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ACUTE KIDNEY INJURY IN CARDIAC SURGERY

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ACADEMIC DISSERTATION

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To Matti, Joel, Iiro and Zoja

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II Ristikankare A, Lemström K, Skrifvars M, Hämmäinen P, Suojaranta-Ylinen R, Salmenperä M, Pöyhiä R. Acute kidney injury and serum cystatin C early after heart transplantation. Submitted.

III Ristikankare A, Lemström K, Skrifvars M, Hämmäinen P, Suojaranta-Ylinen R, Salmenperä M, Pöyhiä R. Acute kidney injury and serum cystatin C early after heart transplantation. Submitted.

IV Ristikankare A, Pöyhiä R, Eriksson H, Valtonen M, Leino K, Salmenperä M. Effects of levosimendan on renal function in patients undergoing coronary artery surgery. J Cardiothorac Vasc Anesth 26: 591-5; 2012

LIST OF ABBREVIATIONS

ACEI	Angiotensin–Converting Enzyme Inhibitor
ADQI	Acute Dialysis Quality Initiative
AKI	Acute Kidney Injury
AKIN	Acute Kidney Injury Network
AKI-RRT	Acute Kidney Injury Requiring Renal Replacement Therapy
ANP	Atrial Natriuretic Peptide
ARB	Angiotensin Receptor Blocker
ASA	Acetylsalicylic acid
ATN	Acute Tubular Necrosis
AUC	Area Under the Curve
AUROC	Area Under the Receiver-Operating Curve
BMI	Body Mass Index
BNP	B-type Natriuretic Peptide
CABG	Coronary Artery Bypass Grafting
CI	Confidence Interval
CI-AKI	Contrast Induced Acute Kidney Injury
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CSA-AKI	Cardiac Surgery Associated Acute Kidney Injury
^{51}CR-EDTA	Chromium-51 labeled ethylenediamine tetraacetic acid
^{51}CR-EDTA-GFR	^{51}Cr-ethylendiamine tetraacetic acid glomerular filtration rate
CRP	C-reactive Protein
CVP	Central Venous Pressure
fHb	Free Hemoglobin
GFR	Glomerular Filtration Rate
IABP	Intra-Aortic Balloon Pump
ICU	Intensive Care Unit
IL-18	Interleukin 18
IQR	Interquartile Range
KDIGO	Kidney Disease: Improving Global Outcomes criteria

KIM-1	Kidney Injury Molecule 1
L-FABP	Liver Fatty Acid-Binding Protein
LVAD	Left Ventricle Assistance Device
MAP	Mean Arterial Pressure
MDRD	Modification of Diet in Renal Disease
NAC	N-Acetylcysteine
NAG	N-Acetyl-β-glucosaminidase
NGAL	Neutrophil Gelatinase-associated Lipocalin
NO	Nitric Oxide
NSAID	Non-Steroidal Anti-inflammatory Drug
OPCAB	Off-pump Coronary Artery Bypass Grafting
PCWP	Pulmonary Capillary Wedge Pressure
RBC	Red Blood Cell
RCT	Randomized Controlled Trial
RIFLE	Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease
RRT	Renal Replacement Therapy

ABSTRACT

Aims

The objective of study I was to evaluate the role of serum cystatin C in elderly cardiac surgery patients and study II in heart transplant patients, and to test if serum cystatin C can detect postoperative acute kidney injury (AKI) earlier than plasma creatinine after cardiac surgery. In study II the aim was to discover if urine N-acetyl-β-glucosaminidase (U-NAG) is able to uncover kidney injury in heart transplant patients immediately after surgery. N-acetylcysteine (NAC) and levosimendan were investigated for the protection of kidneys in studies III and IV, respectively.

Material and methods

Study I included 110 cardiac surgery patients aged 70 or more. Serum cystatin C and plasma creatinine samples were collected before surgery for the baseline values and on postoperative days 1 to 5. Urine output was registered and estimated glomerular filtration rate (eGFR) calculated. AKI was determined by using the risk-injury-failure-loss-end stage (RIFLE) criteria and correlation of plasma creatinine and serum cystatin C with AKI was calculated.

Study II included 41 heart transplant patients. Plasma creatinine and serum cystatin C samples were collected preoperatively and postoperatively on days 1 to 5, and U NAG and creatinine samples preoperatively, at the end of surgery, and on postoperative days 1 to 5. AKI patients were defined according to RIFLE classification.

Study III included 80 patients with preoperative renal dysfunction undergoing cardiac surgery. The patients were randomized to receive in double-blind manner intravenous N-acetylcysteine (n=38) or placebo (n=39) at the induction of anesthesia, followed by 20 hour infusion. Kidney injury was defined as increase of plasma creatinine more than 44 μmol/l or more than 25% from the baseline. Kidney function was determined with plasma creatinine, serum cystatin C, and the ratio of urine creatinine and NAG.

Study IV was a study of 60 patients with left ventricular ejection fraction ≤ 50%. In this randomized, double blind study patients received an infusion of levosimendan or placebo starting after induction of anesthesia and continuing for 24 hours. In both studies kidney injury was determined with U-NAG and renal function was measured with plasma creatinine and serum cystatin C. AKI was defined using RIFLE criteria.

Main results

AKI occurred in 56 % of the patients in study I. There was no significant difference in the correlation of cystatin C and creatinine with AKI at different time points. On the first postoperative day the area under the curve (AUC) for cystatin C was 0.71 (0.61- 0.76) and for creatinine 0.66 (0.55-0.76), Δ AUC 0.05 (0.01 - 0.12), p = 0.11. On the second postoperative day AUC for cystatin C was 0.77 (0.68-0.86) and for creatinine 0.74 (0.64-0.83), Δ AUC -0.03 (-0.09-0.03), p = 0.32. Both markers peaked on the third day after surgery.

In study II 56% of patients developed postoperative AKI according the RIFLE criteria, and 31% of the patients with AKI required renal replacement therapy (RTT). There was no significant difference between the changes of plasma creatinine and cystatin C over time with AKI patients, but in patients without AKI, serum cystatin C increased significantly more than plasma creatinine. U-NAG increased in all study patients after surgery indicating some changes in tubular function. However, there were no significant difference between patients with AKI and patients without AKI.

In study III there was no significant difference between the NAC-group and placebo-group in concentrations of plasma creatinine, serum cystatin C and urine NAG and creatinine ratio. AKI occurred in 45% of all study patients.

In study IV there was no significant difference in renal function between the patients treated with levosimendan or placebo. In the placebo group 13 out of 30 patients developed AKI. In levosimendan group 8 out of 30 patients had AKI, p = 0.167.

Conclusions

In cardiac and heart transplant surgery patients serum cystatin C detects AKI equally as compared plasma creatinine. Pharmacological treatments with N-acetylcysteine or levosimendan did not prevent the development of postoperative AKI after cardiac surgery.

Keywords

Cardiac surgery, acute kidney injury, heart transplantation, cystatin C, N-acetylcysteine, levosimendan

1. INTRODUCTION

Cardiac surgery associated acute kidney injury (CSA-AKI) manifests as rapid decline in glomerular filtration rate (GFR) after cardiac surgery. In a multicenter study it was the second most common cause of AKI after sepsis in the intensive care unit (ICU).[1] CSA-AKI has been associated independently with increased mortality, morbidity, and hospital costs. Even a small increase in serum creatinine after cardiac surgery was associated nearly three-fold increase in 30-day mortality, and in severe AKI requiring RRT mortality increased up to 63%.[2,3]

The reported incidence of CSA-AKI has varied depending on the definition of AKI. During last decade a consensus of the criteria of AKI has been established. Based on acute changes in serum creatinine, GFR, and urine output, Acute Dialysis Quality Initiative (ADQI) proposed The Risk, Injury, Failure, Loss of function, End-stage kidney disease (RIFLE) criteria.[4] Acute Kidney Injury Network (AKIN) modified it in 2007 and Kidney Disease: Improving Global Outcomes (KDIGO) in 2012.[5,6] Based on RIFLE or AKIN criteria the range of CSA-AKI incidence is between 9 and 39%.[2,7-10]

The etiology of CSA-AKI is complex including exogenous and endogenous toxins, metabolic abnormalities, ischemia and reperfusion injury, neurohormonal activation, inflammation, and oxidative stress.[11] These factors overlap and recur during the perioperative period making it more difficult to target renoprotective treatments. Several patient-related risk factors have been identified, of which the most important may be preoperative kidney injury and dysfunction. Furthermore the severity of perioperative cardiac dysfunction may have consequential impact on the development of postoperative AKI.[12]

In cardiac surgery the dilutive effect of cardiopulmonary bypass (CPB) pump prime fluid may postpone the detection of decreased kidney function when using conventional measurement by serum creatinine. Therefore the novel kidney function biomarker cystatin C has been tested to find out if it can detect postoperative AKI earlier than creatinine, but the results have been inconclusive.[13] Also, other novel biomarkers as of kidney damage have been diligently studied to help further refine existing criteria of AKI. Although these biomarkers are not yet in wide clinical use, ADQI consensus conference proposed that some of these markers may be used to diagnose AKI in appropriate clinical settings.[14]

Today, more complex cardiac surgery is performed in older patients who have more co-morbidities predisposing them to the development of CSA-AKI. Although the understanding of the pathophysiology of AKI has increased, considerable progress has been made in more accurate definition of AKI, and more sensitive kidney damage biomarkers have emerged, there has been very little progress in the detection, prevention, and management of SCA-AKI.[15] No pharmacologic interventions have demonstrated clear efficacy in prevention of CSA-AKI.[16] Some therapies may offer protection against AKI,

such as mitigating preoperative anemia, avoiding perioperative red blood cell transfusions, and trying to prevent surgical re-exploration.[2]

2. REVIEW OF LITERATURE

2.1 Nephron

Each kidney contains 1.0 to 1.3 million nephrons, the functional units of the kidney (Figure 1.). In the nephron blood enters the glomerulus via an afferent arteriole and exits through an efferent arteriole. The glomerular blood pressure acts as a driving force for water, amino acids, and free ions to be filtered out from the blood and into the space made by the glomerular capsule (Bowman's capsule). Fluid then flows to the renal tubule, which consist of the proximal convoluted tubule, the loop of Henle, and the distal convoluted tubule. The main function of the proximal tubule is to resorb Na^+ and water, but bicarbonate, Cl^-, glucose, amino acids, phosphate, and lactate are also transported. The main function of the loop of Henle is to create and maintain concentration gradient of osmolality within the renal medullary interstitium. This provides the downstream collecting ducts ability to concentrate urine by osmosis. The resorption of Ca^{2+} and Mg^{2+} occurs also in the loop of Henle. The distal convoluted tubule delivers its filtrate to a system of collecting ducts and is also responsible for subtle changes in Na^+, K^+, Ca^{2+}, phosphate, and acid-base homeostasis. The collecting ducts run down the steep concentration gradient created by the loop of Henle allowing water resorption. This leads in the creation of concentrated, hypertonic urine.[17]

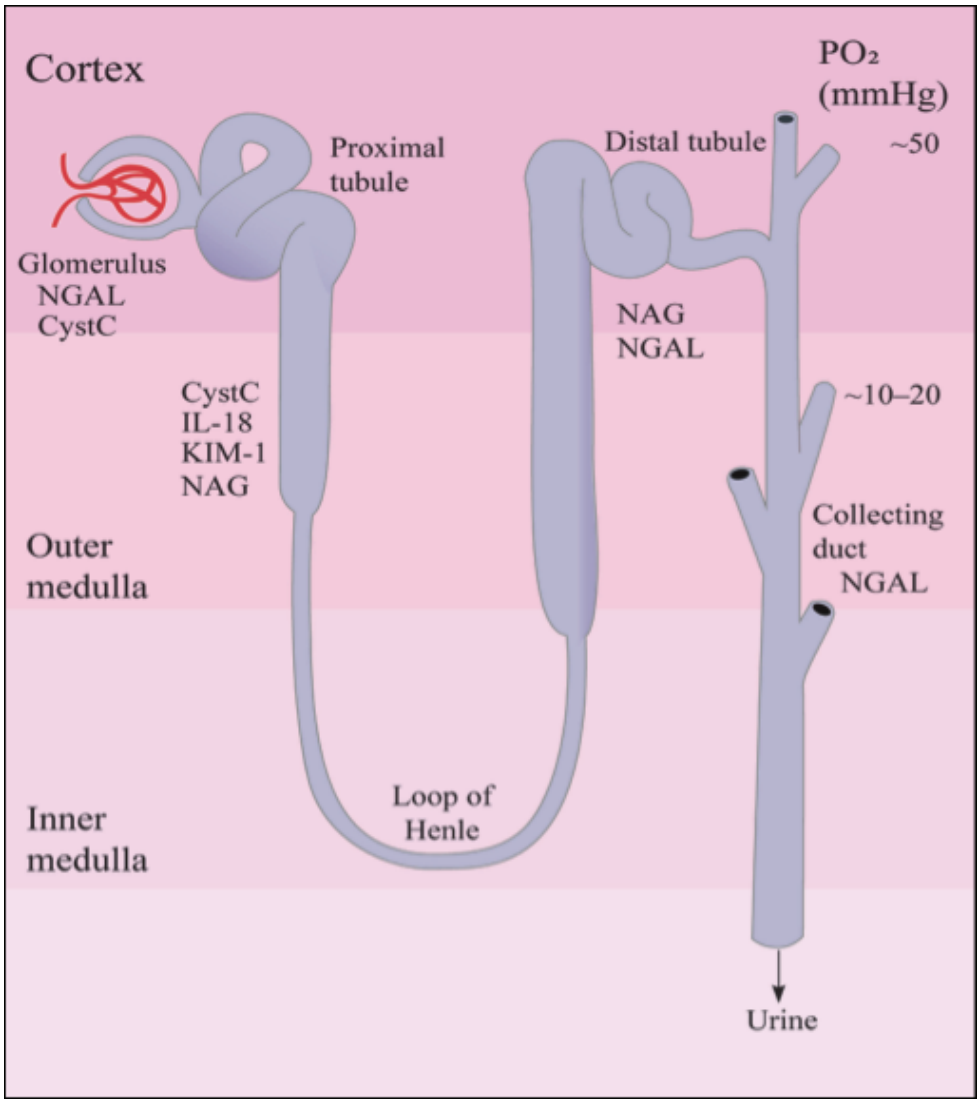


Figure 1. *Nephron. Biomarkers are marked in their main location of their origin. NGAL; Neutrophil gelatinase-associated lipocalin, CystC; Cystatin C, IL-18; Interleukin 18, KIM-1; Kidney injury molecule, NAG; N-acetyl-β-glucosaminidase*

2.2. Acute Kidney Injury (AKI)

2.2.1. Definition of Acute Kidney Injury

The current definition of acute kidney injury is an abrupt and sustained decrease in renal function resulting in retention of nitrogenous products, such as creatinine and urea.[18] The kidney is a complex organ responsible to various functions. Depending on the duration and severity of AKI it can lead to disturbances in salt and water regulation, toxin and metabolite elimination, electrolyte homeostasis, and acid-base balance.[19] There is also growing evidence for the direct negative impact of AKI on other vital organs.[20]

Several definitions of the diagnosis of acute renal failure have been employed, usually including absolute or relative changes in creatinine, glomerular filtration rate values, and reduction of urine output. Generally, the studies have measured the incidence of acute renal failure as a loss or near loss of kidney function and requirement of RRT. However, while it was recognized that even smaller changes in creatinine values have affected short- and long-term outcome of the AKI patients, the development of more sensitive definition of kidney dysfunction was needed. During the search for new criteria the term *acute renal failure* was replaced with a more accurate expression *acute kidney injury*. In 2002 the ADQI group started to develop the consensus of AKI with the definition known as RIFLE, which included 3 different severity stages; risk, injury and failure, and 2 outcome stages; loss of kidney function and end-stage kidney disease. These stages were based on the degree of increase in serum creatinine level or the duration of oliguria, the risk and injury stages increased the sensitivity to define AKI when the failure was a specific stage.[21] This definition was modified by the AKIN group by the addition of an absolute increase in serum creatinine level of more than 26.5 μmol/l and shortening the time limit for AKI diagnosis from 7 days to 48 hours and removing the two outcome stages (Table 1).[6] In validation studies with CSA-AKI patients both definitions have demonstrated increased mortality risk associated with progressively more severe stages of AKI.[22] During the past decade the consensus of the AKI criteria has been developing and according to the latest consensus by KDIGO, AKI is defined as an increase in serum creatinine levels of 26.4 μmol/l or greater within 48 hours, or an increase of serum creatinine more than 1.5 times the baseline within 7 days, or diuresis less than 0.5 ml/kg/h for 6 hours.[23]

All RIFLE, AKIN, and KDIGO criteria include urine output in the definition of AKI. This has been criticized because oliguria may be an appropriate response to volume depletion rather than a symptom of declined renal function. Further, the weight-based definition for AKI limits its use in the obese because of the disproportion between the weight and urine output, and urine output can be manipulated such drugs as diuretics and dopamine.[24] A majority of studies use only creatinine criterion for AKI diagnosis, furthermore, the evaluation of studies using both urine output and creatinine have shown poor correlation between these criteria.[25] However, in a study with critically ill patients it was demonstrated that the use of RIFLE criteria without urine output criteria significantly

underestimated the incidence and grade of AKI, AKI diagnosis was delayed, and it was associated with higher mortality.[26] All three AKI definitions have limitations. They rely on creatinine as it is not an ideal biomarker for AKI, it is also affected by factors independent of GFR, such as age, gender, body weight, and drugs.[27] None of the definitions indicates the origin of the kidney injury.

