacement; CABS, coronary artery bypass surgery; ESRD, end-stage renal disease; ICU, intensive care unit.

3.1.1 The Icelandic End-Stage Renal Disease Registry

The university hospital is the only center providing long-term RRT in Iceland and it records extensive information on all patients who undergo dialysis, such as indication, dialysis modality, and follow-up of kidney function.

3.1.2 Statistics Iceland and the Icelandic Cause of Death Register

All Icelandic citizens have a unique personal identification number consisting of ten digits, the date of birth and four control numbers. These unique numbers enable linkage of separate registries. All foreign-national patients who are admitted to Icelandic hospitals are allocated a personal identification number. All deaths must be reported to the Icelandic national population register, Statistics Iceland (www.statice.is). The Directorate of Health (Landlæknir, www.landlaeknir.is) handles registration of causes of death in the Icelandic Cause of Death Register.

3.2 Study population

3.2.1 Study I

Patients were identified through a centralized database that records all ICU admissions at the university hospital. A total of 1,390 patients were admitted in 2007, from January 1 through December 31, 2007. Individuals under the age of 18 and those 364 patients who were re-admitted to the ICU were excluded. Fourteen other patients were excluded because of missing data, leaving 1,012 patients for final analysis.

3.2.2 Study II

All patients who underwent isolated CABG (on- or off-pump) from January 1, 2001 through December 31, 2013 were identified through the centralized surgical registries already mentioned. Patients who concomitantly underwent other types of cardiac surgery (e.g. mitral valve repair or MAZE anti-arrhythmia surgery) were excluded. In total 44 patients were excluded, 42 as they had missing baseline SCr values and two because they had end-stage kidney disease and were dependent on hemodialysis before the study. This left 1,710 patients for final analysis. The flow chart of the study population is shown in Figure 11.

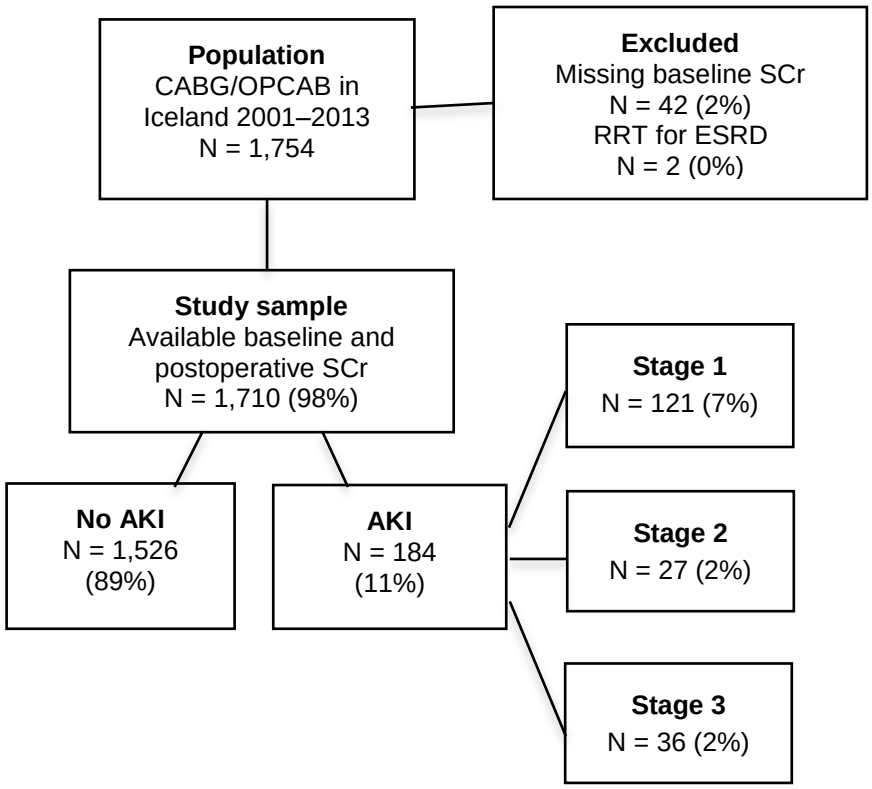

Figure 11. Flow chart of the study population in study II. AKI, acute kidney injury; CABG, coronary artery bypass grafting; ESRD, end-stage renal disease; OPCAB, off-pump coronary artery bypass; RRT, renal replacement therapy; SCr, serum creatinine (µmol/L).

3.2.3 Study III

All patients who underwent AVR due to AS ± CABG from January 1, 2001 through December 31, 2011 were identified through the centralized surgical and diagnosis registries. Of the 436 patients who were operated during the 10-year period, 71 patients were excluded: 31 due to a previous history of cardiac surgery, 27 because the indication for surgery was aortic regurgitation, and 13 due to missing data.

3.2.4 Study IV

All patients who underwent abdominal, cardiothoracic, vascular, or orthopedic surgery from January 1, 2007 through December 31, 2015 were identified through the centralized medical record system and were included. Altogether, 27,685 individuals had 41,361 operations in total. Operations were grouped together according to surgical codes, based on the Nordic Medico-Statistical Committee Classification of Surgical Procedures (NCSP-IS, version 1.14, www.nowbase.org). Of the surgical cases identified, 1,917 (45.7%) were

CABG and/or AVR. Of these patients, 83 were excluded as they had missing postoperative SCr values. The 327 patients identified with first-time AKI were analyzed further regarding recovery of renal function (Figure 12). Information on perioperative factors and registered ICD-10 diagnostic codes were collected from the centralized medical registry.

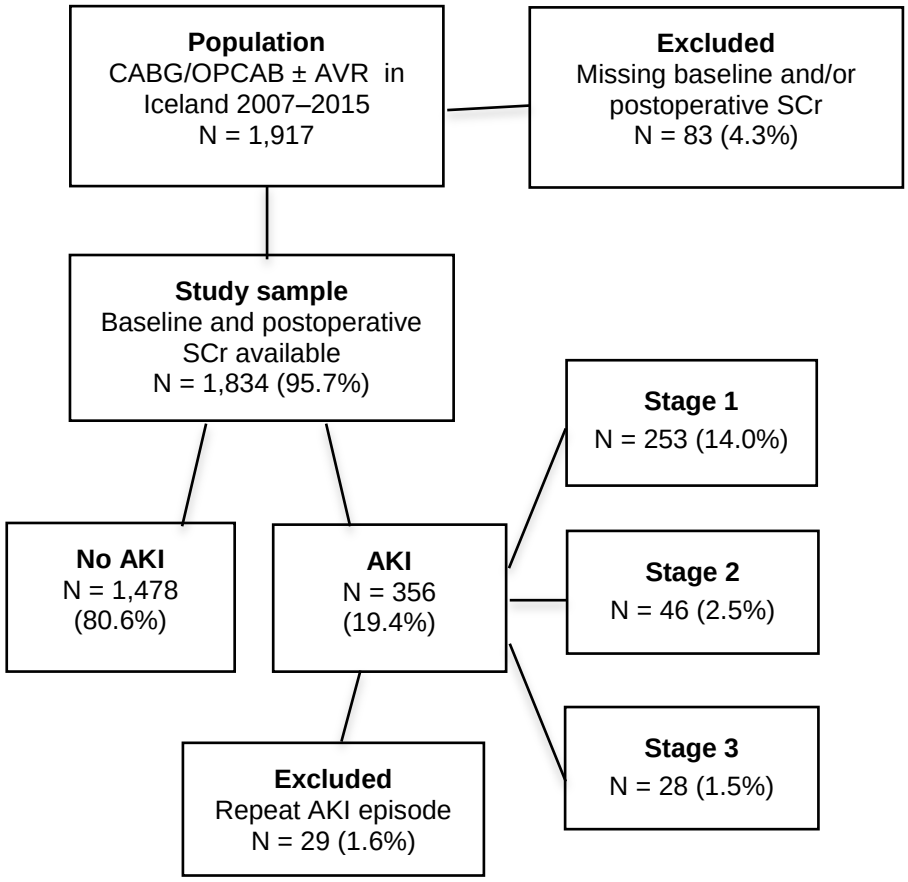

Figure 12: Population flow chart in study IV. AKI, acute kidney injury; AVR, aortic valve replacement; CABG, coronary artery bypass grafting; OPCAB, off-pump coronary artery bypass; SCr, serum creatinine (µmol/L).

3.2.5 Study V

Patients who underwent CABG ± AVR on the indication of AS in Iceland from January 1, 2002 through December 31, 2006 were identified through a computerized diagnosis and operation registry together with the centralized open-heart surgery database. Altogether, 876 patients were identified and 744 of them were included for further analysis. A flow chart of the study population is shown in Figure 13.

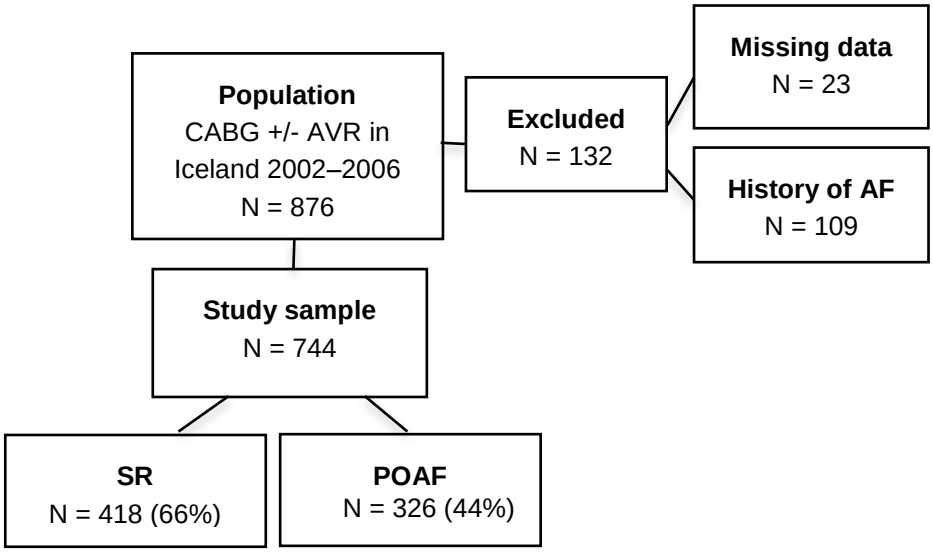

Figure 13. Flow chart of the study population in study V. AF, atrial fibrillation; AVR, aortic valve replacement; CABG, coronary artery bypass graft; SR, normal sinus rhythm; POAF, postoperative atrial fibrillation.

3.3 Data collection

Information on clinical characteristics was collected from centralized registers and multiple variables were registered for each patient, including known risk factors for CVD, comorbidities, and previous medical history. Information on previous RRT was collected from the Icelandic End-Stage Renal Disease Registry. Data on perioperative or postoperative complications was collected from patient charts and also from anesthesiology and surgery reports.

3.4 Risk scores and preoperative comorbidity classification

In study I, the APACHE II score was calculated (Knaus et al., 1985). In studies II, III, and V, patients‘ preoperative symptoms were evaluated with the New York Heart Association (NYHA) classification (New York Heart Association. Criteria Committee. & New York Heart Association., 1979), and their standard EuroSCORE calculated (Roques et al., 1999). In study IV, the American Society of Anesthesiologists physical status classification (ASA score) was documented (Saklad, 1941).

3.5 Laboratory methods

Estimated GFR was derived from SCr using the CKD-EPI (Levey et al., 2009) and MDRD (Levey et al., 1999) equations in studies II and IV and studies I, III, and V, respectively.

CKD-EPI equation:

$eGFR = 141 \times \min(SCr/\kappa,1)^{\alpha} \times \max(SCr/\kappa,1)^{-1.209} \times 0.993^{age}$ [× 1.1018 if female] [× 1.159 if black]

If female: $\kappa = 0.7$, $\alpha = -0.329$

If male: $\kappa = 0.9$, $\alpha = -0.411$

MDRD equation:

$eGFR = 186.3 \times (SCr \text{ (in } \mu mol/L)/88.4)^{-1.154} \times age^{-0.203}$ (× 0.742 for females)

3.6 Classification of AKI

In studies II and IV, the KDIGO criteria (Khwaja, 2012) were used for classification of AKI and in studies I, III, and V we used the RIFLE criteria (Bellomo et al., 2004; Khwaja, 2012). As urine output was not always available, classification was based solely on SCr values and eGFR. Baseline SCr was classified as preoperative SCr closest to surgery, obtained within 30 days of surgery.

3.7 Classification of POAF

POAF was diagnosed with a rhythm monitor/telemetry and/or ECG, with a duration of ≥ 5 min and/or initiation of treatment for AFib. At Landspitali, ECG monitoring is normally continuous for the first postoperative week after open-heart surgery.