	Rifle		AKIN	KDIGO
Definition	S-Cr > 1.5 x baseline over ≤ 7 days		S-Cr > 1.5 x baseline over ≤ 48 hours	S-Cr > 1.5 x baseline over ≤ 7 days
Class		Stage		
Risk	S-Cr > 1.5 x baseline	1	S-Cr > 1.5 x baseline or ↑S-Cr ≥ 26.5 μmol/l	S-Cr > 1.5 x baseline or ↑S-Cr ≥ 26.5 μmol/l
	UO < 0.5 ml/kg/h x 6 h		UO < 0.5 ml/kg/h x 6 h	UO < 0.5 ml/kg/h x 6 h
	↓GFR > 25%			
Injury	S-Cr > 2 x baseline	2	S-Cr > 2 x baseline	S-Cr > 2 x baseline
	UO < 0.5 ml/kg/h x 12 h		UO < 0.5 ml/kg/h x 12 h	UO < 0.5 ml/kg/h x 12 h
	↓GFR > 50 %			
Failure	S-Cr > 3 x baseline or ↑S-Cr ≥ 353.6 μmol/l, with acute rise of ≥ 44.2 μmol/l ↓GFR > 75 %	3	S-Cr > 3 x baseline or ↑S-Cr ≥ 353.6 μmol/l, with acute rise of ≥ 44.2 μmol/l	S-Cr > 3 x baseline or ↑S-Cr ≥ 353.6 μmol/l
	UO < 0.3 ml/kg/h x 24 h or anuria x 12 h		UO < 0.3 ml/kg/h x 24 h or anuria x 12 h	UO < 0.3 ml/kg/h x 24 h or anuria x 12 h
	↓GFR > 75 %			
			Initiation of RRT	Initiation of RRT
Loss	RRT required for > 4 weeks			
End stage	RRT required for > 4 months			

Table 1. Comparison of RIFLE, AKIN, and KDIGO classifications of acute kidney injury

2.2.2. Incidence and outcome of cardiac CSA-AKI

According to RIFLE and AKIN criteria, the range of CSA-AKI incidence is between 9 to 39 %. The observed incidence depends on the clinical profile of the analyzed patients and on the type of surgery. Isolated coronary artery bypass grafting (CABG) has the lowest incidence of AKI, 2 to 5%, whereas in valve or combined valve and CABG surgery AKI occurs in up to 30% of patients.[9] In patients with known risk factors for kidney injury the incidence of AKI may increase to as high as 50%.[28] The requirement of RRT in patients with CSA-AKI is 1 to 5%.[29-32] Postoperative renal dysfunction develops even more often in heart transplant patients, the incidence of AKI being 70%, of which 6 to 25% receive RRT before hospital discharge.[3336] RIFLE and AKIN has been tested for better clinical accuracy of CSA-AKI, and the investigators discovered that both criteria showed good correlation with mortality, but significantly more patients were diagnosed by AKIN than by RIFLE. It was suggested that AKIN, applied in cardiac surgery patients without correction of serum creatinine for fluid balance, may lead to over diagnosis of AKI.[8]

During hospitalization, CSA-AKI is strongly associated with increased mortality, morbidity, and the length of hospital stay, and it affects the long-term survival.[37,38] The incidence of AKI has increased over time, partly due to different definitions of AKI, but the survival of the CSA-AKI has improved. During the period of 1993-2002 the associated mortality has decreased from 32% to 23%. The short-term mortality in patients needing RRT has also decreased from 61% to 49% but there is no improvement in long-term survival in this group.[39] Even a small increase in postoperative serum creatinine is associated with increased mortality, both in short- and long-term follow-up. A decrease in postoperative serum creatinine is associated with reduced mortality but even a small or subclinical increase in creatinine increases 30-day mortality.[3,40] Patients suffering stage I AKI (RIFLE) had higher mortality, higher incidence of neurological dysfunction, longer duration of mechanical ventilation, and longer stay in the ICU and in hospital.[41] Even when the renal function is recovered, the small elevation in postoperative serum creatinine is associated with increased long-term mortality.[42] The extent of postoperative creatinine increase is associated with an increased risk to develop chronic kidney disease, and even a small elevation of creatinine is meaningful.[43] Finally, the duration of AKI seems to be directly proportional to long term mortality.[7]

2.3. Pathophysiology of AKI

2.3.1. Pathophysiology of AKI

Primary causes of AKI in hospitalized patients include ischemia or nephrotoxity.[18] Clinically AKI is broadly divided into three categories: prerenal, renal, and postrenal. Postrenal AKI is caused by obstruction of the urinary collection system. Prerenal AKI

results from decreased renal perfusion, which leads to a reduction in glomerular filtration rate (GFR), which is seen as an increase in serum creatinine. Primary causes leading to prerenal AKI are a failure in general circulation, or isolated failure of the intrarenal circulation caused by hypovolemia, low cardiac output, decreased vascular resistance or occlusion in the renal artery.[44] The kidney is able to autoregulate renal blood flow within limited boundaries. Blood flow to the glomerulus is regulated by the preglomerular afferent and postglomerular efferent arteriolar sphincter tone. During hypotension, vasodilatation of the afferent arterioles occurs mediated by prostaglandin I_2 and nitric oxide generated within the kidney, and the concomitant vasoconstriction of the efferent arterioles is mainly induced by angiotensin II. These adjustments attempt to maintain the glomerular capillary hydrostatic pressure.[45,46] In acute hypovolemia the tubuloglomerular feedback mechanism is initiated to stabilize GFR and fluid delivery to the distal nephron, and this process is mediated by complex interaction between the macula densa and the glomerular microvasculature.[47] Prerenal AKI can be reversed in hours or days if the circulatory failure and renal hypoperfusion are promptly corrected, otherwise persistent hypoperfusion will lead to intrinsic renal failure.

2.3.2. Acute tubular necrosis (ATN)

In the intrinsic renal failure a wide variety of injuries can occur to the kidney. To comprehend the different etiologies the kidney is generally divided in to four major structures that can be damaged: the tubules, the glomeruli, the interstitium, and the intrarenal blood vessels.[18] The tubular damage, acute tubular necrosis, is the main cause of AKI in patients with major surgery or in critically ill patients.[44] Major causes of ATN are ischemia-hypoxia and nephrotoxicity (Figure 2). The nephrotoxic damage is caused by a variety of exogenous compounds (aminoglycosides, radio contrast media), and endogenous compounds (free hemoglobin, myoglobin).[18] However, the term ATP has recently been challenged, because there is a contradiction concerning the severe clinical syndrome of kidney injury and lack of histopathological findings that could be linked together.[48] Investigators emphasized the role of endothelial dysfunction, coagulation abnormalities, systemic inflammation, and oxidative stress in the role of AKI, rather than the term ATN. Also, much of the current understanding of the pathophysiology of AKI is derived from animal research, but this setting rarely applies to the clinical events and more relevant models are needed. [48]

Normally the kidneys receive 25% of cardiac output, but the renal blood flow is not homogeneously distributed within the organ. The cortex and the cortical nephrons receive 90% of the renal blood flow, when the medulla and the juxtamedullary nephrons receive only 10 % of the renal blood flow. If the partial oxygen pressure in the cortex tissue decreases, it results in borderline chronic oxygen deprivation of the highly metabolically active cells in the S3 segment of the proximal tubule and the medullary thick ascending limbs.[49]

In ATN renal tubular epithelial cells undergo rather sublethal changes than actual necrosis, thus lately it has been suggested that tubular injury might be a better term. Although, clear evidence is absent to indicate connection of GFR and tubular injury, clinically ATN has been divided into different phases according to changes at cellular level and GFR. The phases are initiation, extension, maintenance, and recovery.[18] During the early stage of renal ischemia, cellular and vascular adaptations in the kidneys maintain renal epithelial stability, but when further fall in renal blood flow persists, the initiation phase occurs and tubular epithelial cells suffer from injury and dysfunction. The extension phase is characterized by continued hypoxia and inflammation, and both of these are more pronounced in the corticomedullary junction. GFR further decreases when injury, necrosis, and apoptosis are present in the outer medulla, while proximal tubule cells in outer cortex, where blood flow has returned, undergo cellular repair. In the maintenance phase GFR reaches its nadir value, and cells undergo repair process, migration, apoptosis, proliferation, and differentiation in order to re-establish and maintain cellular and tubular integrity. In the recovery phase cellular differentiation proceeds, epithelial polarity is re-established and normal cell and kidney function leads to increased GFR.[50] Delay or inhibition of this repair process can lead to progression of injury and eventually lead to development of chronic kidney injury.[51]

Decrease in GFR results from microvascular and tubular changes in the kidney. Renal vasoconstriction and loss of autoregulation lead to alteration in renal blood flow. Sublethal tubular damage impairs reabsorption of sodium, and activates the potent vasoconstrictor, as well as a potent vasoconstrictor adenosine, resulting in afferent arteriolar vasoconstriction, and related decrease in GFR. Concomitant sympathetic nerve activity and stimulated renin and angiotensin II secretion further increase the vasoconstriction. In addition, elevated levels of endothelin, another potent vasoconstrictor, levels have been reported in patients with AKI.[18] Ischemia-reperfusion injury promotes leukocyte adhesion to activated endothelial cells. This is proposed to impair capillary flow, generate molecules increasing vasoconstriction, cause a parenchymal cell injury, and possibly increase tubular lumen pressure and reduce GFR. These factors may contribute to the resistance to vasodilatory therapy in the extension phase of AKI.[18] The immune response to AKI is complex and involves cells of the innate and adaptive immune systems, the innate immune cells such as neutrophils, macrophages, dendritic cells, natural killer cells, natural killer T cells, and adaptive $CD4^{+}$T cells promote renal injury.[52] The role of lymphocytes, T and B cells, the major effector cells in adaptive immune system, can be either to promote AKI or protect against ischemia-reperfusion injury.[52] Regulatory T cells act as a counterbalance to the pro-inflammatory cells by producing anti-inflammatory cytokines, generating extracellular adenosine and promoting inhibition of dendritic cells.[52]

At tubular cellular level ischemia results in a rapid loss of cytoskeletal integrity and cell polarity, with shedding of proximal tubule brush border, mislocalization of adhesion molecules and other proteins, such as sodium/potassium ATPase and β-integrins, along with apoptosis and necrosis.[53] In severe injury, viable and non-viable cells are desquamated, leaving regions of basement membrane, the only barrier between the filtrate

and peritubular interstitium, and resulting possible back-leak of the filtrate. This can be augmented by cellular debris, which can cause intratubular obstruction and increase the pressure in tubule.[53] The epithelial injury in tubular cells promotes the generation of inflammatory and vasoactive mediators which can increase the vasoconstriction and further elevate inflammation and thus play a pivotal role in AKI.[53]

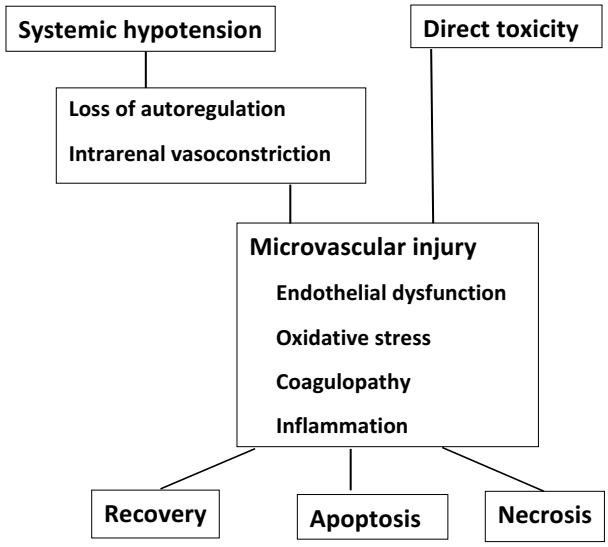


Figure 2. Mechanisms of acute kidney injury

2.4. Pathophysiology of CSA-AKI

Multiple and complex pathophysiological features are thought to participate in CSA-AKI. ADQI consensus meeting has addressed AKI in cardiac surgery and drawn up statements considering the pathophysiology and treatment of AKI.[11] Based on available evidence numerous mechanisms, processes, and pathways were suggested: exogenous and endogenous toxins, metabolic factors, ischemia-reperfusion injury, neurohormonal activation, inflammation, and oxidative stress. During the cardiac surgery these different processes of injury can occur frequently at different times and also overlap with each other leading to AKI. Table 2 presents factors of CSA-AKI.