3.8 Classification of complications and mortality

Postoperative complications were categorized as either minor or major in studies II, III, and V. In studies II and III, minor complications included leg wound infection, POAF, urinary tract infection (UTI), pleural effusion requiring drainage, and pneumonia. Major complications included stroke, deep sternal wound infection (DSWI) with mediastinitis, endocarditis, MI (defined as isolated ST-segment changes or a new left bundle branch block on electrocardiogram along with elevation of creatine kinase MB of ≥ 70 µg/L), reoperation due to bleeding, sternum dehiscence and acute respiratory distress syndrome (ARDS)/multiple organ failure (MOF). In study V, minor complications included leg wound infection, UTI, and pneumonia; major complications included stroke, postcardiotomy mediastinitis, endocarditis, MI, AKI necessitating RRT, reoperation, sternum dehiscence, and ARDS/MOF. Operative mortality was classified as being death ≤ 30 days from surgery.

3.9 Outcome measures

All-cause mortality (overall survival) was an outcome parameter in all the studies. Information on survival and cause of death was obtained from Statistics Iceland and the Icelandic Cause of Death Register, respectively. Other outcome measures for each study are described below.

3.9.1 Study I

The outcome measures were incidence of AKI, long-term survival, and rates of progression to ESRD.

3.9.2 Study II

This study focused on the incidence of AKI, short-term complications including mortality, long-term survival, progression to ESRD, and ratio of RenR.

3.9.3 Study III

The outcome measures were incidence of AKI, short-term complications including mortality and risk of requiring dialysis therapy, long-term mortality, and rates of progression to ESRD.

3.9.4 Study IV

This study examined the ratio of renal recovery according to the optimal definition with regards to one-year survival. Risk factors for reduced long-term survival were evaluated and five-year survival was compared between patients who recovered renal function and a propenisty score-matched group who did not.

3.9.5 Study V

The effect of POAF on short-term complications and mortality was examined, and long-term survival evaluated.

3.10 Statistical analysis

In studies I, II, and V, data collection was done using a standardized Excel data sheet (Microsoft Corp., Redmond, WA, USA). In study IV, all data were processed using custom JAVA scripts. In studies I–III and V, all the statistical analyses were done using R statistical analysis software (R Foundation for Statistical Computing, Vienna, Austria). Study I was conducted using version 2.12.0, study II using version 3.1.1, study III version 3.1.2, and study V version 2.12.1. The survival, Hmisc, MASS, stargazer, Greg, epicalc,

epitools, Resource Selection, FactoMine, MatchIt, and pROC packages were used. Statistical analysis in study IV was conducted in RStudio, version 0.98 (R Development Core Team, 2015).

Results are presented as mean/median ± standard deviation (SD), number of patients, and percent. The level of statistical significance was set at $p < 0.05$. Descriptive analysis was performed using the binary grouping of AKI (RIFLE classification Risk, Injury, or Failure or KDIGO classification of stage 1, stage 2, or stage 3 AKI) as opposed to no AKI in studies I–IV, recovery versus non-recovery of renal function in study IV and NSR versus POAF in study V. Continuous variables were compared with the 2-sample Student's t-test or Mann-Whitney rank-sum test (also known as the Wilcoxon-Mann-Whitney test or the Wilcoxon rank-sum test) based on normality of the residuals for the data. In the Mann-Whitney test, statistics depend only on the ranks of the observations in the combined sample, as opposed to their raw values, and no assumption is made regarding population distribution (Ludbrook, 2008). The parametric Student´s t-test assumes a normal distribution and is more powerful than the non-parametric Mann-Whitney test (Ludbrook, 2008). Categorical variables were compared using either Fisher's exact test or the chi-square test (Ludbrook, 2008). Fisher's exact test is a way of testing association between two variables when the sample size is small, but the chi-square test is used when sample sizes are large. The chi-square test works by computing the expected value for each cell if the relative risk were 1. The difference in observed and expected values is then combined into a chi-square approximation statistic and a p- value is computed. The Fisher exact test gives an exact answer no matter what the sample size is, but it is problematic as it assumes a fixed number of rows and columns in the experiment, which is not the case in the majority of experiments (Ludbrook, 2008).

3.10.1 Calculation of incidence

In studies I–III, incidence included all cases of AKI diagnosed in the cohort. Paper III reported combined postoperative AKI incidence as well as incidence in isolated AVR and combined AVR + lCABG. In study I, the incidence of AKI was calculated using both calculated and measured SCr baseline values. Paper IV reported the incidence of renal recovery as the proportion of patients who were alive on postoperative days 10, 20, and 30. In study V, incidence was calculated in the whole cohort as well as separately for patients undergoing CABG or CABG + AVR. In study II, change in incidence over time was assessed with a Poisson model.

3.10.2 Univariate and multivariate analysis of risk factors

Univariate and multivariate logistic regression analysis was used to identify risk factors for AKI (studies I–IV) and POAF (study V), as well as significant risk factors for postoperative complications, perioperative mortality, and progression to ESRD in study II. In study IV, univariate analysis was used to assess different criteria for renal recovery. Variables judged to be of clinical importance and variables with p-values of < 0.1 in descriptive analysis were used in stepwise multivariate logistic models. In study I, multivariate linear regression was used to correct for age in analysis of ICU stay. Cox proportional hazards models were used to assess the contribution of variables to long-term survival. Odds ratios (ORs) were used in logistic models and hazard ratios (HRs) in Cox models, with 95% confidence intervals (CIs).

3.10.2.1 Study II

The final model for evaluating preoperative risk factors of AKI was corrected for age, sex, body mass index (BMI), history of hypertension (HTN), DM (both insulin- and non-insulin-dependent) and CHF, preoperative eGFR, emergency surgery, and standard EuroSCORE. The model for evaluation of intraoperative and postoperative variables was corrected for operation time, use of inotropes, red blood cell (RBC) transfusions (per unit) intraoperatively and in the first postoperative week, reoperation, and postoperative complications that were significant in univariate analysis. Lastly, the model for predictors of long-term survival was corrected for KDIGO stage of AKI, age, sex, EuroSCORE, and major complications.

3.10.2.2 Study III

Risk factors for AKI were evaluated with a model corrected for transfused RBC units, CPB time, obesity (defined as BMI >30 kg/m^2), insertion of intra-aortic balloon pump (IABP), anemia (defined as hemoglobin (Hb) < 120 g/L in females and < 135 g/L in males), HTN, sex, preoperative CKD (defined as eGFR < 60 mL/min/1.73 m^2) and age. The model for predictors of operative mortality was corrected for AKI, logistic EuroSCORE, RBC transfusion (in units), and CPB time (in min). Finally, the model for predictors of long-term survival was corrected for AKI, logistic EuroSCORE, RBC transfusion (per 5 units), age, CPB time, sex, and obesity.

3.10.2.3 Study IV

Univariate and multivariate logistic regression analysis was done to assess risk factors for decreased one-year survival of AKI patients. The multivariate regression analysis model was constructed using forward elimination to identify factors independently associated with one-year mortality. The final model was corrected for preoperative kidney dysfunction (defined as eGFR < 60 mL/min/1.73 m^2), neoplasm, CHF, ASA score 4/5, ischemic coronary disease, and renal recovery. A Cox proportional hazard model was used to analyze the association of renal recovery with long-term survival. The final model for preoperative factors was corrected for age, preoperative kidney dysfunction (defined as eGFR < 60 mL/min/1.73 m^2), and CHF. The model for intraoperative and postoperative factors was corrected for reoperation, AKI stage, and renal recovery. Proportionality was assessed visually and with the logit function in R.

3.10.3 Receiver operating characteristic curve

In studies IV and V, the predictive ability of models was assessed by calculating the area under the receiver operating characteristic (ROC) curve. A ROC curve (sometimes called a sensitivity vs. (1 − specificity) plot) is created by plotting the true positive rate of a binary classifier system against the false positive rate at varying discrimination thresholds (Hanley & Mcneil, 1982). This analysis can be used to select optimal models and discard suboptimal ones.

3.10.4 Follow-up

Patient survival was followed-up using information from Statistics Iceland and cause of death was documented from the Icelandic Cause of Death Register when possible.

3.10.4.1 Study I

The last follow-up date of survival was October 24, 2011. Median follow-up for patients with AKI was 11 months (range 0–58), but it was 21.4 months (range 0–58) in patients with normal kidney function.

3.10.4.2 Study II

In study II the last follow-up date of survival, using Statistics Iceland, was June 30, 2014 (with a mean follow-up time of 6.3 ± 3.6 years), and last follow-up date of SCr values or whether patients were receiving RRT was June 15, 2015 (with a mean follow-up time of 5.2 ± 3.9 years). Thirteen patients were lost to long-term follow-up of survival.

3.10.4.3 Study III

The last follow-up date for death and cause of death was June 1, 2013 in study II, giving a mean follow-up time of 4.7 years (range 0–11.2). No patients were lost to long-term follow-up. Patients were identified as deceased or living on September 1, 2010 and the cause of death was registered when available.

3.10.4.4 Study IV

In study IV the last follow-up date of survival was May 20, 2016. The median follow-up time in AKI patients was 38.9 months (interquartile range: 16.5–78.7).

3.10.4.5 Study V

The mean length of follow-up in study V was 5 years (range 0–8.1), and none of the patients were lost to follow-up.

3.10.5 Survival analysis

Survival analysis provides methods of comparing the risk of an event (most often death) between groups in a time-dependent fashion. The most commonly used methods were used in all the studies in the thesis, namely Kaplan-Meier to estimate survival curves, the log-rank test to compare groups statistically, and Cox´s proportional hazard analysis to test the effect of other variables on the event in question.

The Kaplan-Meier method is used to measure the probability of surviving beyond a specified length of time (the survival function) by considering time in small intervals (Kaplan & Meier, 1958). It is often used to measure the proportion of patients living for a certain period after treatment/exposure. It is depicted as a series of declining or rising horizontal steps, sometimes shown with small vertical lines indicating individual events (Bewick et al., 2004).

Comparison of survival curves was done with a log-rank test. This is used to test whether there is a difference between survival times in different groups, but does not permit other variables to be taken into account (Bewick et al., 2004). Cox´s proportional hazard analysis was used to assess the contribution of variables to long-term survival (Bewick et al., 2004) in studies II, III, and V.

3.10.6 Propensity score matching

In study IV, nearest-neighbor propensity score matching (PSMing) was used

to evaluate the connection between RenR and long-term survival. Each patient in the group that recovered renal function was assigned a control from the group that did not recover. Matching is based on the closest match to a distance measurement for the pair (Austin, 2011). The groups were matched in a 1:1 ratio with regard to age, preoperative kidney dysfunction (defined as eGFR < 60 mL/min/1.73 m^2), neoplasm, ASA score 4/5, emergency surgery, operative time, and stage of AKI. PSM is used to attempt to reduce the bias introduced by confounding variables in observational statistics—in effect attempting to mimic study randomization (Ho et al., 2007) However, a disadvantage of PSM is that only observed covariates are accounted for, so a hidden bias may remain after matching (Garrido et al., 2014). Survival of the group that recovered renal function was thereafter compared to that of the PSM control group, using the Klein and Moeschberger test (Klein & Moeschberger, 2003).

4 Results

4.1 Study I – Identification of baseline kidney function

4.1.1 Patient characteristics

Altogether, 220 ICU patients (22%; 95% CI: 19–24) were found to have AKI according to the RIFLE criteria. Of these patients 7% (95% CI: 6–9) were in the Risk class, 7% (95% CI: 5–9) were in the Injury class, and 8% (95% CI: 6–10) were in the Failure class. The distribution of AKI in each subgroup of the RIFLE classification can be seen in Figure 14, which also shows that the proportion of patients who experienced AKI increased with age ($p < 0.001$). However, the distribution between subgroups of the classification did not change significantly with age. The proportion of males was 61% in the whole study, and no significant difference was seen in sex distribution between the patients who had AKI and those who did not. The average APACHE II score of AKI patients was 23 ± 8 (median 22; range: 7–48).

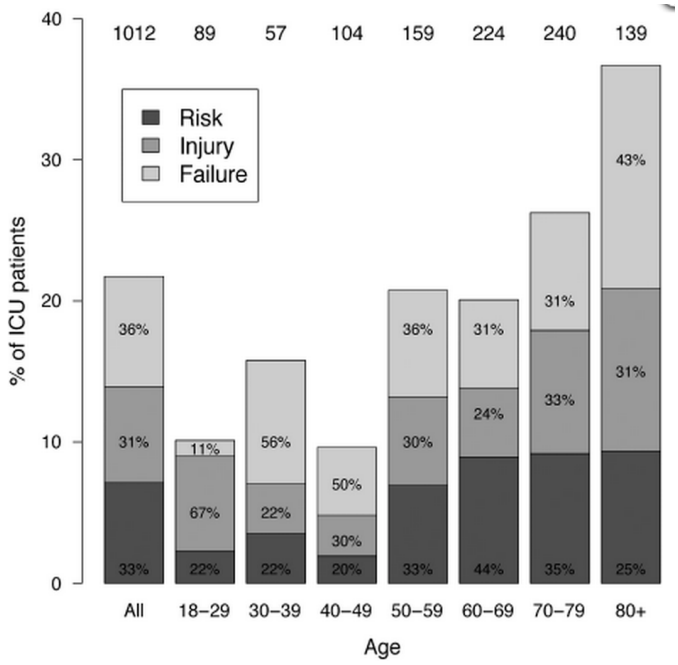

Figure 14. The absolute proportion of patients admitted to the intensive care unit (ICU) who met the RIFLE criteria for acute kidney injury (AKI), and their distribution in the Risk, Injury, and Failure subgroups. The distribution for all patients (All) is shown, and also the distribution for different age groups. The numbers above each column show the number of patients in each subgroup. The percentage value indicates the relative proportion of each RIFLE group in each age group.