Preoperative	Intraoperative	Postoperative
Co- morbidities	Type of surgery	Cardiac low output
Atherosclerotic disease	Emboli	SIRS
Diabetes	CPB	Transfusion
CKD	Hypoperfusion	
Heart failure	SIRS	
Embolism	Hemodilution	
Nephrotoxins	Hemolysis	
Contrasts media	Transfusion	
Other drugs		

Table 2. *Pathophysiological factors in cardiac surgery associated acute kidney injury**.** CKD; chronic kidney disease, CPB; cardio pulmonary bypass, SIRS; systemic inflammatory response syndrome.*

2.4.1. Preoperative period

Preoperative risks for kidney injury are frequently patient derived, or a result of treatment of the cardiovascular disease. The co-morbidities, as atherosclerotic disease, diabetes, chronic kidney disease, and heart failure, are common, and they likely increase the risk for AKI. The emergent or urgent cardiac operation predisposes patients to several potentially detrimental effects on their kidneys, which further increase the risk of AKI.[11]

During this period cardiogenic shock is the most plausible cause to ischemia reperfusion injury to kidneys. In heart failure, caused by myocardial infarction or severe valvular disease, low cardiac output is a direct cause to renal hypoperfusion and AKI. This insult can be exacerbated by the administration of diuretics, non-steroidal anti-inflammatory drugs (NSAIDs), angiotensin-converting enzyme inhibitors (ACEIs), or angiotensin receptor blockers (ARBs), these drugs may impair the autoregulation of renal blood flow.[54] The treatment of low-output patients commonly includes vasodilators and diuretics, which may lead to dehydration, hypovolemia, and hypotension.[11]

Renal artery embolism originating from intracardiac thrombus, vegetation of a valve, or atherosclerotic plaque leads to unexpected impaired renal perfusion. Especially during cardiac catheterization atherosclerotic emboli can be produced leading to a blockade of the renal artery impairing the renal circulation for an uncertain period of time.[55] Due to the fact that the thrombi may dissolve, or collateral flow may restore the blood flow to the kidneys, the adverse event is difficult to recognize and the ischemia time is unknown. Atherosclerotic disease itself manifested as renal artery stenosis can also affect renal perfusion, particularly during hypotension.

Another reason for hypotension is allergic reaction with anaphylactic features caused by antibiotics or other medication given to the patient preoperatively. The treatment of hypotension may be further complicated because of previously administrated vasodilators.[11]

The inflammatory system is activated in the preoperative period by atherosclerotic heart disease and infections, mainly endocarditis. There are some studies showing correlation with elevated inflammatory mediators and adverse outcome after cardiac surgery, but none has addressed the preoperative inflammation and renal function.[56] Some studies have indicated that statins may reduce inflammation and improve endothelial function, but there is no evidence that they reduce AKI in cardiac surgery. [57,58] However, in a recent study with 625 patients divided into two groups to continue preoperative statins versus to discontinue them for 24 hours, the battery of renal biomarkers were significantly decreased with patients continuing statins, although there was no difference in AKI defined by doubling of serum creatinine or requirement of RRT.[59]

In chronic heart failure, the neurohormonal activation may increase the risk in cardiac surgery. In cardiac low output failure the renal blood flow is decreased, which activates the renin-angiotensin-aldosterone system and the sympathetic nervous system. It also increases production of antidiuretic hormone, induces inflammatory mediators, and affects endothelium by reducing nitric oxide production resulting in vasoconstriction and a decrease in the renal blood flow leading to reduced renal filtration and sodium and water retention.[60] Other co-existing diseases, as hypertension, and diabetes or therapies such as ACEIs, ARBs, and diuretics, might further increase the risk of AKI. These patients often have chronic kidney disease preoperatively.

During the preoperative period some other nephrotoxic drugs administrated to the patients may increase renal dysfunction. Endocarditis may be treated with antibiotics like beta-lactam, aminoglycoside, or amphotericin B, which can cause direct injury or interstitial nephropathy.[61] More common is radio contrast-induced nephropathy. Iodinated contrast media can cause a renal insult by inducing vasoconstriction and exposing tubular cells to direct toxic effects, and simultaneous oxidative stress and inflammation may both add injury to the kidneys. Patients with chronic kidney disease are more susceptible to additional injury during catheterization. [62] Cardiac surgery performed less than 24 hours after cardiac catheterization has been demonstrated to cause renal dysfunction in coronary artery bypass patients.[63]

2.4.2. Intraoperative period

During intraoperative period patients are exposed to anesthesia and cardiopulmonary bypass, which can cause hypotension and activate the immune system. The manipulation and cannulation of the aorta can release emboli to circulation before the initiation of the

CPB.[11] The use of epi-aortic echocardiography before cannulation and clamping of the aorta has demonstrated to be beneficial to detect plaques in the ascending aorta.[64]

Pump flow during CPB

The introduction of cardiopulmonary bypass machine more than 60 years ago made complex cardiac surgery possible without high risk, but already in the 1960s the association between CPB and kidney injury became apparent.[65] The materials and the techniques have improved, but CPB is still considered to have a vast influence on the postoperative kidney function of cardiac surgery patients.
The goal of CPB is to maintain regional perfusion at a level that supports optimal organ function.[66] CPB flow rate recommendation 1.8-2.2 l/min/m^2 is based on experimental calculations of global oxygen consumption at different perfusion rates.[67] However, it is not known what the regional flow rates are with this recommendation, and generally flow rates are maintained at the level of normal cardiac index, 2.2-2.4 l/min/m^2. There is debate whether a pulsatile flow preserves kidney function better than a non-pulsatile flow in CPB. In one large study pulsatile flow demonstrated no protection to kidneys as compared to non-pulsatile flow.[68] However, another more recent research showed less acute renal insufficiency and significantly improved whole body perfusion in the elderly undergoing CPB with intra-aortic balloon pump (IABP) induced pulsatile flow.[69] Despite the theoretical benefits of the pulsatile flow, almost all centers perform CPB using non-pulsatile pumps.

Perfusion pressure during CPB

The flow rate and the perfusion pressure determine regional blood flow in CPB. The ideal perfusion pressure to secure sufficient local oxygen delivery to kidneys is unknown, and generally a mean perfusion pressure of 50 to 70 mmHg with normal cardiac output is maintained to ensure adequate renal protection.[70] Furthermore, it is unknown if these recommended flow rates and pressure limits are adequate to preserve renal blood flow in patients with preoperative kidney injury, or in patients with pre-existing ATN and possible loss of autoregulation.[70] One study looked at CPB mean arterial pressure (MAP) ranges of 40 to 80 mmHg in elderly patients and found no correlation to postoperative renal dysfunction.[71] A study in patients with normal preoperative renal function showed association between postoperative AKI and longer CPB time, lower perfusion flow, and longer periods on CPB at pressures below 60 mmHg.[72] Ono et al. measured the excursions of MAP during CBP below the limit of autoregulation, and found that MAP at the limit of autoregulation and the duration and degree to which MAP was below the autoregulation threshold were independently associated with AKI, although the absolute MAP did not differ between the patients with AKI and the patients without kidney injury.[73] In addition, it was demonstrated that MAP variance (preoperative MAP minus intraoperative MAP) more than 26 mmHg was independently associated with AKI in high-risk patients.[74]

Hypothermia during CPB

For organ protection, most procedures performed with CPB employ mild to moderate systemic hypothermia (32-36° C), and more challenging operations may require deep hypothermia (15-25° C) to allow periods of low blood low or circulatory arrest. However, there are conflicting results of hypothermia versus normothermia with regard to renal outcome. One reason for this may be the different sites for temperature monitoring. Bladder, nasopharynx, and blood temperatures may differ several degrees from each other, depending on patient's body habitus and surrounding temperature. The arterial temperature seems to be closest to jugular bulb temperature, which reflects the temperature of the central nervous system.[75] In a recent study, patients on CPB were cooled to 32°C and rewarmed to 34°C or to 37°C.[76] The patient group warmed to 37°C had higher incidence of AKI. Another patient group was sustained in mild hypothermia 34°C, which did not improve the renal outcome.[76] Rewarming, rather than hypothermia, of patients on CPB had more impact on renal outcome, suggesting that rewarming speed may be an important factor to sustain balance of oxygen supply and demand on CPB.

Embolism during CPB

During CPB both gaseous and particulate emboli are generated and may lead to organ injury. The correlation between the number of cerebral emboli and postoperative stroke and kidney injury has been demonstrated.[77] When pulses of embolic signals were registered with transcranial Doppler, pulses of embolic signals were obtained during aortic manipulation, suggesting that atherosclerotic aorta is a risk for stroke and AKI.[77] Air is another source of emboli. It may enter to the left side of heart when left side of the heart is open, for example during valve surgery, or enter from the right side through open foramen ovale. "De-airing"-maneuvers are applied to remove the air, and the use of carbon dioxide aids to remove trapped air from the heart as it is more soluble in blood than nitrogen, the main component of air. [78] Echocardiography is helpful to detect, and to aid the removal, of residual air.[79]

Inflammatory system

CPB activates a systemic inflammatory response, which in some patients clinically manifest as a syndrome (SIRS).[80] Cardiac surgery with CPB pump elevates more systemic inflammatory factors than off-pump operations implicating that CPB itself provokes SIRS.[81] The main triggers of CPB-associated SIRS is the direct contact of blood with the artificial surface of the bypass circuit, development of ischemia-reperfusion injury, and presence of endotoxemia.[82-84] Other possible provoking factors are, operative trauma, non-pulsatile blood flow, mediastinal shed blood during CPB, and pre-existing left ventricular dysfunction.[70] The increased level of circulating inflammatory mediators may elicit endothelial dysfunction and the initiation of AKI amplified by alterations in renal perfusion.[85] The AKI patients demonstrated significantly greater increase in neutrophil CD11b (neutrophil adhesion receptor) density, as well as higher total neutrophil counts, in a study of the markers of leukocyte and platelet activation during CPB. However,

neutrophil CD11b upregulation did not correlate with other clinical variables associated with renal risk, suggesting that this marker of neutrophil inflammatory response may independently predict kidney injury.[86] Further, in this study other inflammatory markers did not differ between patients with AKI and patients without kidney injury. In a small prospective trial with low-risk patients, the group without leukocyte depletion suffered more injury to both renal tubules and glomeruli, than patients with leukocyte depletion, suggesting that leukocytes may also have an important role in post CPB AKI.[87]

Prolonged CPB and cross-clamp time of aorta associates strongly with increased incidence of AKI, although safe time limit has not been determined.[88] Adverse events as SIRS and hemolysis generated by CPB are plausible reasons for increased risk of AKI.

A recent meta-analysis analyzed the randomized controlled trials of anti-inflammatory strategies in aim to reduce AKI in cardiac surgery patients.[89] Based on previous findings they included trials that used interventions as glucocorticoid administration, leukocyte filter application, and minimizedextracorporeal circuits to modulate inflammatory response, and only leukocyte filters effectively reduced worsening of the renal function.[89] The role of inflammation in CSA-AKI is based mainly on animal models of renal ischemia–reperfusion injury, and they clearly demonstrate the role of interstitial inflammation and the elaboration of pro-inflammatory cytokines, as well as reactive oxygen species, in the production of tubular injury.[70] However, large clinical, randomized, and controled trials are needed in order to better evaluate the role of inflammation in CSA-AKI.

Hemodilution

Hemodilution occurs at the initiation of CPB decreasing blood viscosity and improving regional blood flow in the setting of hypoperfusion and hypothermia. Anemia, when hematocrit is less than 21% to 24% during CPB, has been reported to increase the risk of postoperative AKI.[90] AKI risk appeared to increase, when both anemia and hypotension occurred during CPB, compared with anemia alone.[91] Another study could not confirm this result, and it has also been noted, that the harmful effects of anemia could be reduced by increasing the oxygen delivery by increasing the pump flow.[92,93]

Hemolysis

A common consequence of CPB is the development of intravascular hemolysis.[94] In hemolysis there are several contributing factors to kidney injury, as loss of red blood cell (RBC) mass, impaired endothelial function, oxidative damage, and cytotoxic tubular damage.[95] Haptoglobin scavenges circulating free hemoglobin (fHb), but when its capacity is saturated, fHb binds to nitric oxide (NO) derived from endothelium, leading to decreased NO-bioavailability, consequently increasing vascular resistance and decreasing organ perfusion.[96] In a recent study with cardiac surgery patients there was a significant correlation between hemolysis, NO consumption, and kidney tissue damage after CPB and surgery.[97] Furthermore, the structure of RBCs can also be damaged, which diminishes their ability to enter in small vessels and reduces their contact with vessel walls, leading to organ ischemia.[94]

In a setting of CPB, several mechanisms contribute to the destruction of RBCs: shear stress, blood-air and blood-endothelial interface, and positive and negative pressures. The primary source of fHb is the suction from the operative field and active suction from heart chambers. The amount of air that is aspirated together with the blood increases red cell fragility.[98] CPB time is also directly related to the degree of hemolysis.[99] There is no evidence of superiority of the rollers versus centrifugal pumps with respect to hemolysis.[94] The suggested strategies to prevent hemolysis during CBP are to avoid excessive use of suction, to use a separate cardiotomy reservoir to avoid damaged RBCs and fHb, to administer haptoglobin or NO-donors to compensate for the enhanced NO consumption, and to apply a super high-flux hemofilter to remove fHb.[95]

During CPB blood sucked from the operative field can be collected to the venous reservoir and returned directly to the patient through the bypass circuit or after processing blood with a cell saving device. Cell saving device retains RBCs and removes fHb, inflammatory mediators, fat emboli, and heparin, but also plasma and platelets. At present there is no evidence that this cell saving technique has effect on renal outcome after cardiac surgery.[95]

Transfusion

Perioperative RBC transfusion is considered to be a risk factor to AKI in susceptible patients, such as those with preoperative kidney disease or anemia.[100] Especially more than 14 days stored RBCs became less formable, undergo ATP and 2,3-diphosphoglycerate depletion, lose their ability to generate NO, have increased adhesiveness to vascular endothelium, release pro-coagulant phospholipids, and accumulate pro-inflammatory molecules and free iron and hemoglobin. Hence, instead of improving oxygen delivery, they may cause organ injury.[101-104] Transfusion of stored RBCs may elicit harmful effects, such as inflammation, renal hypoxia, and oxidative stress.[100] Patients with preoperative anemia are especially more susceptible to transfusion-related AKI than nonanemic patients.[105] In a recent study, prophylactic RBC transfusion reduced perioperative anemia and RBC transfusions, and possibly reduced plasma iron level.[106] Interventions to avoid perioperative blood transfusion are recommended, such as drugs that increase preoperative blood volume or decrease postoperative bleeding, use of devices that conserve blood, and interventions that protect the patient's own blood from the stress of operation.[95]

Ultrafiltration during CPB

Ultrafiltration is a standard method to remove fluid overload during CPB. It is commonly used in pediatric cardiac surgery and increasingly being employed also in adult cardiac surgery, both perioperatively and postoperatively. There is no data, however, whether this procedure improves renal outcome in adult cardiac surgery, but it is known that ultrafiltration minimizes the adverse effects of hemodilution, and consequently reduces the need for transfusion and also may decrease inflammation.[107]

2.4.3. Postoperative period

Hemodynamic alterations are the most common occurrences to affect kidney function postoperatively. After weaning from the CPB some of the patients may suffer from cardiac low out-put, which necessitates hemodynamic support provided with inotropes, vasopressors, intra-aortic balloon pump (IABP), and occasionally even with a left ventricle assistance device (LAVD). These therapies may affect kidney perfusion, enhance inflammatory response, and combined with diuretics, may lead to inadequate circulating volume.