4.1.2 Estimated versus measured baseline SCr

Baseline SCr was widely available in the study population (in 218 of 220 patients in the AKI group and 592 of 792 patients in the non-AKI group). Table VII shows a comparison of the RIFLE classification using the measured and estimated baseline SCr values. Using the estimated SCr values led to an overestimation of the rate of AKI (4% absolute and 16% relative overestimation; p<0.001) and resulted in the correct RIFLE subgrouping for 82% of the patients. Compared to using measured SCr, estimated values had a sensitivity of 76% (95% CI: 73–79), a specificity of 95% (95% CI: 94–97), a positive predictive value of 88% (95% CI: 83–91), and a negative predictive value of 90% (95% CI: 89–91).

Table VII: Classification of intensive care unit patients into the RIFLE subgroups of AKI using either measured or estimated baseline creatinine derived from eGFR 75 according to the MDRD equation.

		Measured SCr			
		Non-AKI	**Risk**	**Injury**	**Failure**
Estimated SCr	Non-AKI	533	21	5	1
	Risk	40	28	12	0
	Injury	18	19	31	6
	Failure	1	4	21	70

AKI, acute kidney injury; Cr, creatinine; MDRD, Modification of Diet in Renal Disease; SCr, serum creatinine.

4.1.3 Risk factors for AKI

Table VIII shows the frequency of previously defined risk factors for AKI and also the contributory causes to the development of AKI in patients in each RIFLE subgroup. The most common risk factor was ischemic heart disease, cardiogenic shock was the most common contributory cause and, of all types of surgery, AKI was most common after cardiac procedures.

Table VIII: The frequency of comorbid diseases and contributory causes of AKI according to the RIFLE classification. Numbers of patients and percentages within parenthesis are given, except for absolute numbers, where median and range are given.

	Risk	Injury	Failure
n (%)	72 (100)	69 (100)	79 (100)
Risk factors for AKI	2 (0-4)	1 (0-5)	1 (0-4)
Decreased eGFR	20 (28)	10 (14)	23 (29)
IHD	37 (51)	29 (42)	33 (42)
HTN	33 (46)	25 (36)	32 (41)
DM1	1 (1)	2 (3)	2 (3)
DM2	7 (10)	6 (9)	14 (18)
COPD	25 (35)	10 (14)	11 (14)
Liver disease	3 (4)	3 (4)	2 (3)
Cause of AKI	1 (0-3)	1 (0-3)	1 (0-4)
Postoperative	30 (42)	23 (33)	24 (30)
Cardiogenic shock	33 (46)	29 (42)	27 (34)
Septic shock	13 (18)	20 (29)	25 (32)
Hypovolemic shock	5 (7)	5 (8)	4 (6)
Respiratory failure	29 (40)	22 (32)	27 (34)
Trauma	6 (8)	4 (6)	2 (3)
Medication	2 (3)	7 (10)	8 (10)
Bleeding	3 (4)	3 (4)	5 (6)

AKI, acute kidney injury; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; HTN, hypertension; IHD, ischemic heart disease.

4.1.4 Complications and survival

Incidence of RRT and length of ICU stay was inversely associated with the severity of AKI. Only three of the 119 patients who developed AKI, and survived for more than three months, needed chronic RRT for ESKD.

Median length of follow-up for patients with AKI was 11 months (range: 0–58) and it was 21 months (range: 0–58) in non-AKI patients. ICU mortality increased in accordance with the severity of AKI (9%, 11%, 39%, and 39% for the non-AKI, Risk, Injury, and Failure subgroups, respectively; $p < 0.001$). If estimated SCr was used instead of measured SCr, the mortality was 11%, 24%, and 38% for the Risk, Injury, and Failure subgroups, respectively. Similar trends were seen for hospital mortality. Following correction for comorbid causes, contributory factors to AKI, and age, the Injury and Failure subgroups proved to be significant risk factors for mortality (as compared to the Risk subgroup).

Figure 15 depicts the one-year survival of patients in study I. One-year survival was found to be 84%, 63%, 45%, and 45% for the non-AKI, Risk, Injury, and Failure subgroups, respectively, ($p < 0.001$) and was similar whether we used measured or estimated SCr.

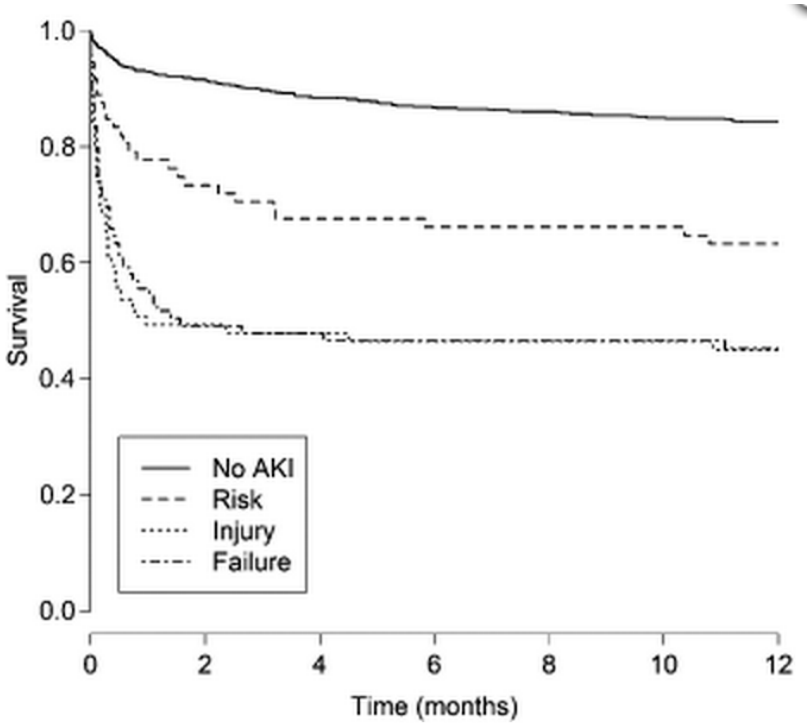

Figure 15. One-year survival of patients admitted to Icelandic intensive care units based on classification according to the RIFLE criteria. AKI, acute kidney injury.

4.2 Study II – AKI following CABG

4.2.1 Patient characteristics

The incidence of AKI was found to be 11% in patients who underwent surgical myocardial revascularization. Figure 16 shows the annual percentage of patients who experienced AKI during the period. Poisson regression analysis revealed a significant overall decreasing trend in incidence during the study time ($p = 0.01$), with an incidence rate ratio of 0.95 annually.

Preoperatively, 236 patients had CKD, three at stage 5, 17 at stage 4, 62 at stage 3B, and 154 at stage 3A. Of those 184 patients who experienced

postoperative AKI, 60 had CKD preoperatively. Of the 184 patients, 121 (7%) had stage 1 AKI, 27 (2%) had stage 2 AKI, and 36 (2%) had stage 3 AKI.

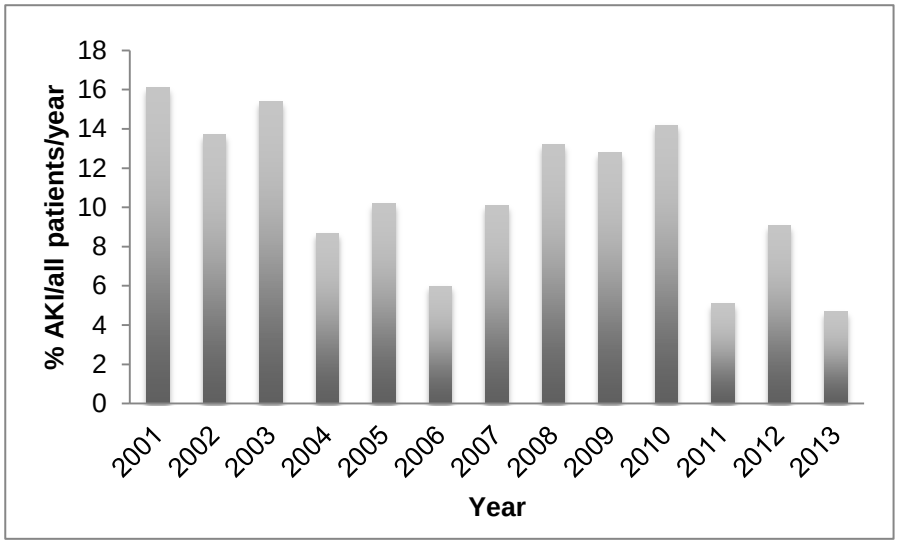

Figure 16. Annual percentage of acute kidney injury (AKI) in patients in study II.

Roughly 80% (n=1,398) of operated patients were male, but there was no significant difference in sex distribution between the groups with and without AKI. Patients with AKI were on average three years older, had significantly higher preoperative risk scores, and were more likely to have undergone emergency surgery. Except for diabetes there was, however, no significant difference between the groups regarding the conventional risk factors for CAD (sex, HTN, family history of CAD, smoking, and dyslipidemia). No significant difference was seen regarding extent of CAD, history of CHF, or COPD, but patients who experienced AKI were more likely to have suffered preoperative MI or acute CHF (Table IX).

The AKI group had significantly higher preoperative SCr values (95 vs. 90 μmol/L, respectively) and they were more likely to have had preoperative CKD (eGFR ≤ 60 mL/min/1.73 m^2). Preoperatively, mean SCr was 94 μmol/L for men and 79 μmol/L for women.

Table IX: Baseline characteristics of patients in study II, classified as either AKI (stage 1, 2, and 3 AKI of the KDIGO criteria[a]) or no AKI.

	Total n = 1,710	**No AKI** n = 1,526	**AKI** n = 184	p-value
Diabetes	270 (16)	225 (15)	45 (25)	0.001
Statin use	1,283 (78)	1,139 (78)	144 (81)	0.39
BMI	28 ± 4	28 ± 4	29 ± 5	0.057
History of MI	383 (23)	331 (22)	52 (29)	0.048
Preoperative CCS score				0.023
0	11 (1)	11 (1)	0 (0)	
1	83 (5)	77 (5)	6 (3)	
2	324 (19)	302 (20)	22 (12)	
3	548 (32)	487 (32)	61 (33)	
4	723 (43)	629 (42)	94 (51)	
Preoperative LVEF, %	55 ± 10	55 ± 10	55 ± 12	0.87
Preoperative NYHA score				0.003
0	185 (13)	175 (14)	10 (7)	
1	98 (7)	90 (7)	8 (5)	
2	363 (26)	336 (27)	27 (18)	
3	473 (34)	411 (33)	62 (42)	
4	289 (21)	249 (20)	40 (27)	
History of arrhythmia	174 (10)	155 (10)	19 (10)	0.9
Pre-existing CKD	236 (14)	176 (12)	60 (33)	< 0.001
Preoperative SCr	91 ± 31	90 ± 25	95 ± 39	0.42
Preoperative eGFR	82 ± 19	83 ± 18	72 ± 23	< 0.001
Preoperative eGFR				< 0.001
≥ 90	649 (38)	607 (40)	42 (23)	
60–89	825 (48)	743 (49)	82 (45)	
45–59 (CKD stage 3A)	154 (9)	122 (8)	32 (17)	
30–44 (CKD stage 3B)	62 (4)	43 (3)	19 (10)	
15–29 (CKD stage 4)	17 (1)	9 (1)	8 (4)	
< 15 (CKD stage 5)	3 (0)	2 (0)	1 (1)	
COPD	120 (7)	106 (7)	14 (8)	0.65
Preoperative Hb	141 ± 14.3	142 ± 14	135 ± 16	< 0.001
Emergency surgery	80 (5)	61 (4)	19 (10)	< 0.001
Preoperative MI	466 (27)	405 (27)	61 (33)	0.066
CHF	231 (14)	193 (13)	38 (21)	0.004
Standard EuroSCORE	5 (± 3)	5 (± 3)	6 (± 4)	< 0.001

[a]KDIGO stages: stage 1 = increase in SCr of ≥ 26.5 µmol/L within 48 h or 1.5–1.99 times baseline within seven days; stage 2 = increase in SCr to 2–2.99 times baseline; stage 3 = increase in SCr to three times baseline or ≥ 354 µmol/L, or initiation of renal replacement therapy.

Mean and standard deviations are shown for continuous variables and percentages are given within parenthesis.

AKI, acute kidney injury; BMI, body mass index in kg/m^2; CABG, coronary artery bypass grafting; CCS, Canadian Cardiovascular Society; eGFR, estimated glomerular

filtration rate in mL/min/1.73 m^2; Hb, hemoglobin in g/L; HF, heart failure; IHD, ischemic heart disease; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; SCr, serum creatinine in µmol/L.