IABP increases cardiac output by reducing left ventricle afterload and improving coronary perfusion. Occasionally it is inserted to high-risk patients in advance preoperatively, but may also be installed as a rescue therapy to wean patients from CPB. IABP has been independently associated with increased acute renal failure after cardiac surgery.[108] On the other hand, in a meta-analysis study, preoperatively inserted IABP reduced hospital mortality in high-risk patients undergoing coronary bypass surgery.[109] The problem with intraoperatively placed IABP arises if the patient presents with atherosclerotic aorta. In a retrospective study the patients with IABP and atherosclerotic descending thoracic aorta, had significantly increased the risk of developing AKI and higher hospital mortality, as compared to the patients without IABP and descending thoracic aorta atheroma.[110]

Cardiac tamponade may also cause circulatory changes after cardiac surgery. The symptoms of postoperative tamponade are variable, which can make it difficult to recognize requiring often echocardiography to confirm the diagnosis. Tamponade and excessive bleeding leads to re-exploration, which is associated with adverse outcomes.[111] In a recent report re-exploration caused higher transfusions requirements and led to increased postoperative AKI.[112] In a further analysis writers found, that not the re-exploration itself, but the blood loss and transfusion were independent risk factors for mortality, which was also higher when re-exploration was delayed and when tamponade was the indication of re-exploration.[112]

Postoperatively administered nephrotoxic drugs present an additional risk for kidney injury. Calcineurin inhibitors, given after heart transplantation as immunosuppressives, are associated with postoperative AKI.[113]

2.5. Measurement of renal function

2.5.1 Creatinine

The renal clearance of a substance is the volume of plasma completely cleared of a substance per unit time.

$C = U \times V/P$

where C = clearance in ml/min; U = urine concentration in mg/min; V = urine volume/time in ml/min; P = plasma concentration in mg/ml.

Glomerular filtration rate is considered to be the sum of the filtration rates for all functioning nephrons in kidneys. It can differ depending on age, sex, race, and muscle mass, and it may show inter-individual and intra-individual variation.[13] GFR is classically measured as renal clearance of inulin, which is considered as a perfect filtration marker because it is freely filterable at the glomerulus, not reabsorbed, secreted, or metabolized by the renal tubule, not bound to plasma proteins, nontoxic, and physiologically inert.[27] Creatinine clearance rate is the volume of blood plasma that is cleared of creatinine per unit time. It is less accurate than inulin clearance, but more practical to measure.

$$GFR \approx U_{creatinine} \times V / P_{creatinine} = C_{creatinine}$$

where GFR = glomerular filtration rate in ml/min, Ucreatinine = urine concentration of creatinine in mg/ml; V = urine flow rate in ml/min; Pcreatinine = plasma concentration of creatinine in mg/ml; Ccreatinine = clearance of creatinine in ml/min.

In healthy and young people the normal GFR is about 120 ml/min/ per $1.73m^2$ of body surface area in men and 100 ml/min/$1.73m^2$ in women.[27] Although inulin is considered an accurate marker of filtration, the measurement is complex, expensive, and impractical in clinical use.[114] Serum creatinine is the standard measurement, although it is not the ideal marker. The serum concentration of creatinine is affected by age, gender, muscle mass, medication, and circulating volume status, and moreover, the serum concentration may start to increase when almost 50% of kidney function have already been lost.[27] The GFR measurements with creatinine necessitate 24-hour urine collection and steady state, which rarely exists in the acute setting, and thus different equations have been presented to estimate the GFR in clinical use. The Modification of Diet in Renal Disease (MDRD) equation has been the most frequently applied formula, but recently it was replaced with equation by Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI), the formulas are presented in equations a and b, respectively:[115,116]

a. $GFR\ (ml/min/1.73m^2) = 186 \times Cr^{(-1.154)} \times Age^{(-0.203)} \times (0.742 \text{ for females}) \times (1.212 \text{ for Afro-Americans})$
b. $GFR\ (ml/min/1.73m^2) = 141 \times \min(Cr/\kappa, 1)^{\alpha} \times \max(Cr/\kappa, 1)^{-1.209} \times 0.993^{age} \times (1.018 \text{ for females}) \times (1.159 \text{ for Afro-Americans})$

Cr = Serum creatinine (mg/dl); $\kappa = 0.7$ if female or 0.9 if male; $\alpha = -0.329$ if female or -0.411 if male; min = minimum SCr/κ or 1; max = maximum SCr/κ or 1

The MDRD equation is 4-variable, as the original formula used six variables including blood urea nitrogen and albumin in addition to serum creatinine, age, ethnicity, and gender.[117] The CKD-EPI equation was developed to be more accurate than the MDRD formula, especially when the actual GFR is greater than 60 ml/kg/1.73m^2.[116] Creatinine continues to be the index marker for the renal function despite its lack of sensitivity. The RIFLE criteria apply serum creatinine, MDRD equation, and urine output to define renal dysfunction, although they use the change of creatinine values, not the absolute values in themselves.[118]

2.5.2. Cystatin C

Cystatin C has several attributes to make it an attractive filtration marker, and it has been challenging creatinine as a more sensitive marker for renal function. It is a 13-kDa endogenous cystein proteinase inhibitor produced at a constant rate by all nucleated cells. It belongs to the family of proteins that has an important role in intracellular catabolism of various peptides and proteins.[119,120] Cystatin C is almost totally filtered by the glomeruli, reabsorbed by proximal renal tubular cells, and catabolised. There is no significant protein binding.[121,122] There is practically no detection of cystatin C in urine. When it can be measured, it may indicate tubular epithelial damage, and urine cystatin C has been proposed as a sensitive biomarker for AKI.[123] Cystatin C is relatively stable, and it can be measured quickly and accurately with assays compatible with automatic analyzers, indicating that it is practical to clinical use.[124]

Serum cystatin C concentrations have exhibited good inverse correlation with radionuclide-derived measurements of GFR.[125] It has been claimed to be less sensitive than creatinine to patients' age, sex, and muscle mass, and therefore a more accurate and sensitive marker for AKI.[126,127] Cystatin C has been evaluated in populations at risk of chronic kidney disease in a number of studies, and it has performed similarly or better than creatinine.[128,129] In a large cross-sectional study cystatin C concentration of less than 1.12 mg/l was evaluated to be normal in 20 to 40 year olds without hypertension or diabetes mellitus. However, large studies have also revealed, that the cystatin C is affected besides age, also with male sex, smoking status, alcohol consumption, elevated C-reactive protein (CRP) levels, body muscle mass and adipose tissue, higher body mass index (BMI) was associated with higher cystatin C.[130,131] In addition, cystatin C levels may be influenced by abnormal thyroid function and corticosteroid therapy.[132,133] The influence of corticosteroids may be dose dependent. The cystatin C concentrations in patients treated in ICU or after cardiac surgery do not seem to be affected, but patients after organ transplant with high dose treatment of corticosteroids have elevated levels of cystatin C values when creatinine values had decreased.[133-135]

Estimation equations of GFR based on cystatin C has in general proved to perform comparable to formulas based on creatinine.[136-139] In acute setting estimated GFR

formulas seem to be less useful than in the diagnosis of chronic kidney disease. In a recent study with critically ill GFR was measured with inulin clearance, and GFR was estimated with four commonly used creatinine-based formulas, with five cystatin C based equations, and one equation combining cystatin C and serum creatinine, and in addition creatinine clearance was measured.[140] The measured urinary creatinine clearance overestimated GFR, but also the estimates of creatinine based GFR had much bias, low accuracy, and precision. Formulas based on cystatin C were free of bias, but the accuracy and precision of the estimates were still inadequate.[140]

Cystatin C in cardiac surgery

Serum and urinary cystatin C have both been assessed in cardiac surgery for the prediction of early postoperative AKI in large cohort studies and in several small clinical studies (Table 3).[141-145] Haase et al. investigated plasma cystatin C and plasma neutrophil gelatinase-associated lipocalin (NGAL) and their combination, in 100 adult cardiac surgery patients to evaluate their ability to predict the duration and severity of AKI.[141] They discovered that on arrival in intensive care unit cystatin C moderately correlated with these outcomes, however, when the patients with preoperative renal dysfunction were excluded the predictive capability of cystatin C was reduced while NGAL values remained the same.[146] After 24 hours all the plasma creatinine values predicted AKI as well as cystatin C and NGAL.[146] Wald et al. had a similar finding They measured plasma cystatin C preoperatively, 2 hours after the conclusion of CPB, and postoperative days one and two, and discovered that plasma cystatin C was higher at all times among patients with AKI.[145] The preoperative cystatin C was elevated in patients who developed AKI, but the discriminatory capacity of cystatin C was modest when measured preoperatively and early after ending of CPB.[145] In a large prospective multicenter cohort study plasma cystatin C and plasma creatinine were compared after cardiac surgery with high-risk patients, and creatinine detected more AKI patients than cystatin C.[144] In this report AKI end points were defined by relative increase in creatinine and cystatin C from baseline, and the number of AKI patients was measured in 25%, 50%, and 100% increase of each marker. At every point there were more patients with AKI when measured with increase of creatinine, but there were no difference in clinical outcomes with these patients. However, the patients with AKI confirmed by both markers had considerably higher risk of the combined mortality/dialysis outcome than the patients with AKI detected by creatinine level alone.[144]

Koyner et al. have measured urinary cystatin levels after cardiac surgery.[142,143] First in a smaller study cystatin C and NGAL were analyzed postoperatively from plasma and urine, and urine cystatin C and NGAL predicted AKI better than plasma cystatin C and NGAL, which were considered useless predictors of AKI.[142] Later in a large prospective multicenter cohort study urinary cystatin C was measured from 1203 adults and 299 children within the first 12 hours after surgery.[143] The early, 6 hours and 12 hours, postoperative measurements of urinary cystatin C correlated with both mild and severe AKI in both groups. However, when the analyses were adjusted for characteristics used

clinically for CSA-AKI stratification, the values did not associate significantly with the development of AKI.[143]

There is evidence to suggest that pre-surgical cystatin C may predict postoperative AKI. In a small study GFR estimated from serum cystatin C, but not GFR estimated from serum creatinine, was an independent risk factor for hospital mortality and morbidity defined as prolonged postoperative stay in hospital.[147] In a larger cohort study serum cystatin C proved to predict postoperative AKI better than creatinine or estimated GFR.[148] The writers adjusted the results with clinical predictors for CSA-AKI risk stratification and discovered that without the kidney markers the receiver operator characteristic (ROC) curve model for the outcome of AKI was 0.70, addition of cystatin C 0.72, and with the addition of creatinine 0.69.[148]

	N	Centers	Population	AKI definition	Measurements	AKI(%)	AUROC	Compared to creatinine
Koyner et al 2008[142]	72	1	Adult cardiac surgery	SCr ≥25% or RRT	Preoper, post CPB, ICU admit, 6 h post ICU, day 1-3	47	0.63	UCyC 6 h post oper predicted AKI; SCyC ≈SCr
Haase et al 2009[141]	100	1	Adult cardiac surgery	SCr ≥50% or ≥27μmol/l within 48 h	Preoper, admit ICU, 6 h post CPB	46	0.74	SCyC Predicted AKI at ICU admittance
Wald et al 2010[145]	150	3	Adult cardiac surgery	SCr ≥50% or ≥27μmol/l	Preoper, 2 h post CPB, day1-2	31.3.	0.67	Modest, 2 h post CPB
Spahillari et al 2012[144]	1150	TRIBE-AKI	Hig risk adult cardiac surgery	SCr ≥25%, ≥50%, ≥100%	Preoper,postoper day 1-5	35	-	SCyC less sensitive than SCr
Koyner et al 2013[143]	1502	TRIBE-AKI	Adult and child cardiac surgery	SCr AKIN I (mild); doubling SCr or need for RRT (severe)	0-6 and 6-12 hours after surgery	Adults 35%, children 41%		UCyC not a reliable predictor of AKI

Table 3. *Cystatin C in cardiac surgery. AKI, acute kidney injury; AUROC, the area under an ROC curve; TRIBE-AKI, Translational Research Investigating Biomarker Endpoints for Acute Kidney Injury; SCr, serum creatinine; AKIN, Acute Kidney Injury Network; RRT, renal replacement therapy; CPB, cardiopulmonary bypass; ICU, intensive care unit; UCyC, urine cystatin C; SCyC, serum cystatin C*

2.5.3. Kidney injury biomarkers

Currently the only definitions of AKI are based on a rise in serum creatinine and a reduction in urine output. After cardiac surgery the changes in serum creatinine occur typically 48 hours after the insult to kidneys, when tubular injury has already occurred, and the diagnosis of AKI and interventions to prevent tubular necrosis will be delayed.[95] This has led to research on several novel biomarkers, which may assist earlier detection and prognosis prediction for CSA-AKI. The most studied biomarkers are NGAL, interleukin (IL-18), kidney injury molecule -1 (KIM-1), liver fatty acid–binding protein (L-FABP), and N-acetyl-β-glugosaminidase (NAG), or a combination of these markers. These biomarkers reflect different nature, magnitude, and site of injury based on their specifity.[149] NGAL expression is up-regulated in kidney proximal tubule cells and urine following ischemic injury, IL-18 reflects an inflammatory process, and KIM-1 is a trans-membrane receptor in tubules to aid the removal of apoptotic bodies. L-FABP is expressed in ischemic proximal tubule cells and protects kidneys by binding free fatty acids, and NAG is a sensitive, but not very specific, lysosomal enzyme, that even subtle alterations in the epithelial cells of the proximal tubules leads to increased secretion of NAG into the urine.[51,149]

Recently in a large, multicenter cohort study in adults the function of NGAL, IL-18, KIM-1, and L-FABP were evaluated in cardiac surgery.[150,151] All the studied biomarkers peaked within six hours after surgery, except KIM-1, which peaked two days after surgery and remained elevated for several days.[151] The writers reported that urine IL-18 and plasma NGAL had the best ability to detect tubular injury leading later to clinical AKI, and only these biomarkers were helpful in predicting progression of AKI.[151] In severe AKI, an area under the receiver-operating characteristics curve (AUROC) for each biomarker increased in magnitude, but only urine IL-18, NGAL, KIM-1, and plasma NGAL were associated with adverse outcomes, such as longer length of ICU treatment and hospital stay, and higher risk for dialysis or death.[151] The AUC of clinical prediction model for AKI was 0.69, and urine IL-18 and plasma NGAL improved the AUROC to 0.76 and 0.75, respectively.[150] The combination of three biomarkers from two different time points also increased the AUROC for AKI up to 0.78.[151] When analyzing the biomarkers' association with three-year mortality after cardiac surgery, the investigators concluded that these biomarkers, especially IL-18 and KIM-1, correlated with mortality in patients with and without AKI.[152]

Other studies have also tested biomarkers alone and in panel to evaluate their performance in SCA-AKI. In one study the AUROC values of urine KIM-1, NAG, and NGAL alone were between 0.61 and 0.67 to predict the development of AKI, and by combining these markers the AUROC increased to 0.78.[153] In evaluation of 32 urine biomarkers to predict the progression of AKI in patients with AKIN stage 1 and 3 after cardiac surgery, IL-18 was the best predictor of worsening AKI or death, and L-FABP, NGAL, and KIM-1 were also good predictors of secondary outcome of AKIN stage 3 or death, but the combination of IL-18 and KIM-1 had an AUROC of 0.93 to predict AKIN

or death.[154] The writers suggested that the combination of IL-18 and KIM-1 directs to identify high-risk patients for enrolment in clinical trials.[154]

2.6. Preventing CSA-AKI

2.6.1. Identification of high-risk patients (risk scores)

There are several well studied, validated, and established independent risk factors for CSA-AKI. The most repeatedly observed risk factors include type of surgery, advanced age, female sex, reduced left ventricular function or congestive heart failure, diabetes mellitus, peripheral vascular disease, chronic obstructive pulmonary disease, anemia, emergency status, blood transfusions, reoperation, and preoperative renal impairment.[2,3032] The last factor, defined as GFR below 60 ml/min or creatinine over 185 μmol/l, is perhaps the most predictive of CSA-AKI.[31] However, preoperative serum creatinine alone has proved to be a relatively poor discriminator to predict postoperative RRT after cardiac surgery.[30] Advanced age and insulin-dependent diabetes have both been associated with glomerular sclerosis or chronic kidney disease, which makes these patients more susceptible to ischemic insults.[155] The patients with unstable preoperative state often suffer from low cardiac output and reduced renal perfusion, which is further compromised during CPB, resulting in increased risk for AKI. Chronic lung disease increases the risk of prolonged ventilation, leading to possible infection, sepsis, and multi organ failure, including renal failure and RRT.[30] A recent large study from Australia found also obesity and infective endocarditis to be significant risk factors for AKI within 30 days of cardiac surgery.[156]

The risk of AKI increases when the surgical procedure includes CABG and valve instead of CABG alone. In a study by Mehta at al. the incidence of RRT occurred in 1.4% of all cardiac surgical patients, when it was 1.1% of CABG patients, and 5.1% of combined mitral valve and CABG patients.[30] More complicated procedures increase the cross-clamp time of aorta and the duration of CPB, thus adding complications associated with CPB. To avoid the SIRS induced by CPB different coatings of the CPB system has been developed. Phosphorylcholine- and various heparin based, bioactive coated circuits aim to improve the bio-incompatibility of blood contact with artificial surface, but there is no evidence of the association between decreased CSA-AKI and coated circuits.[95] Different techniques have been developed to avoid CBP entirely in cardiac surgery. In off-pump coronary artery bypass technique (OPCAB) CPB is avoided and aortic manipulation is minimized to attain more physiological renal perfusion and less systemic embolization, and less SIRS. After several large studies there is no sufficient evidence to prove the superiority of OPCAB versus CPB-CABG technique in regard to reduction of SCA-AKI. In a meta-analysis Niwegar at al. reported significant reduction in overall AKI and AKI requiring RRT (AKI-RRT) in OPCAB cases compared with on-pump CABG technique.[157]

But in two large randomized trials there was no significant difference between on-pump and off-pump techniques regarding AKI-RRT after 30 days follow up, but the other study found significantly less AKI at 30 days in OPCAB group.[158,159] One reason, that there was no difference in the incidence of AKI-RRT in the study of Shroyer et al., may be that the patient population was not considered very high-risk for AKI.[159] In a large retrospective study in elective patients with chronic kidney disease there was less death and incidence of RRT in the OPCAB group.[160] It appears that patient selection may affect the results of OPCAB, and high-risk patients with chronic kidney disease may benefit from this technique. In valve surgery transcatheter aortic valve implantation (TAVI) technique has made it possible to avoid invasive surgery and CPB in high-risk patients. The incidence of AKI after TAVI ranges between 1.1 and 28%, depending on the definition of AKI.[95] Mortality in AKI patients after TAVI is 4 times higher than in patients without AKI.[161] In a randomized trial with high-risk group of patients the incidence of AKI and need for RRT were similar in patients treated with TAVI and in patients with surgical aortic valve replacement at 30 days and 1 year.[162] A new definition of AKI, modified from RIFLE, for TAVI patients was introduced in 2011.[163] In a recent meta-analysis the incidence of AKI stage II-III was 7.5% with both definitions, and another study reported a 14.6% and 11.5% TAVI-AKI incidence according to new definition and RIFLE criteria, respectively.[164,165] Plausible causes of TAVI-AKI are associated with the use of contrast medium, hypotension during the procedure, and emboli in patients with severe atherosclerosis. The only predictor of AKI was blood transfusion in a study by Barbash et al.[164]

Several validated risk-predictive models of CSA-AKI requiring RRT have been developed to identify patients at risk preoperatively. Chertow et al. were among the first to develop a risk index to predict postoperative need for RRT, but after that several prediction models have been published and validated.[29] In risk-predictive model comparisons the Cleveland Clinic score has been most widely tested and it has performed to some extent better than the other models.[166,167] It has also been validated in a single-center cohort to predict not only AKI-RRT, but also milder AKI, defined as doubling of the baseline creatinine, and it performed well for both outcomes, AUROC being 0.86 and 0.81, respectively.[168] The Cleveland Clinic score (table 4) was formed on an analysis of total of 33 217 open-heart surgery patients.[31] The score was based on 13 preoperative factors resulting in a range minimum of 0 to a maximum of 17 points, and patients with the lowest scores (0-2 points) had 0.4% risk of developing AKI requiring dialysis, while patients with highest score (9-13 points) had a risk of 21.5% of AKI-RRT.[31] Mehta at al. used a cohort of 449 524 patients undergoing CABG, or valve surgery, or a combination of both, participating in The Society of Thoracic Surgeons National Cardiac Surgery database to develop a bedside risk algorithm for estimating patients' probability for dialysis postoperatively.[30] Wijeysundera et al. created a simplified renal index, which used only eight preoperative factors to predict dialysis after cardiac surgery.[32] These predictive models may be valuable to plan protective strategies in high-risk patients, or to select patients for clinical trials.

Risk Factor	Points
Female gender	1
Congestive heart failure	1
Left ventricular ejection fraction <35%	1
Preoperative use of IABP	2
COPD	1
Insulin-requiring diabetes	1
Previous cardiac surgery	1
Emergency surgery	2
Valve surgery only	1
CABG + valve surgery	2
Other cardiac surgeries	2
Preoperative creatinine 107 to <186 μmol/l	2
Preoperative creatinine ≥186 μmol/l	5

***Table 4**. Cleveland Clinical score to predict AKI requiring dialysis after cardiac surgery*

2.6.2. Pharmacological interventions to prevent CSA-AKI

The multi-factorial pathophysiology of CSA-AKI and numerous discovered risk factors have initiated research of various preventive strategies. The main target of these interventions has been to improve renal blood flow or alter inflammatory reaction. Currently the evidence of these studies is inconsistent and there are no known drugs that have conclusively proved to protect kidneys in cardiac surgery. The pharmacological agents used in randomized controlled studies are listed in Table 5.

Anti-inflammatory	Natriuretics / diuretics	Vasodilators	Other
NAC	Nesiritide	Diltiazem	Albumin
Leukodepletion	ANP/BNP	Dopexamine	Early CRRT
Acetylsalicylic acid	Furosemide	Dopamin	RRT
Dexamethasone	Urodilatin	Fenoldopam	Insulin
Methylprednisolone	Mannitol	ACEIs/ARBs	Clonidine
Sodium bicarbonate	Mannitol + furosemide + dopamin	Sodium nitroprusside	Hydration with 0.5% saline
NAC + fenoldopam		Theophylline	
		Nifedipine	
		Levosimendan	
		Dopamin + fenoldopam	
		Dopamin + mannitol	
		Dopamin + nitroprusside	
		Dopamin + furosemide	
		Dopamin+ phenylephrine	
		Dopamin + diltiazem	

Table 5. *Agents and actions tested in randomized, controlled trials to prevent or treat CSA-AKI. None of the pharmacological treatments prevents the development of AKI, whereas early start of RRT may improve the outcome of AKI patients. NAC, N-acetylcysteine; ANP, atrial natriuretic peptide; BNP, brain natriuretic peptide; ACEI, Angiotensin-converting enzyme inhibitor; ARB, Angiotensin II receptor blocker; CRRT, continuous renal replacement therapy; RRT, Renal replacement therapy*

Acetylsalicylic acid (ASA)

Patients presented to cardiac surgery are usually medicated with ASA, which has been proved to reduce cardiovascular events in patients with coronary artery disease. Mangano et al. investigated in a large cohort study of 5065 patients the impact of ASA use within 48 hours of CABG surgery on AKI, including dialysis and death caused by renal failure.[169] ASA therapy was associated with a 74% reduction in the incidence of renal failure. In a recent retrospective study ASA therapy within 5 days preceding surgery significantly reduced the risk of 30-day mortality, postoperative renal failure, and requirement of dialysis.[170] In a randomized, blinded, clinical trial of 6905 patients undergoing non-cardiac surgery the patients were assigned to take ASA or placebo 2 to 4 hours before surgery and then ASA or placebo daily up to 30 days after surgery, ASA did not change the risk of AKI, which occurred 13.4% in the ASA group and 12.3% in the placebo group, but ASA increased the risk of major bleeding.[171]

Angiotensin-converting enzyme inhibitors (ACEI) and angiotensin II receptor blockers (ARB)

It is common to patients undergoing cardiac surgery to receive long-term treatment with ACEI or ARB. Their effect during anesthesia and surgery is difficult to predict because

when they usually increase renal blood flow, during renal hypoperfusion the maintenance of GFR is dependent on renal angiotensin II-induced efferent arteriolar vasoconstriction, and thus ACE inhibition may lead to reduction in GFR.[172] Some studies have demonstrated higher postoperative risk for AKI with preoperative use of ACEIs/ARBs, and discontinuing this therapy before surgery may reduce the incidence of AKI.[173] Other studies, however, have found that preoperative ACEIs do not increase, but rather reduce, the incidence of postoperative AKI.[174] Appropriately sized randomized controled trials are needed to find conclusive evidence of the perioperative use of these drugs.

Dopamine, mannitol, furosemide

Several prospective randomized clinical trials have found that dopamine has no effect on the prevention of AKI.[175,176] Also, a meta-analysis of cardiac surgery patients revealed that dopamine failed to reduce the incidence of acute renal failure, need for dialysis or risk of death.[177] In a trial of dopamine and mannitol, the excretion rates of beta2-microglobulin were measured in patients undergoing CABG surgery with CPB, and dopamine alone, or in combination with mannitol, increased the beta2-microglobulin excretion rates, which indicated tubular dysfunction.[178]

Mannitol is an osmotic diuretic and widely used in the priming fluid for CPB. In a small prospective trial patients with normal renal function or with renal dysfunction were randomized to receive 0.5 g/kg of mannitol or an equivalent volume of Hartmann's solution in the pump prime.[179,180] There were no differences between the groups in plasma creatinine, change in creatinine from baseline, urine output, urinary retinol binding protein, or urinary microalbumin postoperatively. In a recent study in a treatment of CSA-AKI mannitol infusion induced renal vasodilatation and increased renal blood flow. Mannitol treatment did not affect filtration fraction or renal oxygenation, suggestive of balanced increases in perfusion/filtration and oxygen demand/supply.[181] Mannitol seems to be safe to use in priming fluid, but it has not demonstrated any renal protection in cardiac surgery. The therapeutic role of mannitol needs further studies.

A double-blind randomized controlled trial evaluated the effectiveness of dopamine or furosemide in prevention of SCA-AKI.[175] Patients with normal preoperative renal function received a continuous infusion of dopamine, or furosemide, or placebo from the start of the surgery and continuing for 48 hours. The effect of dopamine and placebo did not differ in preventing renal dysfunction, but furosemide was associated with the highest rate of renal impairment.[175] Also a preoperative use of diuretics has been associated with increased risk of RRT in a retrospective study.[182]

N-acetycysteine

The formation of free oxygen radicals has been proposed to be associated with cardiopulmonary bypass and cardioplegic arrest, thus radical scavenging may protect kidney function in cardiac surgery.[11] NAC is a thiol compound with antioxidant and

vasodilatory properties, and it has been found to reduce oxygen free radical production, pump-related ischemia-reperfusion injury, and pro-inflammatory cytokine levels.[183-185] Cardiac surgery patients are often exposed to contrast media during cardiac catheterization prior surgery, and the kidneys suffer two insults in a short time interval. NAC was first used to prevent contrast-induced AKI (CI-AKI), and many small studies of NAC administrated before the kidney insult have demonstrated a protective effect on CI-AKI.[186] However, a prospective trial in patients with renal insufficiency undergoing cardiac catheterization did not find difference in renal protection between the groups hydrated with sodium bicarbonate, or sodium chloride, or oral NAC.[187] The result was the same in a trial where patients were hydrated with sodium bicarbonate or normal saline: NAC did not reduce CI-AKI in either group.[188] Although the evidence of renoprotective effect of NAC is conflicting, in 2012 KDIGO suggest using oral NAC, together with intravenous isotonic crystalloids, in patients at increased risk of CI-AKI.[189]

A list of randomized, controlled trials (RCT) using prophylactic administration of NAC to prevent postoperative CSA-AKI is seen in Table 6. Fischer et al. performed a retrospective review of 40 patients from the authors' recent RCT.[190] NAC was associated with reduced rise in serum creatinine and improved creatinine clearance after cardiac surgery. After that Burns et al. published a paper of adequately powered RCT of high-risk patients undergoing elective or urgent CABG.[191] They discovered no difference in development of postoperative AKI in the NAC group compared to the control group, there were also no significant difference in postoperative interventions between the groups. Wijeysundera et al. investigated the effect of NAC in patients with moderate preoperative renal dysfunction.[192] They were able to demonstrate that perioperative NAC resulted in a trend to reduced reduction in eGFR, but there was not a significant difference between the NAC group and the control group. There was no statistically significant difference in the need for RRT. However, there was a significant reduction ($P = 0.007$) in mortality in the NAC group, although the study was not powered for this secondary outcome. Haase et al. performed a RCT in 60 patients at high-risk of postoperative AKI.[193] They could not find any difference in the absolute change in serum creatinine or peak serum creatinine, and writers concluded that administration of high-dose NAC is no more effective than placebo at decreasing AKI in high-risk patients following cardiac surgery. Sisillo et al. conducted a trial in 254 patients with chronic kidney disease undergoing elective cardiac surgery.[194] AKI, defined as more than 25% increase in serum creatinine, occurred in 40% of NAC-treated patients and in 52% of control patients, but the difference was not significant ($p = 0.06$). However, NAC was associated with reduction in duration of mechanical ventilation and length of stay in ICU. Adabag et al. carried out a RCT in 102 patients with pre-existing renal insufficiency undergoing cardiac surgery.[195] They found that NAC did not reduce the incidence of AKI or rise in serum creatinine. NAC also had no impact on requirement of RRT, mortality, and length of stay in ICU or hospital. Because of the many RCTs without adequate power to prove the effect of NAC in CSA-AKI, Niwekar and Kandula conducted a meta-analysis of twelve studies comprising 1324 patients.[196] The authors deduced that NAC did not reduce the risk of AKI, RRT requirement, mortality, or length of stay in ICU. Adabag et al. performed a systematic review including ten RCTs with 1163 patients[197]. They came to the similar conclusions, NAC did not reduce the

incidence of postoperative CSA-AKI. Prasad et al. carried out a RCT in 70 high-risk patients for AKI undergoing CABG with off-pump technique.[198] There was no significant difference in the incidence of AKI, and the writers concluded that NAC did not have any beneficial effect on renal function in this patient group. The latest study presents a small, single-center RCT of high-dose NAC in 70 patients with GFR < 60 ml/min undergoing CABG surgery with CPB or with OPCAB technique.[199] Writers discovered a significant difference in the incidence of AKI between the groups. In the NAC-group the incidence of AKI was 29% versus 80% in the control group, although in more than 80% of patients, the severity of AKI was limited to Stage 1 defined with AKIN criteria. The incidence of AKI differed most between the patients who had CPB and did not receive NAC (63%), compared to patients who received NAC and had OPCAB surgery (8%).

The evidence of beneficial effects of NAC on CSA-AKI is controversial, the different doses, administration timing and methods may influence the inconsistent results.