4.2.2 Operative factors and postoperative complications

Patients with AKI who underwent CABG had on average CPB times that were 15 min longer, and total operative times (skin-to-skin) were 13 min longer in the AKI group. The AKI group was more likely to need intraoperative inotrope support, but there was no significant difference between the groups regarding the type of surgery performed, i.e. conventional CABG or OPCAB.

Postoperatively, AKI patients had longer hospital and ICU stays, had more postoperative bleeding, and received three times as many units of packed RBCs than patients who did not sustain AKI. Furthermore, the AKI group was more likely to need postoperative RRT (either CRRT or intermittent hemodialysis) (Table X). The most common postoperative complication was POAF, which was significantly more likely to be diagnosed in the group that had AKI than in those who did not (53% vs. 38%; $p = 0.001$). Operative death was significantly higher in the AKI group (9% vs. 2%; $p < 0.001$), and AKI proved to be an independent predictor of both minor and major complications, with an OR of 1.78 (95% CI: 1.29–2.47; $p < 0.001$) and 2.49 (95% CI: 1.65–3.76; $p < 0.001$), respectively.

Table X: Intraoperative and postoperative characteristics of patients in study II, classified as either AKI (stage 1, 2, and 3 AKI of the KDIGO criteria[a]) or no AKI.

	Total n = 1,710	**No AKI** n = 1,526	**AKI** n = 184	p-value
Surgical procedure: CABG vs. OPCAB	1,350 (79)	1,202 (79)	148 (80)	0.63
CPB time, min	91 ± 34	89 ± 31	104 ± 50	< 0.001
X-clamp time, min	47 ± 17	47 ± 17	50 ± 23	0.25
Total operative time, min	212 ± 57	211 ± 54	224 ± 74	0.041
Use of IABP	92 (5)	76 (5)	16 (9)	0.054
Intraoperative inotrope use	885 (53)	776 (52)	109 (60)	0.028
Postoperative bleeding, mL	985 ± 1,018	942 ± 636	1,341 ± 2,478	0.002
RBC transfusion, units[b]	3 ± 4	2 ± 3	6 ± 7	< 0.001
ICU stay, days	2 ± 3	2 ± 3	3 ± 6	< 0.001
Total hospital stay, days	11 ± 8	11 ± 7	14 ± 12	< 0.001
Death < 30 days	40 (2)	24 (2)	16 (9)	< 0.001
RRT for AKI	19 (1)	0 (0)	19 (10)	< 0.001
Postoperative SCr	102 ± 55	98 ± 44	137 ± 105	< 0.001
ESRD	5 (0.3)	4 (0.3)	1 (0.5)	0.43
Major complication	183 (11)	144 (10)	39 (21)	< 0.001
Stroke	9 (1)	8 (1)	1 (1)	1
Mediastinitis	17 (1)	15 (1)	2 (1)	0.7
Myocardial infarction	82 (5)	66 (4)	16 (9)	0.016
Reoperation due to bleeding	118 (7)	95 (6)	23 (13)	0.003
Sternum dehiscence	26 (2)	21 (1)	5 (3)	0.19
ARDS or MOF	53 (3)	35 (2)	18 (10)	< 0.001
Minor complication	834 (49)	723 (48)	111 (60)	0.001
POAF	671 (39)	574 (38)	97 (53)	0.001
Leg wound infection	179 (11)	159 (10)	20 (11)	0.8
Urinary tract infection	59 (4)	50 (3)	9 (5)	0.28
Pleural effusion	191 (11)	160 (11)	31 (17)	0.013
Pneumonia	113 (7)	94 (6)	19 (10)	0.04

[a]KDIGO stages: stage 1 = increase in SCr of ≥ 26.5 µmol/L within 48 h or 1.5–1.99 times baseline within seven days; stage 2 = increase in SCr to 2–2.99 times baseline; stage 3 = increase in SCr to three times baseline or ≥ 354 µmol/L, or initiation of RRT.
[b]Units of RBCs transfused intraoperatively and during the first postoperative week.
Mean and standard deviations are given for continuous variables and percentages are shown in parenthesis.
AKI, acute kidney injury; ARDS, acute respiratory distress syndrome; CABG, coronary artery bypass grafting; CPB, cardiopulmonary bypass; ESRD, end-stage renal disease; IABP, intra-aortic balloon pump; ICU, intensive care unit; MOF, multiple

organ failure; OPCAB, off-pump coronary artery bypass; POAF, postoperative atrial fibrillation; RBC, red blood cell; RRT, renal replacement therapy; SCr, serum creatinine in umol/L.

4.2.3 Risk factors for AKI

Independent risk factors for AKI were found to be preoperative eGFR, BMI, DM, standard EuroSCORE, units of packed RBCs transfused intraoperatively and in the first postoperative week, and reoperation due to bleeding (Table XI).

Table XI: Independent risk factors for AKI in study II.

	Unadjusted OR (95% CI)	**Adjusted OR** (95% CI)	p-value
BMI	1.04 (1.01–1.08)	1.04 (1–1.08)	0.037
Diabetes	1.94 (1.34–2.82)	1.66 (1.11–2.47)	0.016
Preoperative mean eGFR	0.97 (0.96–0.98)	0.97 (0.96–0.98)	< 0.001
EuroSCORE	1.08 (1.01–1.15)	1.11 (1.06–1.16)	< 0.001
RBC transfusion, units[a]	1.19 (1.13–1.25)	1.23 (1.16–1.31)	< 0.001
Reoperation due to bleeding	2.07 (1.09–3.94)	0.37 (0.15–0.93)	0.024

[a]Units of RBCs transfused intraoperatively and during the first postoperative week. BMI, body mass index in kg/m^2; eGFR, estimated glomerular filtration rate in mL/min/1.73 m^2; OR, odds ratio; RBC, red blood cell.

4.2.4 Renal recovery and long-term kidney function

AKI was found to be a significant risk factor for development of CKD (HR 2.08; 95% CI: 1.49–2.9; p < 0.001) but not ESRD. On postoperative day 10, the majority of patients who experienced AKI had recovered renal function (defined as an SCr ratio of < 1.25 of baseline). On postoperative day 20, almost 95% of the patients had recovered their kidney function (Figure 17). Regression analysis showed that patients who had recovered renal function had a higher probability of long-term survival than those who did not (OR 0.38; 95% CI: 0.2–0.73; p = 0.004 vs. OR 0.16; 95% CI: 0.06–0.39; p < 0.001, respectively).

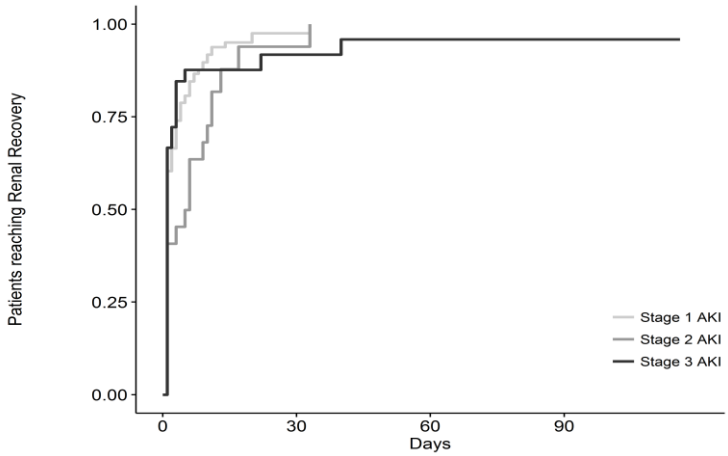

Figure 17. Kaplan-Meier plot of recovery of renal function (defined as an SCr ratio of < 1.25 baseline SCr) in patients in study II. AKI, acute kidney injury.

4.2.5 Survival

Figure 18 shows the substantial difference in survival between patients with no AKI and patients with AKI. Survival was inversely associated with the severity of AKI, and the 10-year survival of patients without AKI and those with AKI of stages 1, 2, and 3 was 76%, 63%, 56%, and 49%, respectively ($p < 0.001$). Patients in the Failure group had a fourfold higher risk of dying than patients with no AKI (log-rank test, $p < 0.001$).

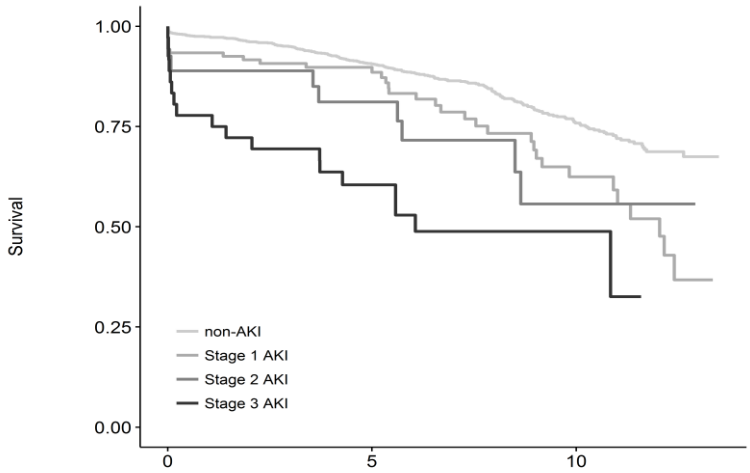

Figure 18. Kaplan-Meier curve showing comparison of survival of patients with no AKI and those with AKI in study II. AKI, acute kidney injury.

Finally Table XII shows the independent risk factors for mortality. The interaction between POAF (the single most common postoperative complication) and AKI was not found to significantly affect long-term mortality. However, upon testing of possible interaction, only POAF was significantly correlated to long-term survival in a model that was also corrected for age, sex, preoperative standard EuroSCORE, and the diagnosis of at least one major complication (adjusted OR 1.63; 95% CI: 1.2–2.2; p = 0.002).

Table XII: Independent risk factors for long-term mortality in study II. The model was corrected for extent of acute kidney injury (AKI), age, sex, standard EuroSCORE, and major complications.

	HR (95% CI)	**p-value**
KDIGO AKI:		
Stage 1	1.42 (0.99–2.04)	0.059
Stage 2	1.65 (0.84–3.22)	0.143
Stage 3	2.02 (1.22–3.33)	< 0.001
Age (per year)	1.02 (1.01–1.04)	< 0.001
Standard EuroSCORE	1.22 (1.18–1.26)	< 0.001
Major complications	1.86 (1.40–2.48)	< 0.001

AKI, acute kidney injury.

4.3 Study III – AKI following AVR

4.3.1 Baseline patient characteristics

Patient characteristics of the cohort in study III are shown in Table XIII. The majority of patients were male (n = 230) and the average age was 71 (± 10) years. The majority of surgeries (55%) were concomitant AVR and CABG surgery. Half of the patients (n = 184) received a stentless biological prosthesis, 31% a stented biological prosthesis (n = 114), and 18% (n = 67) a mechanical valve.

Table XIII: Baseline patient characteristics of patients in study III. Patients were classified as either having AKI (in the classes Risk, Injury, or Failure of the RIFLE criteria[a]) or not having AKI. Mean and standard deviations are shown for continuous variables and percentages are shown in parentheses.

	No AKI n = 283	**AKI** n = 82	p-value
Male	188 (66)	42 (51)	0.017
BMI	27 ± 4	29 ± 6	0.01
DM	34 (12)	20 (24)	0.01
HTN	189 (67)	65 (79)	0.043
Dyslipidemia	117 (42)	38 (46)	0.51
History of smoking	189 (67)	44 (54)	0.041
History of MI	29 (10)	19 (23)	0.005
History of chronic HF	49 (17)	29 (35)	0.001
Reduced preoperative renal function[b]	72 (25)	37 (45)	0.001
Preoperative SCr	93 ± 44	98 ± 27	0.25
Preoperative Hb	139 ± 13	132 ± 15	< 0.001
Preopartive anemia[c]	65 (24)	29 (35)	0.034
NYHA score III–IV	159 (56)	61 (74)	0.005
EuroSCORE, log	8 ± 10	14 ± 15	0.001
Preoperative left ventricular EF	57 ± 9	55 ± 9	0.15

[a]RIFLE: Risk = increase in SCr of ×1.5 or decrease in GFR of > 25%; Injury = increase in SCr of ×2 or decrease in GFR of > 50%; Failure = increase in SCr of ×3, a decrease in GFR of > 75%, or SCr ≥ 354 µmol/L concomitant with an acute rise in SCr of ≥ 44 µmol/L.
[b]Defined as eGFR < 60 mL/min/1.73 m^2.
[c]Defined as Hb < 120 g/L in females and < 135 g/L in males.
AKI, acute kidney injury; BMI, body mass index in kg/m^2; DM, diabetes mellitus; EF, ejection fraction; Hb, hemoglobin in g/L; HF, heart failure; HTN, hypertension; MI, myocardial infarction; NYHA, New York Heart Association; SCr, serum creatinine in µmol/L.

A total of 82 patients (23%) developed AKI according to the RIFLE criteria; 40 (11%) in the Risk class, 28 (8%) in the Injury class, and 14 (4%) in the Failure class. The group that experienced AKI was older on average (74 years vs. 70 years; p < 0.001), had more comorbidity, had higher preoperative risk assessment scores, and were more likely to have reduced preoperative kidney function.