Study	N		NAC dose	Patients	Surgery	Definition of AKI	NAC group	Control group	Sig.
Burns, 2005[191]	295	RPCT	4 x 600 mg i.v.	High-risk with >1 criteria: sCr>124 μmol/l Age >70 y, DM, EF<35%, complex surgery or re-do	CABG 88%, CABG+valve 14%, valve 1%	sCr↑>44 μmol/l or 25%	29.7%	29%	No
Fischer, 2005[190]	40	RPCT	100 mg/kg(in CPB prime) + 20 mg/kg i.v. during CPB	Normal renal function	CABG	sCr ↑, CrCl ↑	NR	NR	Yes
Wijeysundera, 2007[192]	177	RPCT	100 mg/kg in 30 min + 20 mg/kg/h for 4 h i.v.	High-risk, GFR < 60 ml/min	CABG 53%, valve + CABG 27%, valve 19%	sCR ↑>44 μmol/l or 25%	28%	32%	No
Haase, 2007[193]	60	RPCT	150 mg/kg in 15 min + 50 mg/kg in 4 h + 100 mg/kg in 20 h i.v.	High-risk with >1 criteria: sCr > 120 μmol/l, age > 70 y, DM, EF <50%, re-do	CABG 30%, valve + CABG 31%, valve 39%	sCR ↑>44 μmol/l sCR ↑> 25%	30% 60%	30% 63%	No
Sisillo, 2008[194]	254	RPCT	4 x 1200 mg i.v.	High-risk, GFR < 60 ml/min	CABG 41%, valve + CABG 13%, valve 46 %	sCR ↑> 25%	40%	52%	No
Adabag, 2008[195]	102	RPCT	14 x 600 mg p.o.	High-risk, GFR < 60 ml/min	CABG 65%, valve + CABG 17%, valve 19 %	sCR ↑>44 μmol/l or 25%	44%	37%	No
Prasad, 2010[198]	70	RCT	2 x 600 mg p.o., 6x 600 mg i.v.	High-risk with >1 criteria: sCr >133 μmol/l, age > 70 y, hypertension, EF < 35%	OPCAB	sCR ↑>44 μmol/l or 25%	8.6%	11.4%	No
Santana-Santos, 2014[199]	70	RPCT	150 mg/kg in 2 h + 50 mg/kg in 6 h	GFR < 60 ml/min	CABG on pump or OPCAB	sCR ↑>44 μmol/l or 25% CPB	46% 28.6%	57:1% 63%	Yes

Table 6. *Randomized, clinical studies on prophylactic use of N-acetylcysteine to prevent AKI after cardiac surgery.AKI, acute kidney injury; CABG coronary artery bypass grafting; CrCl creatinine clearance; sCr serum creatinine; CPB cardiopulmonary bypass; DM diabetes mellitus; EF ejection fraction; GFR glomerular filtration rate; NAC N-acetylcysteine; RCT randomized controlled trial; RPCT, randomized placebo-controlled trial.*

Fenoldopam

Fenoldopam is a selective dopamine-1-agonist, which causes relaxation of smooth muscle, vasodilatation, and inhibition of tubular re-absorption of sodium in the kidney. It is considered to cause renal protection through its selective renal vasodilatory and natriuretic effects, and it has been associated with decreased risk of CSA-AKI in several small trials. Landoni et al. conducted a meta-analysis of 13 randomized and case-matched studies on 1059 patients undergoing cardiac surgery, and they concluded that fenoldopam significantly decreased the requirement for RRT and decreased ICU length of stay and in-hospital mortality.[200] Later Zangrillo et al. carried out a meta-analysis of randomized, placebo-controled trials on 440 patients and discovered that fenoldopam significantly reduced the risk of CSA-AKI, odds ratio (OR) = 0.41; 95% CI 0.23-0.74; P = 0.003.[201] However, fenoldopam did not decrease the requirement for RRT or mortality. The latest study of fenoldopam was a multicenter, randomized, doubleblind, placebo-controlled, and parallel-group trial on patients with early postoperative CSA-AKI, defined as 50% increase of serum creatinine from the baseline or oliguria for more than six hours.[202] This study was stopped because it was futile after a planned interim analysis. In the fenoldopam group 20% of patients, and in the placebo group 18% of patients received RRT. The mortality at 30 days was 23% in the fenoldopam group and 22% in the placebo group, and furthermore, there was significantly more hypotension in the fenoldopam group than in the placebo group. The authors concluded that given the cost, lack of effectiveness, and the increased incidence of hypotension, the use of fenoldopam for renal protection in cardiac surgery is not justified.

Natriuretic peptides

Natriuretic peptides, atrial natriuretic peptide (ANP) or B-type natriuretic peptide (BNP), can induce renal arterial vasodilatation, and at the same time block the renin-angiotensin-aldosterone system and renal vasoconstrictor, endothelin, and thus increase glomerular filtration and also promote diuresis. A multicenter, randomized, placebo-controlled trial of nesiritide, human B-type natriuretic peptide, in 303 patients with left ventricular dysfunction undergoing cardiac surgery with CPB demonstrated that nesiritide improved renal function, even more in patients with preoperative renal dysfunction.[203] The hospital stay was also shorter in the nesiritide group. The most recent meta-analysis of 15 RCTs of natriuretic peptides in cardiovascular surgery patients discovered that the infusion of ANP significantly decreased peak serum creatinine levels, the incidence of arrhythmia, and RRT.[204] It also showed that perioperative ANP or BNP infusion significantly decreased both ICU and the length of hospital stay, but the data was insufficient to determine the long-term outcome. There are three recent trials showing beneficial effects of ANP in CABG surgery in three different patients populations. Patients with preoperative normal renal function, and patients with reduced left ventricular function, treated with ANP suffered less of AKI than patients in the placebo-control group, but the patients with preoperative renal dysfunction treated with ANP had also less RRT postoperatively.[205-207] The authors concluded, that larger, adequately powered, multicenter trials are needed to confirm their findings.

Sodium bicarbonate

Hemoglobinuria has been associated with CSA-AKI. Urine alkalization may protect kidneys from injury induced by oxidant substances, iron-mediated free radical pathways, complement activation, and tubular hemoglobin cast formation and hemoglobin induced pigment nephropathy.[208] Haase et al. conducted a RCT with 100 cardiac surgery patients and discovered significant reduction ($p < 0.043$) in postoperative AKI, defined as an increase of 25% from baseline creatinine, and a significant decrease in urinary NGAL in association with the use of perioperative sodium bicarbonate infusion.[209] However, the authors conducted a multicenter, doubleblind RCT, but they could not confirm these findings, as patients administrated sodium bicarbonate developed more AKI than patients in the control group (47.7 % vs 36.4%, OR 1.60; 95%CI 1.04-2.45).[210] Also urinary NGAL increased more in patients receiving sodium bicarbonate infusion, the incidence of RTT was similar in both groups, but the hospital mortality was increased in bicarbonate group of patients. According to current data sodium bicarbonate is not recommended to use as renal protection in cardiac surgery.

Levosimendan

Levosimendan is a calcium sensitizer that enhances myocardial contractility without increasing myocardial oxygen use.[211] In cardiac surgery patients, an early postoperative infusion of levosimendan produced significant increase in renal blood flow and glomerular filtration rate, decreased renal vascular resistance, but did not increase renal oxygen consumption, or renal oxygen extraction, compared to patients in placebo group.[212] Harrison et al. conducted a meta-analysis of 1115 patients in 14 RCTs, and evaluated the effect of perioperative levosimendan on renal function, and found that it significantly reduced the need for dialysis (risk difference, RD -4.9%; 95%CI -8.2%, - 1.6%; p=0.003). In a smaller meta-analysis of 529 patients in 5 randomized trials the authors suggested that levosimendan might reduce renal injury in cardiac surgery.[213] A board of experts published recently an evaluation of the use of levosimendan in cardiac surgery and concluded the favorable effects of levosimendan on renal parameters, but evidence of its ability to reduce CSA-AKI is still lacking.[214]

2.6.3. More strategies to prevent CSA-AKI

Preoperative anemia defined as hemoglobin less than 125 mg/l, as well as perioperative transfusion of red blood cells, have been identified as risks to SCA-AKI.[105] The strategies to avoid these events may reduce the risk of renal injury. In a parallel-group randomized pilot study a prophylactic transfusion of red blood cells to anemic (hemoglobin 100-120 mg/l) cardiac surgery patients reduced perioperative anemia and transfusion, but there was no difference between the groups in the incidence of postoperative AKI.[106] However, the patients who received perioperative red blood cell transfusion, had higher postoperative transferrin saturations, which was associated with postoperative AKI. In a small pilot

study the administration of prophylactic erythropoietin prevented AKI and improved postoperative renal function.[215] In a placebo controlled trial with patients undergoing valvular surgery, a group of anemic patients received a prophylactic dose of erythropoietin plus iron supplement, the treatment group had significantly less perioperative transfusion, and also less AKI.[216]

In cardiac surgery studies on the relationship between optimized perioperative hemodynamics and postoperative renal function are lacking. In a small, randomized study the cardiac surgery patients with chronic kidney disease received intravenous hydration of 0.45% saline at 1 ml/kg/hour for 12 hours before surgery versus no hydration, AKI developed in 53% of patients in the control group versus 30% in the hydration group ($p < 0.01$).[217] RRT was needed in four patients in the control group, but none in the hydration group. More studies are needed to confirm these results, but avoidance of hypovolemia, and perhaps diuretics, before cardiac surgery is associated with reduced kidney injury.

The optimal time to initiate RRT in CSA-AKI is still not certain, but there is some evidence that early start of RRT may improve the outcome of these patients.[218] In a retrospective, observational, multi-center study including 204 patients from 24 hospitals the patients were divided in two cohorts based on the time at which RRT was initiated: before the third postoperative day, early-RRT group, or after that, late-RRT group. The late RRT group had significantly higher in-hospital mortality (80.4% vs. 53.2%; $p<0.001$), longer adjusted hospital stays by 11.6 days (95% CI: 1.4-21.9), and higher adjusted relative increase in creatinine at discharge than the patients in early-RRT group.[218] The KDIGO guideline on renal support therapy for AKI proposed initiating RRT without delay when life-threatening changes in fluid, electrolyte, and acid-base balance exist.[189] The same guidelines suggest continuation of RRT as long as it is required, and it should be discontinued when intrinsic kidney function has recovered to maintain patient needs. Furthermore, KDIGO also recommends not to use diuretics to improve the recovery of kidney function or to reduce the duration or frequency of RRT.[189]

3. AIMS OF THE STUDY

The aim of this thesis was to examine the kidney injury during and after cardiac surgery. The specific aims of the studies I-IV were:

1. To determine if serum cystatin C can disclose mild renal failure earlier than creatinine in elderly patients recovering from cardiac surgery

2. To study the suitability of cystatin C, NAG and creatinine in the detection of renal failure after cardiac transplantation

3. To investigate the renoprotective effects of N-acetylcysteine in patients with mild preoperative renal failure undergoing cardiac surgery

4. To evaluate the effects of levosimendan on post-cardiac surgical renal function in patients with preoperatively compromised heart function

4. PATIENTS AND METHODS

4.1. Patients

The studies I to IV were conducted at the Helsinki University Hospital between 2004 and 2010, study IV was carried out also at Turku University Hospital. The Ethics Committee of Helsinki University Central Hospital approved all study protocols, and The Finnish National Agency of Medicines approved the Studies III and IV. Written informed consent was obtained from all 288 cardiac surgery patients participating in these studies. The design of study, number of patients, inclusion and exclusion criteria, aims, and kidney laboratory measurements are listed in Table 4. The demographic data of the patients are presented in Table 7.

Variables (n)	Study I	Study II	Study III	Study IV
Number of patients	110	41	77	60
Age	77	52	70	64
Gender (male)	60 (54%)	23 (56%)	62 (80%)	54 (90%)
BMI		24	28	28
ACE/AT2		37 (90%)	51 (66%)	34 (57%)
Statins	*	15 (37%)	*	39 (65%)
LVEF				
>50%	81 (74%)	0	36 (47%)	0
50 to 35 %	23 (21%)	0	15 (19%)	15 (25%)
< 35%	6 (5%)	41 (100%)	26 (34%)	45 (75%)
Diabetes	29 (26%)	2 (5%)	28 (36%)	23 (38%)
Peripheral vascular disease	19 (17%)	10 (24%)	15 (19%)	*
CABG	34 (31%)	0	38 (49%)	60 (100%)
Valve	44 (40%)	0	13 (17%)	0
CABG + valve	32 (29%)	0	26 (34%)	0
Heart transplantation	0	41 (100%)	0	0

Table 7. *Demographic data of Studies I – IV*
**Not assessed in the study*
Data are presented as median or number (%)

4.2 Study design

Study I

In study I we tested whether serum cystatin C is able to detect AKI earlier than plasma creatinine after cardiac surgery with elderly patients. The blood samples for plasma creatinine and serum Cystatin C were collected before surgery in the operation room as a baseline, and on the days 1 to 5 thereafter, the samples were analyzed immediately after they were collected. The patients with AKI were categorized to three different groups based on the changes in plasma creatinine, urine output, or eGFR according to the RIFLE criteria. In the morning of the operation the patients received their routine cardiac medication excluding ACEIs or ARBs. The attending anesthesiologist decided the administration of aprotinin or tranexamic acid, otherwise the anesthesia and CPB management followed the standardized protocol. GFR was calculated with the MDRD equation. We also assessed hemodynamic data, medication with vasoactive drugs, diuretics, transfusions, and fluid balance. Table 8 lists study designs I-IV.

Study II

The primary aim of the study II was to find out whether cystatin C increases before creatinine in heart transplant patients with postoperative AKI. Preoperative renal function was determined with ^{51}Cr-EDTA-GFR (35 patients) or calculated with the MDRD equation (6 patients). The baseline blood samples for plasma creatinine and serum cystatin C were collected a few hours before the heart transplantation, 24 hours after the beginning of the operation, and on days 1 to 5 postoperatively. In addition, the urine samples for NAG and creatinine were obtained in the beginning of the transplantation, at the end of the surgery, and on days 1 to 3 postoperatively. We used RIFLE criteria to identify the patients with AKI. The information of administrated vasoactive medication, hemodynamic values and calculations, administrated fluids, and blood products were collected from a computerized data collection.

Study III

We evaluated the effect of N-acetylcysteine (NAC) in patients with preoperative renal dysfunction. The kidney function was measured with plasma creatinine, serum cystatin C, and urine NAG. Eighty patients scheduled to elective CABG with CPB were randomized to receive NAC (Group NAC), or placebo (Group Placebo). One patient in the NAC-group was excluded from analysis due to protocol violation, and with one patient in NAC-group and one in placebo-group operation was inverted to off-pump coronary artery bypass. Before the induction of the anesthesia NAC (Parvolex®, Celltech Pharmaceuticals Ltd, Slough, UK), prepared in saline 0.9%, was administrated as a loading dose of 150 mg/kg in 15 minutes, followed by 50 mg/kg for next 4 hours, and thereafter, 100 mg/kg for 16 hours. The placebo group was given similar volumes of saline 0.9%. The hospital pharmacy carried out the randomization and prepared study medications. The anesthesia

and CPB were performed according to a standard protocol, none of the patients received aprotinin.

The urine and blood baseline samples were collected before the study drug was started. The other urine samples were collected from the urine excreted between following time-points: from the insertion of the urinary catheter to the start of CPB, from the beginning of CPB until the end of surgery, first 6 hours after surgery, from 6 to 12 hours after surgery, and the last on the fifth day after operation. To avoid the effect of variations in the concentration of urine we calculated urine creatinine and NAG ratio by dividing the value of NAG (unit/l) with that of creatinine (μmol/l). The other blood samples for creatinine and cystatin C were obtained in the morning of the first, third, and fifth day postoperatively.

The primary outcome measure was an increase in urine NAG/creatinine ratio at 30% above baseline. The changes of plasma creatinine and serum cystatin C were also analyzed. Postoperative renal dysfunction was defined as an increase of plasma creatinine from baseline over 25%, or more than 44μmol/l, or an increase of serum cystatin C level above 1.4 mg/l. We also assessed 30-day mortality, need for RRT, length of ICU stay, and possible side effects of NAC.

Study IV

The study was performed in two centers, 42 patients were treated in center one and 18 patients in center two. Demographic data are shown in Table 5, no differences were found between the groups. The aim was to assess the effect of levosimendan on postoperative renal function in patients with impaired left ventricular function undergoing CABG surgery with CPB. This study was performed with the same patients as a previous study evaluating levosimendan for weaning patients from CPB, and the power of study was also calculated for that purpose.[219] Sixty patients were randomized to receive levosimendan or placebo infusion. After the first hemodynamic measurements using a pulmonary artery catheter, study drug infusion was administrated as a bolus dose of 12 μg/kg of levosimendan in 10 minutes, followed by a continuous infusion of 0.2 μg/kg/min for a total infusion period of 24 hours. The kidney function was evaluated with plasma creatinine, serum cystatin C, and urine NAG. GFR was calculated with MDRD equation. Plasma creatinine and serum cystatin C samples were collected at the baseline before surgery, at 6 and 24 hours after de-clamping of the aorta, and on the second and fifth postoperative day. Urine NAG was analyzed at the baseline, and at 6 hours and 24 hours after de-clamping of the aorta. AKI was determined with RIFLE criteria.

	STUDY I	STUDY II	STUDY III	STUDY IV
Study design	Prospective Observational Cohort	Prospective Observational Cohort	Prospective Randomized Placebo-controlled Double-blind	Prospective Randomized Placebo-controlled Double blind substudy
Patients	110 cardiac surgery	41 heart transplant	77 cardiac surgery	60 CABP surgery
Inclusion criteria	70 years or older Elective surgery	Patients approved to heart Transplantation	Plasma creatinine > 100 μmol/l	LVEF < 50%
Exclusion criteria	Surgery without CPB Preoperative RRT Kidney transplant	Preoperative RRT Kidney transplant	Surgery without CPB Plasma creatinine > 400 μmol/l Kidney transplant Preoperative RRT Allergy to NAC Radio contrast therapy or NAC therapy < 1 month before surgery	Surgery without CPB Levosimendan therapy < 1 month before surgery End-stage of chronic kidney disease
Aims	To discover if S-Cyst C can detect mild renal failure earlier than P-Crea	The capacity of P-Crea, S-Cyst C, and U-NAG to detect AKI after heart transplantation, and whether S-Cyst C detected AKI earlier than P-Crea	To evaluate if NAC has renoprotective effects in patients with CKD. The outcome was an increase in U-Crea/U-NAC ratio at 30% above baseline.	To evaluate the effect of levosimendan on renal function
Kidney laboratory measurements	P-Crea, S-Cyst C, eGFR	P-Crea, S-Cyst C, U-NAG, U-Crea, eGFR	P-Crea, S-Cyst C, U-NAG, U-Crea, eGFR	P-Crea, S-Cyst C, U-NAG, U-Crea, eGFR

Table 8. *Studies I to IV. CABG; coronary artery bypass grafting, LVEF; left ventricle ejection fraction, CPB; cardiopulmonary bypass, RRT; renal replacement therapy, NAC; N-acetylcysteine, S-CystC; serum cystatin C, P-Crea; plasma creatinine, U-NAG; urine N-acetyl-β-glucosaminidase, CKD; chronic kidney disease, U-Crea; urea creatinine, eGFR; estimated glomerular filtration rate.*

4.3. Anesthesia and CPB management

Anesthesia was induced with intravenous propofol or etomidate and sufentanil and maintained with inhaled sevoflurane and continuous infusion of sufentanil. Muscle relaxation was provided by rocuronium. During the induction of anesthesia MAP of 60 to 70 or higher was maintained with boluses of phenylephrine and Ringer's solution when needed. The filling pressure of left ventricle was maintained at the base level or at he pulmonary capillary wedge pressure (PCWP) of 10 to 12 mmHg. The cardiac performance and valve dysfunctions were evaluated with transesophageal echocardiography (TEE).

CPB was performed using nonpulsatile flow of 2.4 l /min/m^2, a hollow-fiber membrane oxygenator, and arterial filter. The perfusion circuit was primed with Ringer's acetate and 100 ml of from 6% to 15% mannitol, depending on the study protocol. During the perfusion, the mean arterial pressure was maintained between 50 and 90 mmHg, the hematocrit above 22%, and mixed venous saturation above 70%. Myocardial protection was achieved with intermittent, cold crystalloid cardioplegia with blood in ratio of 4:1 or 8:1, except in heart transplantation where we used cold crystalloid cardioplegia. During CPB the patients were allowed to cool passively to 30°C to 32°C, and rewarmed to 36°C before weaning from CPB. During CPB mediastinal suction blood was returned to the venous reservoir, and after the patients were withdrawn from CPB, the content of the circuit was collected and returned to the patients.

After CPB cardiac function was evaluated with TEE and cardiac index was measured with a pulmonary artery catheter, the intended goal was above 2.0 l/min/m^2. If the cardiac index was below the threshold, and pulmonary wedge pressure was maintained at least 10 mmHg, epinephrine infusion was started, and milrinone infusion was added for further support. MAP was maintained above 70 mmHg, and norepinephrine infusion was administrated when needed. In severe low- output syndrome, or when the patients could not be weaned from CPB, IABP or LVAD was installed. In heart transplantation the right ventricle dysfunction was treated with nitric oxide. In the ICU the sedation was provided with propofol, until the patients were weaned from the respirator according to the routine guidelines.

4.4. Laboratory analysis

All laboratory samples were analyzed at the HUSLAB, Helsinki University Hospital. Serum cystatin C samples were analyzed with the particle-enhanced immunoturbidimetric assay (Dako Cytomation, Glostrup, Denmark A/S), the reference value of normal limit was 1.2 mg/l. Plasma and urine creatinine were analyzed with the enzymatic assay method (Roche Diagnostics GmbH, Mannheim, Germany) and on a Hitachi Modular analyzer, the reference value of plasma creatinine above normal limit being 95 μmol/l. Urine NAG was measured with the colorimetric assay (Roche Diagnostics GmbH). In study III plasma and urine samples were stored at - 20°C and analyzed later. In this study the within-series coefficient of variation to NAG was 2.1 and 3% at 8.9 and 4.7 U/liter, respectively, and

the between–series coefficient of variation was 5.2% at 8.0 U/liter. In other studies all laboratory parameters were analyzed after the collection with the standard procedures of HUSLAB.

Definition of AKI

In Studies I, II, and IV we defined AKI with the increase of plasma creatinine, and urine output according to the RIFLE-criteria.[21] AKI was determined during the first 5 postoperative days and the patients with kidney injury were categorized to the following groups: (i), Risk, if plasma creatinine increased by 1.5 fold, or GFR decreased over 25%, or urine output was less than 0.5 mg/kg/h for more than six hours; (ii), Injury, if plasma creatinine increased by 2.0 fold, or GFR decreased over 50%, or urine output was less than 0.5 mg/kg/h for more than 12 hours; (iii) Failure, if plasma creatinine increased by 3.0 fold, or GFR decreased over 75 %, or plasma creatinine was above 356.6 μmol/l with acute increase of more than 44.2 μmol/l, or RTT was administrated, or urine output was less than 0.3 ml/kg/h for 12 hours, or anuria for more than 12 hours.
We used plasma creatinine to calculate the estimated GFR. GFR was with MDRD: GFR ($ml/min/1.73m^2$) = 186 x $Cr^{(-1.154)}$ x $Age^{(-0.203)}$ x (0.742 for females).[115]

4.5. Monitoring and data collection

All the patients were continuously monitored using a standard protocol; electrocardiography, peripheral capillary oxygen saturation, nasopharyngeal and bladder temperature, and neuromuscular block and bispectral index monitoring during anesthesia. A radial artery cannula was inserted for arterial pressure recording and blood sampling. After induction of anesthesia a pulmonary artery catheter was introduced for monitoring of hemodynamic variables, and for continuous recording of mixed venous oxygen saturation (SvO_2). During anesthesia TEE was performed at he beginning of the anesthesia and thereafter whenever needed. The continuously measured hemodynamic data, heart rate, MAP, central venous pressure (CVP), mean pulmonary artery pressure, and SvO_2, were collected from the clinical data management system (PICIS, Wakefield, MA, USA). The regular manual measurements of cardiac index and PCPW were also recorded to PICIS. Clinical data included also administration of inotropes, vasopressors, fluids, blood products, and hourly urine output, blood loss, fluid balance, and routine blood sample parameters.

4.6. Statistical methods

The statistical analyses in studies I-IV were performed using statistical software (SPSS package, versions 11.5, 13.0, 19.0; Chicago, IL and Analyse-it software Ltd; Leeds; UK). In studies I to IV, the patient data are reported as absolute numbers and percentages, as

median values with interquartile ranges (IQR, 25th and 75th percentiles), or as means and standard deviations (SD). A *p*-value <0.05 was considered statistically significant in all studies.

In study III the sample size was calculated as 40 patients per group to have 80% power in detecting a significant (30%) difference in the levels of NAG at 95% CI limits (α = 0.05). In the study IV the power was calculated for the primary outcome measure, the effect of levosimendan in weaning patients with heart dysfunction from CPB.[219]

In studies I and II we compared the groups using the Mann-Whitney *U* test or independent samples *t* test and categorical variables using the χ^2 -test, followed by Fisher exact test when appropriate. The changes in kidney laboratory measurements between the groups were performed with repeated measures analysis of variance (ANOVA). Same method was used to compare the proportional changes of creatinine and cystatin C values in AKI and None-AKI patients groups, with values over the time (five time points) as within factors, the marker (creatinine or cystatin C) as the between factors, and the interactions of these two markers over time. The appropriate F value as a measure of variance and *p* values for testing for statistical significance of the factors were calculated. In Study II to demonstrate the discriminative ability of creatinine and cystatin C to predict postoperative AKI at different time points we used receiver operating characteristics (ROC) curves with the respective areas under the curve (AUC). The studied time points were before surgery, and on the first and second postoperative days. The ROC curves and the AUC values were compared with a nonparametric method.

In studies III and IV comparison between the groups were performed with the independent samples *t*-test for continuous variables, and for categorical data the χ^2 -test, followed by Fisher exact test when appropriate, The continuous variables were compared using a repeated measures analysis of variance model with effects for treatment, time point, and treatment-time point interaction. They were also evaluated separately at each time point by treatment using ANOVA.

5. RESULTS

5.1. Ability of cystatin C to detect postoperative acute kidney injury in elderly cardiac surgery patients (I)

The incidence of AKI was 56.4% according to RIFLE criteria. Sixty-two patients out of 110 suffered AKI: 48 patients had a Risk, 12 patients belong to Injury group, and 1 patient had renal Failure. The number of patients in the AKI group with > 50% increase of the plasma creatinine and serum cystatin C in studies I and II are presented in Table 9. The median and interquartile range (IQR) values of plasma creatinine and serum cystatin C in studies I and II are presented in Table 10. The ANOVA analysis indicated that in the AKI group the proportional change of serum cystatin C and plasma creatinine was significant over time, but the changes occurred in a similar way. The concentration of the both markers peaked on third postoperative day. The ROC curves for the absolute values of creatinine and cystatin C demonstrated equal correlation with AKI at different time points. On postoperative day 1 the AUC for creatinine was 0.66 (0.55-0.76) and for cystatin C 0.71 (0.61-0.81), $p = 0.11$, and on postoperative day 2 the AUC for creatinine was 0.74 (0.64-0.83) and for cystatin C 0.77 (0.68-0.86), $p = 0.32$.

There were no differences between the patients with AKI and without AKI in hemodynamic measurements, use of inotropes and diuretics, fluid balance, blood loss, and red blood cell transfusions. One patient required RRT during the study period. Four patients needed IABP postoperatively, one of them was the patient receiving RRT. The 30-day mortality was 2.7%.

5.2. AKI after heart transplantation, the roles of NAG, cystatin C, and creatinine (II)

AKI occurred in 23 out of 41 patients (56%) after heart transplantation. Using RIFLE criteria patients with AKI were categorized to three groups: Risk included 5 patients, Injury 4 patients, and Failure 14 patients. In the AKI-patients serum cystatin C and plasma creatinine increased significantly compared to patients without AKI, both plasma creatinine and serum cystatin C peaked on postoperative day 5 at the end of the study period. Preoperatively 17 (41 %) patients had creatinine and cystatin C above normal limits. On day one creatinine increased over 25 % in 15 (36.6%) patients, 7 of these patients had increased preoperative values. On day one cystatin C increased over 25 % in 12 (29.3%) patients, but only 2 of those patients had preoperative cystatin C value above the normal limits. In the patients without AKI these markers behaved differently, as creatinine decreased from the baseline on postoperative days 1 to 5, but cystatin C first decreased on postoperative day one and increased thereafter. Urine NAG/creatinine ratio increased significantly in both AKI and non-AKI patients groups at the end of the surgery,

but there was no significant difference between the groups. The values returned close to baseline on postoperative day 1 and remained low in the rest of the measurements. The proportional changes of creatinine and cystatin C were compared with repeated measures of ANOVA, which demonstrated that, in patients with AKI, both markers increased significantly over the time ($p < 0.001$). There was a significant difference between the two markers, but the interaction over time was not significant, thus the changes of the markers occurred in a similar way over the period of time. In patients without AKI, the proportional changes of plasma creatinine and serum cystatin C performed differently, cystatin C increased 38% from the baseline and creatinine decreased 7% during the study period ($p < 0{,}001$).

The patients in the AKI group, had significantly more previous heart surgery (p=0.011), they had more more blood loss (p=0.036), they received more red blood cell transfusions (p=0.040), they were administrated more diuretics (p=0.019), and their urine output was less (p=0.005) compared to patients without kidney injury. They also received more nitric oxide treatment (52% vs. 22%, p=0.05) and the length of stay in ICU was significantly longer (p<0.001). Thirteen (31%) patients required RTT, but after one year after transplantation only one patient remained in dialysis. Four patients were placed on extra-corporeal membrane oxygenation after the transplant surgery due to primary graft dysfunction; two patients recovered, one patient was re-transplanted, and one patient died.