4.3.2 Intraoperative characteristics and postoperative complications

Intraoperatively, patients who experienced AKI had longer aortic X-clamp and total operative time, and perioperatively they were more likely to need insertion of an IABP. There was no significant difference regarding whether patients underwent emergency surgery or whether they had concomitant CAGB surgery together with AVR.

The postoperative complications are also given in Table XIV. Complications were generally more common in the AKI group—both minor and severe. As was the case following isolated CABG, the most common postoperative complication was POAF (diagnosed in 68% of patients (n = 249)). There was, however, no significant difference in rates of POAF between the group that experienced AKI and the group that did not. Patients with AKI were also transfused significantly more units of packed red blood cells. Median length of stay in the surgical ward was four days longer (13 vs. 9; $p < 0.001$) and ICU stay was five days longer (6 vs. 1; $p < 0.001$). Fifteen patients (4%) received RRT postoperatively, four of whom died while on CRRT, and six patients continued to have intermittent hemodialysis following discharge from the ICU. Only one patient (0.3%) developed ESRD and required RRT for more than three months postoperatively.

Table XIV: Intraoperative characteristics and postoperative complications of patients in study III. Patients were classified as either having AKI (in the classes Risk, Injury, or Failure of the RIFLE criteria[a]) or not having AKI. Means and standard deviations are shown for continuous variables and percentages are shown in parentheses.

	No AKI n = 283	**AKI** n = 82	p-value
Emergency surgery	4 (1)	1 (1)	0.86
Urgent surgery	23 (8)	17 (21)	0.003
IABP	8 (3)	15 (18)	< 0.001
CABG	150 (53)	49 (60)	0.34
Aortic clamp time, min	111 ± 31	135 ± 40	< 0.001
CPB time, min	151 ± 46	191 ± 58	< 0.001
Stented biological valve	86 (30)	28 (34)	0.61
Stentless biological valve	138 (49)	46 (56)	0.3
Mechanical valve	59 (21)	8 (10)	0.034
Lowest intraoperative temperature (°C)	35 ± 1	35 ± 1	0.2
Minor complications	171 (60)	69 (84)	< 0.001
Superficial wound infection	19 (7)	11 (13)	0.086
POAF	185 (65)	64 (78)	0.086
Pleural effusion	25 (9)	24 (29)	< 0.001
Pneumonia	16 (6)	24 (29)	< 0.001
UTI	11 (4)	28 (34)	< 0.001
TIA	5 (2)	2 (2)	0.66
Major complications	63 (22)	53 (65)	< 0.001
MI	25 (9)	24 (29)	< 0.001
Sternal dehiscence	3 (1)	4 (5)	0.048
Stroke	6 (2)	2 (2)	1
Deep sternal infection	3 (1)	1 (1)	1
Reoperation due to bleeding	31 (11)	23 (28)	< 0.001
First 24 h bleeding, mL	1,060 ± 771	1,320 ± 1,064	0.041
RBC transfusion, units	6 ± 6	13 ± 11	< 0.001
Length of stay in ICU, days	1 (0–15)	6 (1–80)	< 0.001
Length of stay in surgical ward, days	9 (0–41)	13 (0–127)	< 0.001
≤ 30-day operative mortality	6 (2)	15 (18)	< 0.001

[a]RIFLE: Risk = increase in SCr of ×1.5 or decrease in GFR of > 25%; Injury = increase in SCr of ×2 or decrease in GFR of > 50%; Failure = increase in SCr of ×3, a decrease in GFR of > 75%, or SCr ≥ 354 μmol/L concomitant with an acute rise in SCr of ≥ 44 μmol/L.

AKI, acute kidney injury; CABG, coronary artery bypass grafting; CPB, cardiopulmonary bypass; IABP, intra-aortic balloon pump; ICU, intensive care unit; MI, myocardial infarction; POAF, postoperative atrial fibrillation; RBC, red blood cell; SCr, serum creatinine in μmol/L; TIA, transient ischemic attack; UTI, urinary tract infection.

4.3.3 Risk factors for AKI

Multivariate analysis revealed that independent predictors of AKI were packed RBC transfusions (OR 1.64; 95% CI: 1.33–2.07 per 5 units), longer CPB time (OR 1.10; 95% CI: 1.04–1.15 per 10 min), and obesity (BMI > 30

kg/m^2) (OR 2.71; 95% CI: 1.41–5.22).

4.3.4 Survival

Operative mortality was ninefold higher in the AKI group (18% vs. 2%; p < 0.001). After adjusting for standard EuroSCORE, CPB time, and transfusions of RBCs, AKI proved to be an independent predictor of 30-day mortality. Furthermore, AKI patients had significantly lower five-year survival than patients with normal postoperative kidney function (66 vs. 87%; p < 0.001). However, AKI was not predictive of long-term survival (HR 1.44; 95% CI: 0.86–2.42).

4.4 Study IV – Recovery of renal function following AKI

In total, 41,361 operations were performed on 27,685 individuals during the study period. The majority were orthopedic surgery (17,821 operations; 43.1%), followed by abdominal surgery (13,129 operations; 31.7%), vascular surgery (5,285 operations; 12.8%), and cardiothoracic surgery (5,126 operations; 12.4%) (Figure 19). In this chapter of the thesis, only outcome of CABG and/or AVR operations will be analyzed further, i.e. 1,917 of the 41,361 operations (4.6%). Baseline and postoperative SCr was available in 1,834 (95.7%) of these operations and could therefore be included in the study.

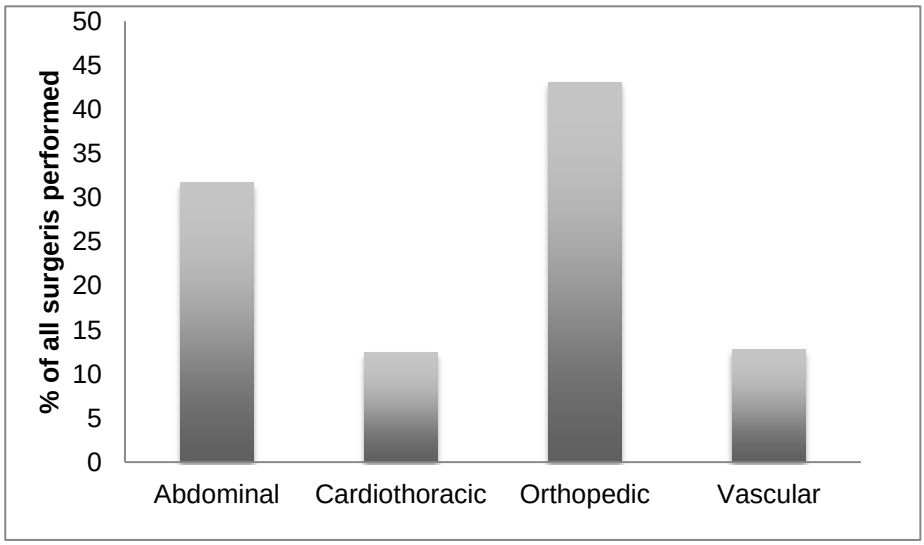

Figure 19. Types and proportions of surgeries included in study IV.

A total of 356 patients who underwent open-heart surgery (19.4%) had complications involving postoperative AKI. Of these cases, 29 repeat AKI cases were excluded, leaving a total of 327 cases of AKI that was diagnosed for the first time for further analysis. Of these cases, 253 (14.0%), 46 (2.5%), and 28 (1.5%) were stage 1, stage 2, and stage 3, respectively, according to the KDIGO criteria.

4.4.1 Assessment of criteria for renal recovery

Analysis according to pre-specified criteria for renal recovery (see Materials and methods) showed recovery rates varying from 52% to 95% (Table XV).

Table XV: Renal recovery of individuals with AKI at postoperative days 10, 20, and 30 in study IV.

Criteria	**10 days (n = 297)**	**20 days (n = 291)**	**30 days (n = 290)**
SCr < 1.5 × baseline	254 (85.6)	254 (87.3)	254 (87.6)
SCr < 1.25 × baseline	203 (68.4)	210 (72.2)	214 (73.8)
SCr < 1.10 × baseline	154 (51.9)	127 (56.4)	165 (56.9)
[a]Recovering eGFR > 60	142 /150 (94.7)	143/150 (95.3)	143/150 (95.3)
Recovering preoperative CKD category			
3A (eGFR > 45)	78/90 (86.7)	79/88 (89.8)	80/87 (92.0)
3B (eGFR > 30)	41/49 (83.7)	41/46 (89.1)	42/46 (91.3)
4 (eGFR > 15)	15/20 (75.0)	15/20 (75.0)	15/20 (75.0)

Data are number (percentage).
[a]Individuals with baseline eGFR ≤ 60 mL/min/1.73 m^2 were excluded from analysis.
eGFR, estimated glomerular filtration rate in mL/min/1.73 m^2; SCr, serum creatinine.

ROC analysis of the specified criteria (as listed in Materials and methods) revealed that all the criteria had poor ability to predict one-year mortality, with AUC in the 0.3–0.6 range (Figure 20, Table XVI).

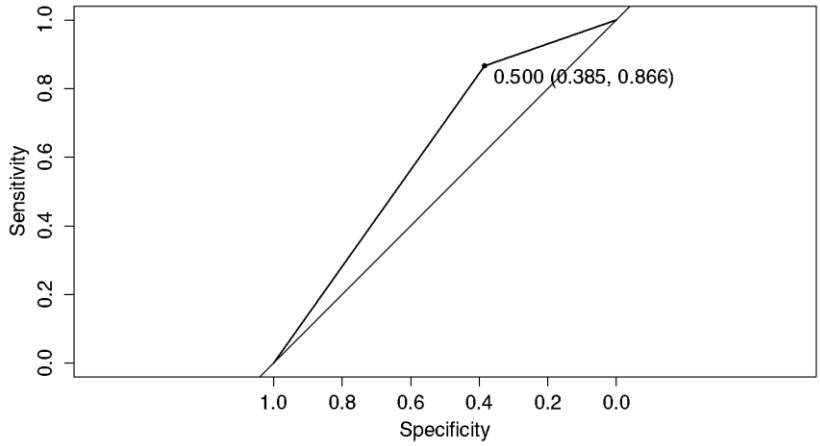

Figure 20. Graphic representation of ROC analysis of predictive value of renal recovery (to SCr < 1.5 × baseline SCr) on one-year mortality of patients in study IV.

Table XVI: Comparison of different renal recovery criteria at 10, 20, and 30 days after surgery, and their relation to one-year survival of patients in study IV.

	Cases	Controls	AUC	95% CI
< 1.5 × baseline SCr				
10 days	284	13	0.63	0.49–0.76
20 days	284	7	0.51	0.37–0.65
30 days	284	6	0.52	0.36–0.69
< 1.25 × baseline SCr				
10 days	284	13	0.54	0.40–0.68
20 days	284	7	0.43	0.29–0.57
30 days	284	6	0.45	0.29–0.62
< 1.10 × baseline SCr				
10 days	284	13	0.49	0.35–0.63
20 days	284	7	0.35	0.21–0.49
30 days	284	6	0.37	0.20–0.53
eGFR > 60				
10 days	149	1	0.47	NA-NA
20 days	149	1	0.48	NA-NA
30 days	149	1	0.48	NA-NA

AUC, area under curve; eGFR, estimated glomerular filtration rate; SCr, serum creatinine.

Univariate Cox analysis revealed that the only renal recovery criteria significantly linked to one-year mortality was reduction in SCr to < 1.5 times baseline SCr on postoperative day 10 (HR 0.32; 95% CI: 0.17–0.63) (Table XVII).

Table XVII: Univariate Cox analysis of all patients diagnosed with AKI, to compare the relationship between long-term mortality and the different criteria for renal recovery.

Variable	HR (95% CI)	p-value
SCr < 1.5 × baseline SCr		
10 days	0.32 (0.17–0.63)	< 0.001
20 days	0.48 (0.21–1.08)	0.075
30 days	0.50 (0.21–1.20)	0.122
SCr < 1.25 × baseline SCr		
10 days	0.84 (0.46–1.53)	0.582
20 days	1.28 (0.61–2.68)	0.51
30 days	1.34 (0.62–2.89)	0.461
SCr < 1.1 × baseline SCr		
10 days	0.96 (0.55–1.68)	0.878
20 days	1.32 (0.71–2.45)	0.381
30 days	1.51 (0.79–2.86)	0.212
Recovering eGFR > 60 mL/min/1.73 m^2		
10 days	0.24 (0.07–0.85)	0.027
20 days	0.33 (0.08–1.47)	0.147
30 days	0.33 (0.08–1.47)	0.205
Recovering preoperative CKD category		
10 days	0.53 (0.24–1.15)	0.107
20 days	1.03 (0.36–3.00)	0.954
30 days	1.12 (0.33–3.75)	0.854

CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; SCr, serum creatinine.

4.4.2 Renal recovery

The recovery rates are presented graphically in Figure 21. Renal recovery at 10 days decreased in line with the severity of the initial AKI stage (98.1%, 88.2%, and 64% for AKI stages 1, 2, and 3, respectively; $p < 0.001$).

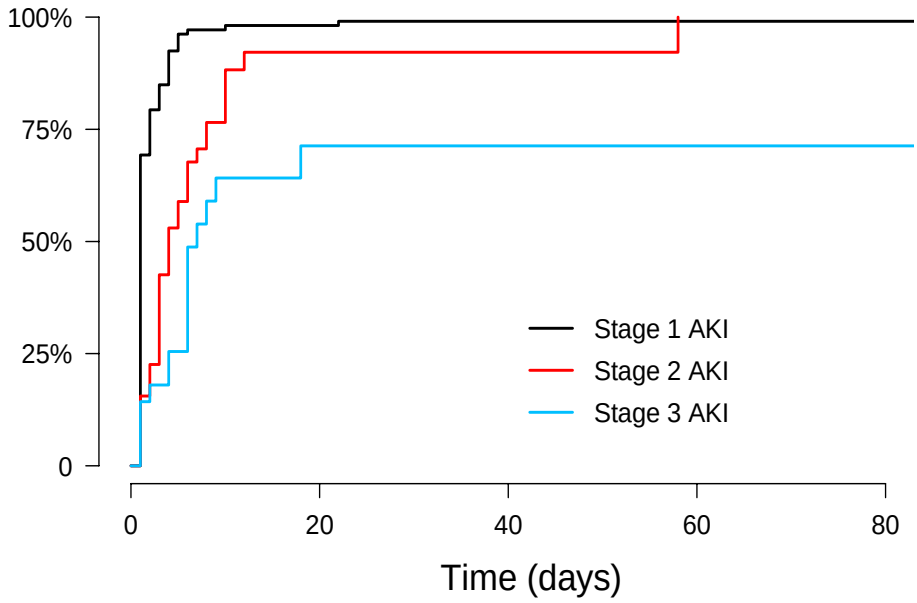

Figure 21. Renal recovery rates for patients in study IV shown according to the initial stage of postoperative AKI. Renal recovery was defined as reaching SCr ratio < 1.5 × baseline SCr.

A comparison of the group that had recovered renal function and the group that did not is given in Table XVIII. Patients who had recovered renal function following AKI had significantly higher eGFR before surgery (61 vs. 50 mL/min/1.73 m^2; $p < 0.001$), but they were less likely to have undergone emergency surgery than the group that did not recover renal function. No significant difference was observed between the groups regarding preoperative risk assessment scores, hypertension, DM, neoplasms, age, or gender.

Table XVIII: Comparison of preoperative and intraoperative characteristics of patients who did and did not recover renal function (defined as reaching SCr ratio < 1.5 × baseline SCr on postoperative day 10).

Variable	Renal recovery N = 265	No recovery N = 62	p-value
Patient-related factors			
Age, years	74 (67–80)	74 (68–80)	0.471
Gender (male)	192 (72.5)	46 (74.2)	0.906
Baseline SCr	99 (82–117)	118 (94–134)	< 0.001
Preoperative eGFR	61 (48.8–78.6)	50.4 (42.2–58.6)	< 0.001
> 90	21 (8.0)	3 (4.8)	< 0.001
60–89	120 (45.8)	11 (17.7)	
30–59	105 (40.0)	43 (69.4)	
15–29	14 (5.3)	5 (8.1)	
< 15	2 (0.8)	0 (0)	
Hypertension	86 (32.5)	26 (41.9)	0.205
Congestive heart failure	67 (25.3)	16 (25.8)	1
Ischemic heart disease	190 (71.7)	45 (72.6)	1
COPD	11 (4.2)	2 (3.2)	1
Diabetes mellitus	43 (16.2)	12 (19.4)	0.686
Liver disease	5 (1.9)	0 (0)	0.607
Neoplasm	48 (18.1)	17 (27.4)	0.140
ASA classification:			
1	0 (0)	0 (0)	NA
2	2 (0.8)	0 (0)	
3	139 (56.3)	23 (41.1)	
4	92 (37.2)	27 (48.2)	
5	14 (5.7)	6 (10.7)	
Surgery-related factors			
Emergency surgery	71 (26.8)	29 (46.8)	0.004
Length of surgery, min	241 (174–305)	222 (132–344)	0.339
Length of hospital stay, days	14 (10–20)	12 (4–34)	0.523

Data are presented as median (interquartile range) for continuous variables and number (percentage) for categorical variables.

AKI, acute kidney injury; ASA, American Society of Anesthesiologists physical status classification system; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate in mL/min/1.73 m^2; SCr, serum creatinine.

4.4.3 Survival

Median follow-up time in AKI patients was 38.9 months (interquartile range: 16.5–78.7). Univariate logistic regression analysis showed independent risk factors for one-year mortality to be AKI stage 2 (unadjusted OR 3.59; 95% CI: 1.64–7.63; p = 0.001), ischemic heart disease (unadjusted OR 0.49; 95% CI: 0.25–0.96; p = 0.0342), preoperative kidney dysfunction (defined as eGFR <

60 mL/min/1.73 m^2) (unadjusted OR 6.96; 95% CI: 3.05–18.81; p < 0.001), an ASA classification of 4/5 (unadjusted OR 3.59; 95% CI: 1.66–8.44; p = 0.0018), emergency surgery (unadjusted OR 3.46; 95% CI: 1.80–6.74; p < 0.001), reoperation (unadjusted OR 2.76; 95% CI: 1.42–5.34; p = 0.0025), operative time longer than 100 min (unadjusted OR 0.28; 95% CI: 0.13–0.62; p = 0.0012), and recovery of renal function (unadjusted OR 0.25; 95% CI: 0.08–0.85, p = 0.019). Multivariate logistic regression revealed that preoperative kidney dysfunction and chronic heart failure were independently associated with one-year mortality (Table XIX).

Table XIX: Risk factors for reduced one-year survival after surgery (by multivariate logistic regression). Renal recovery was defined as reaching SCr ratio < 1.5 × baseline SCr on postoperative day 10.

	Adjusted OR (95% CI)	**p-value**
Congestive heart failure	6.13 (1.47–29.07)	0.015
eGFR < 60 mL/min/1.73 m^2	8.41 (1.44–160.02)	0.050
Ischemic heart disease	0.28 (0.07–1.14)	0.071
Neoplasm	0.26 (0.03–1.14)	0.134
ASA classification 4/5	3.87 (1.01–19.49)	0.064
Renal recovery	0.26 (0.06–1.07)	0.058

eGFR, estimated glomerular filtration rate.

CHF, preoperative kidney dysfunction, AKI stage 2 and 3, and reoperation were all found to be significantly and negatively associated with long-term mortality in multivariate Cox proportional hazard analysis of risk factors for long-term mortality, as shown in Table XX. Renal recovery was found to be protective against long-term mortality (HR 0.5), but the effect did not prove to be significant in multivariate analysis (p = 0.071).

Table XX: Multivariate Cox proportional hazard analysis of risk factors of long-term mortality. Renal recovery was defined as reaching SCr ratio < 1.5 × baseline SCr on postoperative day 10.

	Adjusted HR (95% CI)	p-value
Preoperative factors		
Congestive heart failure	1.89 (1.03–3.45)	0.039
Advanged age (per year)	1.03 (0.99–1.07)	0.163
eGFR < 60 mL/min/1.73 m^2	2.40 (1.26–4.55)	0.008
Postoperative factors		
AKI stage 1	1	
stage 2	3.44 (1.71–6.91)	< 0.001
stage 3	2.89 (1.09–7.74)	0.034
Reoperation for bleeding	2.22 (1.17–4.20)	0.014
Renal recovery	0.50 (0.24–1.06)	0.071

eGFR, estimated glomerular filtration rate.

Propensity score matching with a patient who did not recover renal function was achieved for 43 pairs of patients. PSM matching analysis showed that long-term survival of the group that reached renal recovery was significantly higher than in the group that did not, with a five-year survival of 76.3% as compared to 65.6% (p = 0.04) (Figure 22).

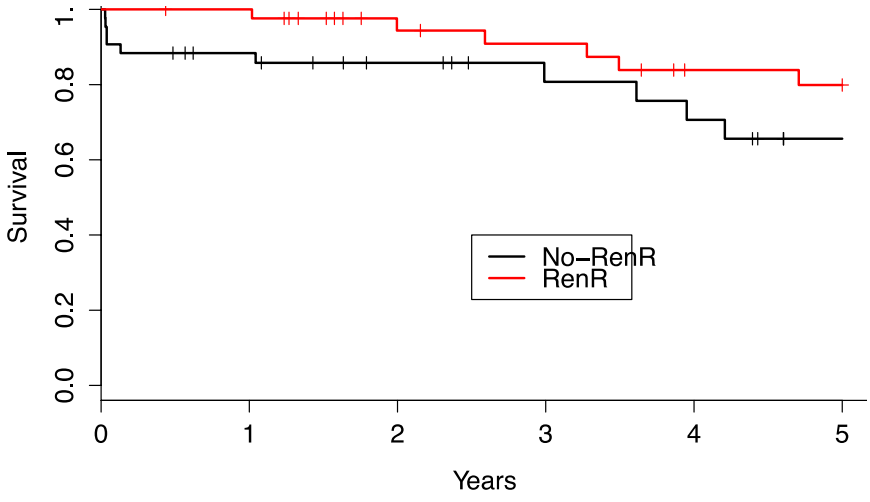

Figure 22. Comparison of long-term survival of individuals who achieved renal recovery (SCr < 1.5 × baseline SCr within 10 days from surgery) and a propensity score-matched control group of individuals who did not recover renal function.

4.5 Study V – Postoperative atrial fibrillation

In the whole study population, the incidence of POAF was 44% (326 of 744). Annual incidence ranged from 36% to 52%, but the difference was found to be insignificant in Poisson regression analysis (p = 0.08) The incidence was significantly higher following CABG as compared to OPCAB, and following AVR or combined surgery as compared to isolated CABG. Table XXI shows a comparison of baseline characteristics of the group diagnosed with POAF and those with SR following surgery. Patients who experienced POAF were on average older and more likely to be female, compared to the group with SR. The extent of coronary artery sclerosis was less in the POAF group than in the SR group, but the former group had lower LVEF and higher preoperative risk assessment scores. No significant difference was seen regarding preoperative use of β- or Ca^{2+} blockers.

Table XXI: Comparison of baseline characteristics in study V, between the group with sinus rhythm (SR) and the group with postoperative atrial fibrillation (POAF). Unless otherwise stated, mean and standard deviation is given for continuous variables and percentages are given in parentheses.

	POAF n = 326	**SR** n = 418	p-value
Male	244 (74)	349 (83)	0.005
Age, years	70 ± 9	64 ± 9	< 0.001
DM	62 (19)	60 (14)	0.11
HTN	213 (65)	248 (59)	0.11
Dyslipidemia	161 (49)	263 (63)	< 0.001
Smoker	58 (18)	111 (35)	0.005
CHF	66 (20)	35 (8)	< 0.001
No. of affected coronary arteries	2	3	< 0.001
LVEF, %	51	55	< 0.001
Standard EuroSCORE	6	4	< 0.001
Preoperative β-blocker use	201 (62)	291 (70)	0.074
Preoperative Ca^{2+}-blocker use	67 (21)	80 (19)	0.58
Preoperative statin use	201 (63)	316 (76)	< 0.001

AVR, atrial valve replacement; CHF, congestive heart failure; DM, diabetes mellitus; HTN, hypertension; LVEF, left ventricular ejection fraction.

4.5.1 Postoperative complications and survival

Table XXII gives an overview of the postoperative complications. Chest tube output in the first 24 h and RBC transfusion rates were significantly higher in

the POAF group, as was the incidence of deep surgical wound infections and MOF. Furthermore, length of total hospital stay and ICU stay was higher: three and five times more, respectively ($p < 0.001$). Finally, operative mortality was about sevenfold higher in the POAF group than in the SR group.

Table XXII: Intraoperative characteristics of patients in study V, and postoperative complications. Comparison of the group with sinus rhythm (SR) and postoperative atrial fibrillation (POAF). Unless otherwise stated, mean and standard deviation is given for continuous variables and percentages are given in parentheses.

	POAF n = 326	**SR** n = 418	p-value
Bleeding in first 24 h, mL, mean (range)	850 (120–4,980)	773 (120–31,820)	< 0.001
CABG/OPCAB	233 (37)	391 (63)	< 0.001
OPCAB	270 (46)	313 (54)	0.01
AVR	42 (73)	15 (27)	< 0.001
AVR + CABG	51 (81)	12 (19)	< 0.001
Skin-to-skin time, min, (range)	205 (90–640)	200 (100–555)	< 0.001
CPB time, min, (range)	95 (38–366)	80 (28–265)	< 0.001
Aortic clamp time, min, (range)	49 (19–209)	40 (13–204)	< 0.001
Sternum dehiscence	15 (5.0)	3 (0.7)	0.24
MOF/ARDS	25 (8.0)	1 (0.2)	< 0.001
Reoperation due to bleeding	14 (4)	20 (5)	0.88
Pneumonia	34 (10)	16 (4)	< 0.001
Superficial surgical wound infection	31 (10)	36 (9)	0.66
UTI	26 (8)	11 (3)	0.002
Total hospital stay, days, mean (range)	15 (1–110)	10 (1–47)	< 0.001
ICU stay, days, mean (range)	3 (1–13)	1 (1–41)	< 0.001
≤ 30 day operative mortality	15 (5)	3 (1)	0.001

AKI, acute kidney injury; ARDS, acute respiratory distress syndrome; AVR, atrial valve replacement; CABG, coronary artery bypass grafting; CPB, cardiopulmonary bypass; ICU, intensive care unit; MI, myocardial infarction; MOF, multiple organ failure; OPCAB, off-pump coronary artery bypass; UTI, urinary tract infection.

Long-term survival of patients who suffered POAF was significantly less than in the group with SR. One-year survival for the POAF and SR groups was found to be 92% versus 98% ($p < 0.001$). Similarly, five-year survival was 85% versus 93% ($p < 0.001$), respectively.

The survival of patients in study V is shown in Figure 23. When corrected for age, emergency operation, AVR, and standard EuroSCORE in the final regression analysis model, POAF was found to be an independent predictor of mortality (HR 2.63; 95% CI: 1.76–3.93, $p < 0.001$).

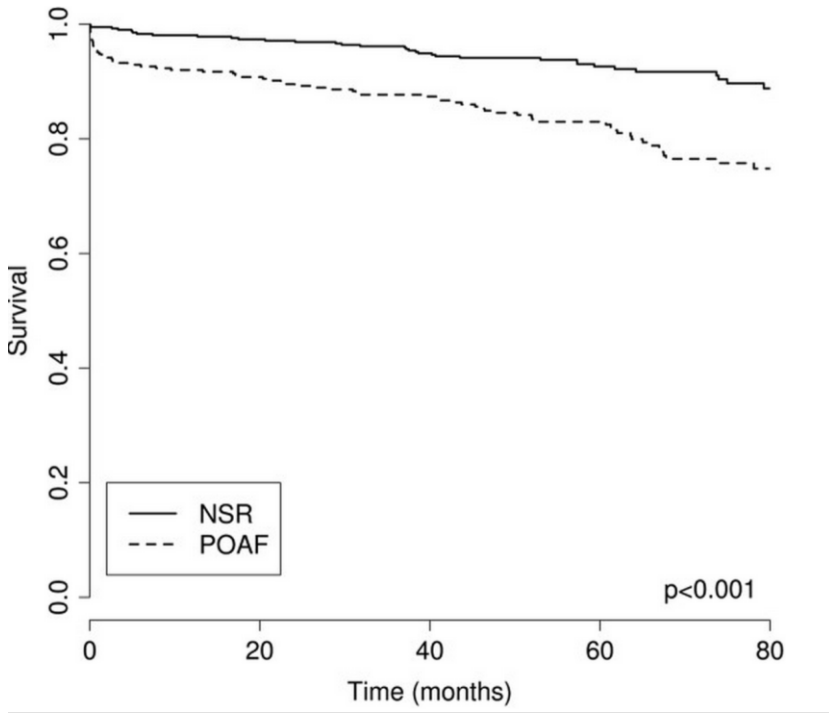

Figure 23. A Kaplan-Meier survival curve comparing patients with postoperative atrial fibrillation (POAF) and normal sinus rhythm (NSR) following CABG/OPCAB or AVR ± CABG in Iceland, 2002–2006.

4.5.2 Risk factors for POAF, and probability assessment

Multivariable logistic regression analysis revealed that the strongest independent risk factors for POAF were AVR, CHF, standard EuroSCORE, and advanced age (Table XXIII).

Table XXIII: Independent risk factors for POAF in study V

	OR (95% CI)	p-value
Aortic valve replacement	4.36 (2.68–7.07)	< 0.001
Congestive heart failure	1.81 (1.10–2.99)	< 0.001
Standard EuroSCORE (per point)	1.10 (1.03–1.17)	< 0.001
Age (per year)	1.05 (1.03–1.07)	< 0.001

Lastly, a risk score based on standard EuroSCORE, age, and type of surgery, was created to predict the probability of POAF following CABG/OPCAB or AVR+CABG for patients without any previous history of AFib (Table XXIV).

Table XXIV: Probability chart for POAF in study V. A risk score is given to evaluate the probability (in %) of POAF following CABG/OPCAB or AVR ± CABG for patients with no previous history of atrial fibrillation.

Isolated CABG/OPCAB

	EuroSCORE					
Age	0	2	4	6	8	10
50	14	17	20	24	29	34
55	17	20	24	29	34	39
60	20	24	29	34	39	44
65	24	29	34	39	44	50
70	29	34	39	45	50	56
75	34	39	45	50	56	61
80	39	45	50	56	61	67

AVR ± CABG

	EuroSCORE				
Age	2	4	6	8	10
50	47	53	58	64	69
55	53	59	64	69	74
60	59	64	69	74	78
65	64	69	74	78	82
70	69	74	78	82	85
75	74	78	82	85	87
80	78	82	88	88	90

< 30%
30–70%
> 70%

AVR, aortic valve replacement; CABG, coronary artery bypass grafting; OPCAB, off-pump coronary artery bypass.

5 Discussion

In this thesis, the association between AKI and adverse patient outcomes has been elucidated, in both the short term and the long term. Although a causal relationship cannot be definitely established in retrospective studies, AKI was found to be significantly associated with less favorable outcome following myocardial revascularization surgery and also AVR. This was mainly seen in higher rates of complications and worse survival in patients who experienced AKI. The same held true for patients who experienced POAF. Importantly, the finding that kidney dysfunction negatively affects patient outcome is in line with the finding that recovery of renal function was associated with better postoperative outcome regarding long-term survival.

5.1.1 Study I – Identification of baseline kidney function in AKI studies

A major point of criticism of the RIFLE criteria is the requirement for baseline SCr values, which are often missing in the clinical setting. The RIFLE criteria recommend assumption that baseline eGFR is 75 mL/min/m^2, when there is no history of CKD, and back-calculation of SCr using the MDRD equation, which in many cases appears to be too rough an approximation (Bagshaw et al., 2009; Pickering & Endre, 2010). Previous studies on the incidence of ICU-associated AKI have found variable rates of AKI ranging from 20% to 80% (Crowley & Peixoto, 2009; Hoste et al., 2006; Medve et al., 2011; Ostermann & Chang, 2007). This is believed to be in part due to the fact that assuming a normal baseline SCr value in the ICU population overestimates the incidence of AKI, whereas using the lowest SCr measured during ICU admission is likely to lead to underestimation of AKI. This was supported by a recent study that showed an overestimation of incidence of AKI of 11% when using back-calculation of SCr with the MDRD equation, as compared to documented baseline SCr (Pickering & Endre, 2010). Before embarking on further research on the subject of AKI, we therefore set out to evaluate the importance of thorough identification of baseline kidney function, as opposed to ascertaining incidence based on back-calculations. Indeed in this study, the use of estimated instead of measured baseline SCr led to a relative overestimation of AKI by 16% (absolute overestimation: 3.5%).

After meticulous identification of baseline SCr, the incidence of AKI in adults admitted to the ICU was found to be almost 22%, with equal distribution between the three RIFLE outcome classes.

In line with studies II and III in the thesis, patients who experienced AKI were more likely to have adverse outcomes, and hospital mortality was four times higher than in the patients who did not have AKI. Furthermore, 1-year survival was significantly less. However, during the three years of follow-up, only three patients required long-term RRT.

Research in the field of AKI took great strides following the publication of consensus criteria for AKI. However, contemporary studies are still often impeded by insufficient data on baseline SCr. What is more, as previously discussed, research is hindered by the inherent flaws of SCr in the detection of acute changes in kidney function. Thus, the search for biomarkers more sensitive in the recognition of AKI is ongoing. In the work included in this thesis, we based our need for rigorous identification of baseline SCr on the results of study I, namely a relative overestimation of AKI incidence of 16% when using back-calculation methods.

5.1.2 Study II – AKI following CABG

Owing to comprehensive nationwide registries, SCr could be identified in 98% of the patient cohort in study II, thus permitting reliable identification of postoperative AKI. Furthermore, study II showed that roughly 10% of patients had postoperative AKI, which is in the lower range compared to most previous studies on patients who undergo CABG (Machado et al., 2009; Parolari et al., 2012).

Worldwide, the incidence of AKI has been increasing (Hsu, 2010). Underlying reasons might be changes in the characteristics of hospitalized patients (e.g. greater comorbidity, higher severity of illness scores, and higher age), the advent of more complex interventions, and prolongation of life support (Bellomo, 2006). However, in this study an overall decreasing incidence of AKI over time was observed. The reasons for this are not obvious, but they might have to do with improved perioperative care or increased awareness of AKI following the publication of the RIFLE criteria. However, factors such as the increasing use of lung-protective ventilation (Koyner & Murray, 2010), and focus on optimal peri- and postoperative fluid balance, may play a role (Payen et al., 2008; Prowle et al., 2014). Development of AKI in general may also be significantly influenced by delays in adequate treatment of infections, as shown in a 2010 study—in which delays in the treatment of sepsis resulted in a 3.4% increase in SCr per hour (Kiers et al., 2010).

In study II, independent risk factors for AKI were higher BMI, DM, lower preoperative eGFR, higher EuroSCORE, reoperation due to bleeding, and higher numbers of RBC transfusions. The common physiological pathway behind these risk factors may be related to the kidney's sensitivity to non-pulsatile and reduced blood flow, especially in cases of preceding renal dysfunction (Bellomo et al., 2004; Mao et al., 2013). Hypertensive patients are generally more dependent on blood pressure to drive kidney perfusion, and suboptimal conditions such as emergency surgery and the intraoperative need for inotropes are known to affect tissue perfusion (Brenner, 2005).

The most common postoperative complication following CABG was POAF (diagnosed in 39% of patients). Moreover, the incidence of POAF was found to be significantly higher in the AKI group than in those who did not sustain AKI (53 vs. 38%; $p = 0.001$). Previous studies have indicated a similar relationship between decrease in kidney function and increased risk of POAF (Barbosa et al., 2011). A recent prospective study in which AKI was found to be an independent risk factor for development of POAF after cardiac surgery further supports this (Ng et al., 2016). The total incidence of AKI and POAF in the study was 30% and 17%, respectively. However, patients who developed AKI had a rate of POAF of 28%, and had twice the risk of developing POAF (RR 1.7; 95% CI: 1.43–2.01; $p < 0.001$) (Ng et al., 2016).

In study II, AKI was found to be an independent risk factor for incident CKD, but not ESRD. Furthermore, patients who developed AKI were likelier to experience postoperative complications and had a higher 30-day mortality. Importantly, long-term survival was inversely correlated to severity of AKI, even though the vast majority of patients had recovered kidney function (defined as a reduction in SCr to < 1.25 times baseline SCr). However, when the model for risk factors of long-term survival was corrected for interaction between AKI and POAF, only POAF was found to be a significant risk factor for 30-day mortality, possibly indicating a detrimental role of POAF in patient outcome.

At postoperative day 10, renal recovery rates were 96%, 78%, and 94% for AKI stages 1, 2, and 3, respectively. By day 20, rates for recovery of patients classified as stage 2 had risen further to 96%. Comparison of studies reporting renal recovery is, however, not straightforward—as highly variable definitions have been used. Even so, in line with various studies, our results showed that patients with recovered renal function had a higher probability of long-term survival than those who did not (Pannu et al., 2013; Swaminathan et al., 2010).

5.1.3 Study III – AKI following AVR

This study further demonstrated the substantial risk of acquiring AKI after

open-heart surgery, as well as the association between AKI and adverse postoperative outcomes and increased 30-day mortality. However, it is noteworthy that AKI was not found to be significantly associated with long-term survival, but type-II error cannot be excluded.

As compared to patients who underwent isolated CABG, patients who underwent AVR had an increased risk of AKI. In addition, they more often had reduced preoperative eGFR, they were 4 years older on average, and they generally underwent longer and more complex surgery, which may all lead to an increased risk of AKI.

In line with previous research, obesity, prolonged CPB time, and a higher number of RBC transfusions were independent risk factors for AKI. Interestingly, even in healthy populations, obesity has been linked to increased risk of renal failure (Chang et al., 2016). Prolonged CPB time is also a previously well described risk factor for AKI in cardiac surgery patients, but the underlying pathophysiology is complex. However, reduced perfusion pressure, lower oxygen tension in the renal parenchyma, erythrocyte hemolysis, alterations in regional kidney blood flow due to non-pulsatile CPB flow, and induction of the systemic inflammatory response, caused by contact with the artificial surface of the CPB circuit, are believed to have key roles (Ascione & Angelini, 2003; Okusa, 2002).

Observational studies with similar design to that of study II have shown that transfusion of RBCs is independently associated with AKI (Karkouti et al., 2009). In Iceland, transfusion rates are appreciably higher after AVR than after CABG, as seen in studies II and III in this thesis. The transfusion rates are indeed high compared to transfusions of comparable populations undergoing AVR in neighboring countries (Ternstrom et al., 2014). This relationship between transfusions and AKI, which was also observed in study II, remained significant even after correction in the logistic regression model for preoperative anemia, perioperative bleeding, and reoperation for bleeding. Notably, studies have indicated that storage of RBCs might induce structural changes to erythrocytes, impairing oxygen delivery capacity and predisposing to hemolysis (Karkouti, 2012; Tinmouth et al., 2006). The increased concentrations of free erythrocyte constituents, such as iron and hemoglobin, can subsequently exhaust physiological scavenger systems (i.e. transferrin and haptoglobin), exacerbate oxidative stress to tissues, and even lead to tissue damage (Okusa, 2002). However, a recent prospective study underscored the fact that a causal relationship cannot be assumed in

observational studies, and both higher transfusion rates and increased risk of AKI may be due other comorbidities (Murphy et al., 2015).

As in study II, POAF was the most common postoperative complication after AVR; it was diagnosed in 68% of patients, which is in line with other studies on patients who have undergone AVR (Maisel et al., 2001). This complication was diagnosed in 78% of patients in the AKI group as opposed to 65% of non-AKI patients, but this difference was not significant.

Only 4% of patients required RRT following surgery, which is a low rate compared to various other studies (Hobson et al., 2009; Lawman et al., 2002). Of the 15 patients who needed RRT, three went on to fulfill criteria for diagnoses of RIFLE classification L. Ultimately, the one patient who progressed to RIFLE classification E was free of dialysis after 108 days. AKI was, however, associated with other adverse postoperative outcomes in addition to operative mortality. Furthermore, long-term survival was lower in the group that experienced AKI, even though AKI was not found to be independently associated with long-term survival. This contrasts with the results of various other studies, which have shown a relationship between AKI and both short-term and long-term survival (Hobson et al., 2009; Hoste et al., 2006; Lafrance & Miller, 2010). However, when AVR and AVR + CABG patients were analyzed separately, a significant relationship was found between long-term survival and AKI in those who underwent combined surgery. This finding might be explained by confounding effects of other underlying risk factors. The sub-population of patients who underwent both AVR and CABG is likely to have had a different comorbidity profile, mainly regarding risk factors for coronary atherosclerosis. In turn, atherosclerosis affects both the risk of AKI and death (Lekawanvijit & Krum, 2014).

5.1.4 Study IV - The importance of renal recovery following AKI

The main focus of this study was renal recovery following AKI and how it affects long-term outcome in patients. The results of study IV indicate that patients who develop AKI fare better if they subsequently recover their kidney function. This might suggest that AKI after cardiac surgery is not only a marker of worse patient status, but in itself associated with adverse outcome.

The main finding in study IV was that by postoperative day 10, 52–95% of patients had recovered their renal function following AKI, depending on the definition used. However, in our study, we did not find any criteria for renal recovery that were sufficiently associated with survival to predict a causative relationship. This might be due to the stronger effect of other variables on

one-year mortality, such as worse preoperative state and emergency surgery. Nevertheless, a favorable relationship was found between renal recovery, defined as recovery to within 1.5 times baseline SCr by postoperative day 10, and one-year survival. What is more, five-year survival was almost 11% higher than in a propensity score-matched group of patients who did not have recovery of renal function.

Previous studies have shown that kidney function following AKI may be highly variable, with periods of recovery and deterioration at inconstant rates (Schiffl & Fischer, 2008). These studies have also highlighted that a kidney insult compounding previously developed AKI significantly reduces the chances of complete renal recovery (Schiffl & Fischer, 2008). This has been confirmed in a 2016 study showing that relapse occurs in 37% of patients who have had renal recovery (defined according to the ADQI criteria (Bellomo et al., 2004)), most commonly in the first three days after the recovery (Kellum et al., 2016). Furthermore, both relapse and non-recovery of renal function were found to be associated with significantly higher one-year mortality rates than in patients who had early recovery of renal function (31%, 60%, and 10%, respectively; $p < 0.001$) (Kellum et al., 2016). This shows a limitation of our study design, as postoperative SCr was measured prospectively, thereby reducing our ability to reliably identify relapse in kidney function after renal recovery. However, rates of renal recovery were higher in study IV than in the previously mentioned study (86% as compared to 60%). This may be largely explained by the differing study groups, i.e. inclusion of all patients who experienced first-time postoperative AKI in study IV as opposed to only stage 2–3 AKI in critically ill patients in the comparison study.

Ultimately, the results of study IV show the need for studies of long-term prognosis of AKI. As a systematic review from 2015 stressed, future AKI studies should reliably report both pre-AKI kidney function and post-AKI kidney function at fixed follow-up points (Sawhney et al., 2015).

5.1.5 Study V – POAF, the most common complication of heart surgery

In studies II and III, POAF was found to be the most common postoperative complication after open-heart surgery. Like AKI, POAF is a common and potentially serious complication of cardiac surgery. The incidence of POAF was found to be high in our cohort, occurring in 44% of cases as opposed to the 20–30% reported in most other observational studies (Andrews et al., 1991; Creswell et al., 1993; Echahidi et al., 2008). A hypothesis of this study

was that one of the reasons for the high incidence might be the limited systematic use of prophylactic treatment, such as β- and calcium channel-blockers, during the study period, as well as dietary and genetic factors (Arnar et al., 2016; Stefansdottir et al., 2011).

As in studies II and III, study V showed that patients who experienced POAF also had significantly higher RBC transfusion rates. This might be due to the fact that patients who experience POAF, and thereby have decreased cardiac output, are possibly more sensitive to the effects of perioperative anemia (Ng et al., 2016). However, as previously mentioned, transfusion of RBCs leads to a pro-inflammatory response, thereby possibly predisposing to both POAF and AKI (Bruins et al., 1997; Fried et al., 2004; Shlipak et al., 2003). However, causality cannot be confirmed, and, all these outcomes may indeed be markers of an increased pathophysiological burden of a patient.

Independent risk factors for POAF were advanced age, the complexity of the surgical procedure, a history of CHF, a low ejection fraction, and a higher EuroSCORE. These factors have also been reported as independent risk factors for AKI—and it could be conjectured that POAF and AKI might share underlying pathophysiological mechanisms, e.g. the activation of the systematic inflammatory response (Albahrani et al., 2003; Creswell, 1999; Ng et al., 2016). When AKI occurs, pro-inflammatory cytokine clearance is decreased and oxidative stress is increased (Friedrichs et al., 2011). In turn, reactive oxygen species and inflammatory markers have been found to affect the function of cell ion channels and gap junctions, thereby affecting cellular electrical stability and conduction of impulses, which are necessary for the proper function of the atrial myocytes (Friedrichs et al., 2011). In line with this, the incidence of both POAF and AKI peaks at postoperative days 2–3 and coincides with peak levels of inflammatory markers (Chung et al., 2001; Ng et al., 2016).

Various studies have shown that both POAF and AKI negatively affect long-term survival (El-Chami et al., 2010). Causality can, however, be difficult to determine, as studies are mostly retrospective. In studies II and V, we did not find a significant interaction between AKI and POAF regarding association with long-term survival. Both were, however, found to have a negative effect on survival.

5.2 Strengths and limitations

This thesis is based on five retrospective observational cohort studies. There is therefore an inherent risk of shortcomings, mainly the distorting effect of

unrecognized confounding factors and bias. However, it has been shown that well-designed observational studies will not necessarily systematically overestimate the association between exposure and outcome when compared to the gold standard of evidence-based medicine, i.e. randomized controlled trials (RCTs) (Benson & Hartz, 2000; Concato et al., 2000). What is more, observational studies usually carry the additional advantage of lower cost and a broader range of patient population. In the case of the epidemiology of AKI, RCTs might even be impossible or unethical, so observational studies may be better suited to the task.

The chance of misclassification cannot be excluded in our studies. As is often the case in retrospective studies on AKI, there was no comprehensive registration of urine output in our datasets. The diagnosis of AKI was therefore solely based on the SCr component of the RIFLE and KDIGO criteria. This might lead to underestimation of the incidence of AKI, but studies have shown that patients diagnosed with AKI based on urine output usually have milder disease and survival rates comparable to those in patients without AKI (Kellum et al., 2015). The RIFLE and KDIGO criteria for the classification of AKI are based on functional markers of kidney injury (namely SCr) rather than direct histological evidence of renal tissue pathology or biomarkers of injury. Furthermore, patients may be incorrectly diagnosed as having or not having AKI in cases where baseline SCr is missing. Indeed, as already pointed out, a major point of criticism regarding the use of the RIFLE, AKIN, and KDIGO criteria in observational studies is the sometimes unreliable documentation of baseline SCr in clinical practice (Pickering & Endre, 2010). It has even been shown that back-calculation of baseline SCr, as proposed in the RIFLE criteria, can lead to misclassification of AKI (Pickering & Endre, 2010). This was highlighted further in the findings of study I, which showed overestimation of the incidence of AKI in the ICU when baseline SCr was calculated from a presumed normal eGFR. In study II, baseline SCr was available for approximately 98% of the population and the 44 patients missing baseline SCr were excluded from the study. In study III baseline SCr was missing in 15 patients (4% of the cohort), and in those cases the mean baseline SCr of the cohort was used instead.

In all five studies included in this thesis, multivariate regression analysis was used in an attempt to correct for confounding factors. Data on numerous variables were registered for every patient in the study, and the databases used were continuously updated during the research period. However, as with all retrospective studies, registration of clinical variables is not all-encompassing and is sensitive to under-reporting, e.g. patients' non-

disclosure of true smoking status. Based on our studies, we cannot determine whether AKI has a direct causal relationship with the outcomes measured. It might be that AKI is a surrogate marker of worse overall status of patients who are prone to adverse outcomes rather than being a direct cause of worse prognosis. However, RCTs to measure the true effect of AKI on patients would likely unachievable and ethically questionable.

Lastly, the risk model presented in study V has not been validated in prospective studies, and the risk of overfitting cannot be excluded. Essentially, this means that our risk model might describe a random error rather than an underlying relationship between POAF and risk factors used to construct the model. However, the model was constructed using only three risk factors, which to some extent limits the probability of overfitting. Furthermore, we believe that the simplicity of the model might possibly aid in its possible future clinical application.

A major strength of the studies included in the thesis is their nationwide nature. The Icelandic nation can in most respects be considered to be similar to other western countries with regard to age, sex distribution, and comorbidities—leading to wide generalizability of our results to countries with similar levels of healthcare. Furthermore, in Iceland all patients are assigned a unique personal identification number, allowing consistency in gathering of individual patient data. Data are collected into centralized nationwide registers, permitting thorough analysis. Also, the small size of the nation, with negligible migration, permits extremely comprehensive long-term follow-up regarding morbidity and mortality. Importantly, we were able to cross-reference three separate databases to ensure that patients were reliably registered in our studies. Furthermore, in study II we were able to collect long-term follow-up SCr values in the majority of patients who had AKI, thereby facilitating diagnosis and analysis of recovery of renal function. In addition, we were able to follow up long-term need for RRT in all patients with the help of the Icelandic End-Stage Renal Disease Registry, which comprehensively registers data on all patients who undergo RRT for CKD in Iceland.

6 Conclusions and future studies

AKI is a serious complication in various clinical settings and is associated with adverse outcomes, such as increased hospital stay and ICU stay, higher complication rates, and higher mortality. Despite advances in assessment and treatment of the complications of AKI (e.g. fluid overload and electrolyte disturbances), with measures ranging from increased hydration to hemodialysis, AKI is still a costly condition and these patients are still found to fare worse later on. Furthermore, recovery of renal function is significantly associated with better outcome in patients who have suffered postoperative AKI.

We were unable to show any significant interaction between AKI and another common complication of cardiac surgery, POAF, although both were significantly correlated to worse survival. Indeed, based on our studies a causal relationship cannot be shown between AKI and POAF and other adverse outcomes. AKI and POAF, which are both more likely in states of inflammation, may be markers of more severe illness rather than being directly causative factors of worse prognosis.

However, our results further highlight the need to concentrate on the population prone to AKI and POAF. Research on the subject remains important for elucidation of possible, as yet unknown, risk factors and links between AKI and POAF and other complications in the postoperative period.

Epidemiological studies are valuable, as they provide insight into potentially modifiable risk factors. However, in the case of AKI, clinical research was for a long time impeded by the lack of consensus criteria. Despite the strides that were taken following the publication of the RIFLE criteria, studies on AKI are still marred by the inherent flaw of basing the definition on SCr. Ideally, a biomarker for acute kidney injury should be kidney-specific, site-specific (to aid in differentiation of pre-renal, intrinsic, and post-renal causes), detectable early in the process of tissue injury, and inexpensive and reliably measurable. To date, no such marker exists. Studies have yielded biomarkers such as NGAL and KIM-1. They have not, however, been validated extensively and it is still important to continue this research.

Future studies might also try to identify factors that could affect recovery of renal function. Before that, however, a consensus must be reached as to

what constitutes renal recovery. This might be achieved in a large prospective observational study in which patients who experience AKI would have closer monitoring of kidney function at predefined time intervals as well as long-term follow-up.

Unfortunately, except for RRT, there are no supportive measures for patients with AKI. Thus, up until now treatment has been directed at avoiding further injury of the kidney through goal-directed resuscitation and avoidance of nephrotoxic drugs whenever possible. Ideally, the perfect study would help in identification of measures that would be applicable in both prevention and treatment of this serious complication.

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