	Plasma creatinine		**Serum cystatin C**	
	Study I n=110	Study II n=41	Study I n=110	Study II n=41
Patients	30	21	17	19
Day 1	7 (23)	8 (38)	3 (18)	7 (37)
Day 2	8 (27)	7 (33)	9 (53)	7 (37)
Day 3	15 (50)	6 (29)	5 (29)	5 (26)

Table 9. *The number (%) of patients with > 50% increase of plasma creatinine or serum cystatin C on days 1 to 3 postoperative day.*

	AKI patients		None AKI patients	
	Study I	Study II	Study I	Study II
Creatinine μmo/l Day 0	72 (61-92)	106 (74-1389)	72 (60-85)	94 (62-116)
Day 1	88 (64-110)	114 (90-167)	69 (60-85)	79 (64-106)
Day 2	106 (77-122)	152 (115-214)	73 (64-89)	76 (59-106)
Day 3	105 (80-135)	161 (119-227)	71 (62-93)	75 (59-114)
Cystatin C mg/l Day 0	1.04 (0.86-1.27)	1.41 (1.02-1.64)	0.99 (0.83-1.08)	1.25 (0.79-1.54)
Day 1	1.10 (0.87-1.45)	1.48 (1.02-1.67)	0.89 (0.75-1.01)	0.99 (0.86-1.34)
Day 2	1.30 (1.09-1.69)	1.89 (1.42-2.14)	0.99 (0.90-1.17)	1.04 (0.97-1.53)
Day 3	1.38 (1.11-1.65)	2.17 (1.81-2.92)	1.02 (0.93-1.08)	1.20 (1.05-1.82)

***Table 10**. Median and Interquartile Range Values of plasma creatinine and serum cystatin C before surgery and postoperative days 1 to 3 in Studies I and II*

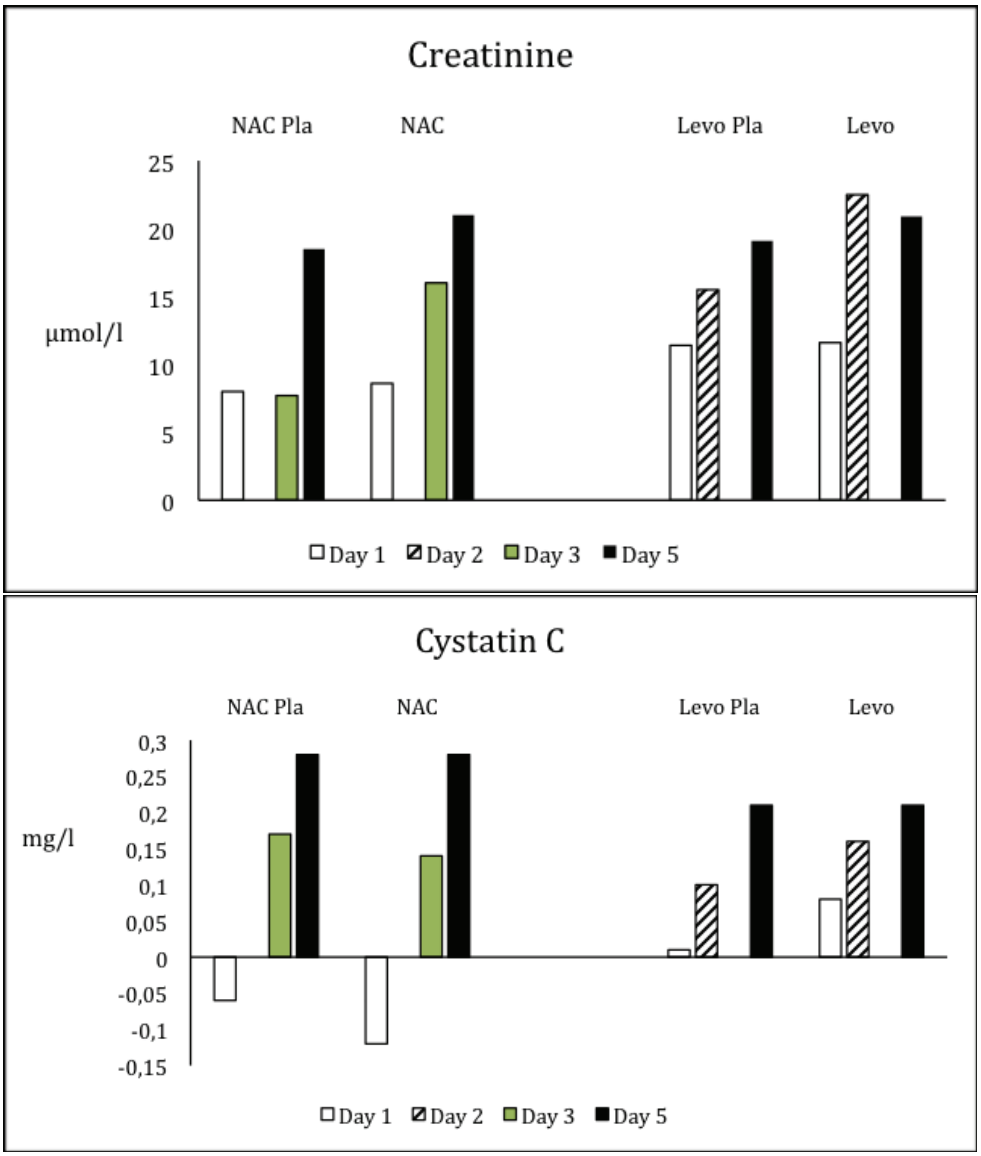
5.3. Effect of N-acetylcysteine on kidney function in cardiac surgery patients with chronic kidney disease (III)

At the base level there was no significant difference in the mean (SD) plasma creatinine, which was 127 (26) μmol/l in the N-acetylcysteine (NAC) group and 134 (45) μmol/l in the placebo group (p=0.376). According to the definition of AKI, 35 (45%) patients had postoperative AKI; 16 (42%) in the NAC group, and 19 (49%) in the placebo group. The U-NAG/creatinine ratios did not differ between the study groups. Furthermore, there was no significant difference in plasma creatinine and serum cystatine C values between the groups during the five day study period. The patients in the NAC group received significantly more fluids (p=0.009), had more blood loss (p=0.018), and they also had significantly more diuresis (p=0.045) compared to the patients in the placebo group during the first 24 hours after surgery. Three patients, one patient in the NAC group and two patients in the placebo group, died during the 30-day period after surgery.

5.4. Effect of perioperative levosimendan on renal function in coronary artery surgery patients with compromised heart function (IV)

Sixty patients with reduced left ventricle function were randomized to have levosimendan or placebo for 24 hours starting after the induction of anesthesia. In the levosimendan group and in the placebo group the mean (SD) baseline values of creatinine were 72.9 (15.9) μmol/l and 71.8 (23.9) μmol/l, respectively, p > 0.05. During the five-day period 13 (43.3%) patients developed AKI in the placebo group and 8 (26.6%) patients in the levosimendan group (p = 0.167). There were no significant differences between the renal markers plasma creatinine, serum cystatin C, and urine NAG, between the groups at any measurement point during the study period.

During surgery the patients in levosimendan group required more phenylephrine boluses than patients in the placebo group, but in ICU there were no significant differences in the doses of norepinephrine between the groups. After they were weaned from the CPB four patients in the placebo group needed IABP compared to none in the levosimendan group. During the study period two patients died, both were in the placebo group. Figure 3. presents the changes of plasma creatinine, serum cystatin C, and U-NAG in the NAC-group, in the levosimendan group, and in the placebo groups in studies III and IV.



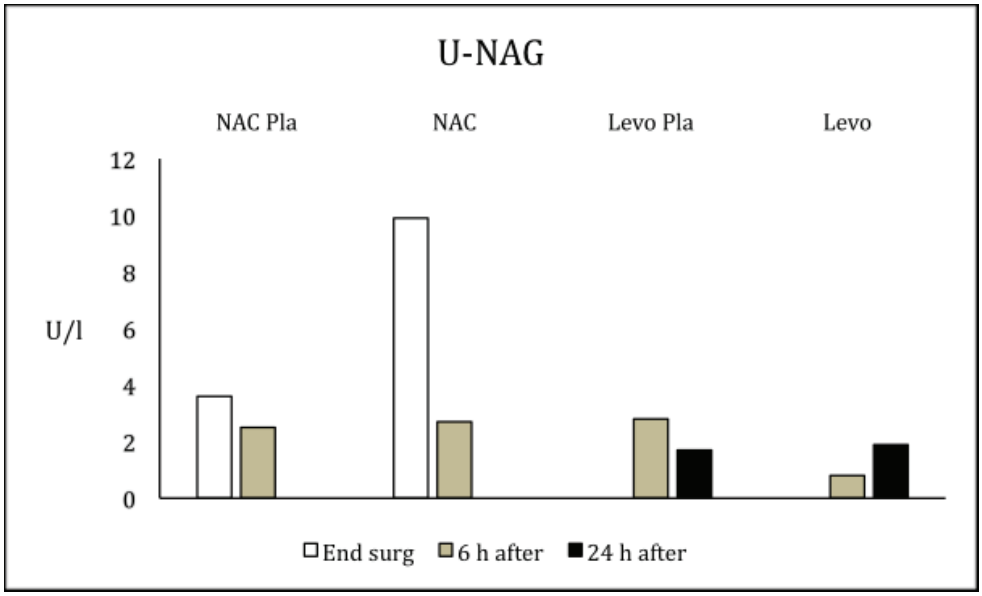


Figure 3. *Changes in plasma creatinine, serum cystatin C and urine NAG in studies III and IV. Changes were all insignificant between the study groups and placebo groups, p > 0.05. NAC;N-acetylcysteine, Levo; levosimendan, Pla; placebo.*

6. DISCUSSION

6.1. Measurement of acute kidney injury and renal function (I-IV)

Studies I and II demonstrated that cystatin C could not detect AKI before serum creatinine in elderly patients undergoing cardiac surgery or in patients after heart transplantation.

Serum creatinine has remained the benchmark measurement of renal function in spite of the following limitations; it has poor sensitivity and specificity, delayed change in concentration levels, and interference by age and body mass.[118] Cystatin C has challenged creatinine as a marker of renal function, especially in population at risk or with chronic kidney disease. According to meta-analysis of 16 studies with subject population of adults and children and healthy volunteers and patients with varying degrees of renal dysfunction by different conditions, cystatin C demonstrated better correlation coefficients (0.82 vs. 0.74, $p < 0.001$) and greater AUROC values (0.93 vs. 0.84, $p < 0.001$) with GFR than serum creatinine.[128] However, in setting of AKI in ICU or after cardiac surgery the results have been inconclusive.

In a meta-analysis of 13 studies including patients after cardiac surgery, pediatric patients, and critically ill patients AUROC of serum cystatin C to predict AKI was 0.96 (95% CI, 0.95-0.97), but the AUROC of urinary cystatin C excretion was only 0.64 (95% CI, 0.62-0.66).[220] A subgroup analysis of this study showed that serum cystatin C was of diagnostic value when measured early, as within 24 hours after the renal insult. Two smaller studies in cardiac surgery patients have found cystatin C to predict postoperative AKI similarly or slightly better than serum creatinine, and cystatin C also correlated with the duration and severity of AKI.[141,145] Both studies discovered, that preoperative serum cystatin C was elevated in the patients who developed postoperative AKI, although serum creatinine could not detect decreased GFR in these patients. However, in large, multi-center cohort studies, both serum and urine cystatin C, could not predict postoperative AKI better than serum creatinine.[143,144] With high-risk cardiac surgery patients there was not a significant difference between the general clinical outcomes between the AKI patients detected by serum creatinine or cystatin C. However, the patients with AKI confirmed with both markers had a significantly higher risk of RRT or morbidity than the patients with AKI detected by creatinine alone ($p = 0.002$).[144]

Additionally, timing of cystatin C measurements seems to play an important role in its sensitivity to detect decreased GFR.[13] Haase-Fielitz et al. compared cystatin C and NGAL with creatinine and urea to find out if the novel biomarkers were more sensitive to predict AKI after cardiac surgery, and they discovered that both cystatin C and NGAL had good predictive value on the arrival in ICU, while creatinine and urea had poor predictive value analyzed with AUROC.[146] After 24 hours from surgery this difference had disappeared and all the markers had similar predictive values. Spahillari et al. measured cystatin C shortly after the patient's arrival in ICU and found it less sensitive to detect AKI. In

studies I and II the first postoperative renal marker measurements were performed early in the morning on day one, which is in the time range less than 24 hours after the surgery. However, this sort of delay in measurements after the putative kidney damage during surgery may have affected our results, although according to the results of meta-analysis of cystatin C in AKI, our measurements were within the time limit for cystatin C to have the predictive value to detect AKI.[220]

It has been suggested that the postoperative increase in cystatin C may reflect the preoperative mild renal impairment more than acute change in GFR.[146] In study I the population were elderly, thus they had presumable decline in renal function. In this study, preoperatively all the median values of creatinine, cystatin C, and eGFR were within normal limits in patients with postoperative AKI, and did not differ form the values in patients without postoperative AKI. In study II, preoperatively above of the normal cystatin C values did not carry over postoperatively in as many patients as creatinine values did, although in this study other factors, as steroids, might have influenced the cystatin C values.

Cystatin C is considered to be influenced less by extra renal factors compared to creatinine. However, factors such as age, systemic inflammation, and use of corticosteroids have been proven to have an effect on serum cystatin C concentration.[13] Especially the influence of the administration of corticosteroids to cystatin C levels is controversial. Herget-Rosenthal et al. discovered no effect of corticosteroids on cystatin C with critically ill patients, but high dose steroids have been shown to increase the cystatin C levels with renal transplant patients.[135,221] In study I the administration of corticosteroid did not affect cystatin C values, although the doses of hydrocortisone were less than 200 mg per day, and were given only to the patients with preoperative use of steroids. In study II all the patients received immunosuppressive therapy, thus the doses were notably larger. On postoperative day one the proportional increase of creatinine was more (32.5 %) than the proportional increase of cystatin C (18.5 %) in patients with AKI, while with patients without AKI creatinine decreased below the baseline and cystatin C increased above the baseline, this change carried over the study period. Although the effect of steroids could not be disregarded, there was no systematic influence of them on cystatin C concentrations in study II.

Cystatin C is considered an unreliable marker of GFR during RRT, because its elimination depends on dialysis dose, volume, the type of membrane, and ultrafiltration rate used in RRT, and thus the reduction ratio might vary.[222] In study II 56 % of AKI patients received RRT, the median starting day being postoperative day two. This may well explain why cystatin C increased more than creatinine on day four and five in patients with AKI. However, same trend appeared in patients without AKI, the proportional increase of cystatin C from the baseline being more than 30 % from the baseline on day three and four while creatinine levels remained below the baseline in this group demonstrating different behavior of these markers with heart transplant patients.

In cardiac surgery serum cystatin C predicts AKI similarly as plasma creatinine. In high-risk patients cystatin C may produce additional information, but based on published data it cannot replace creatinine, or be used as a sole marker of GFR. In heart transplant patients cystatin C seems to be a less reliable marker of AKI than creatinine, and thus cannot be recommended for routine use.

Urine N-acetyl-β-glucosaminidase was measured as an indicator of tubular injury in studies II, III, and IV. Increased U-NAG levels have been reported in several different chronic and acute settings of AKI, including with critically ill patients and following cardiopulmonary bypass.[51] Katagiri et al. combined urinary NAG and L-FAB, and presented that together these markers detected AKI adequately after cardiac surgery (AUROC 0.81).[223] In our studies U-NAG levels increased at the end of surgery returning quickly close to base level. The increase of U-NAG levels occurred in patients with and without AKI. There was no significant difference between the groups in which the patients had been treated with NAC, levosimendan, or placebo. U-NAG may be a sensitive marker of tubular function, but it could not predict which of the patients would develop postoperative AKI. Researchers have combined different markers to attain better diagnostic accuracy, as one marker generally reflects one putative pathophysiological mechanism of AKI. ADQI published a workgroup statement in 2013 and referred novel biomarkers, urine and plasma NGAL and urine IL-18, to be used together with clinical evaluation and serum creatinine to diagnose AKI after cardiac surgery.[14]

6.2. Effects of N-acetylcysteine and levosimendan on renal function in patients undergoing cardiac surgery

In study III N-acetylcysteine had no protective effect on renal function in cardiac surgery in patients with preoperative CKD. Our results are in concordance with the majority of evidence accumulated in this subject.

In cardiopulmonary bypass NAC has attenuated reactive oxygen species, which may have mediated myocardial stress, and reduced ischemia–reperfusion injury.[184,185] NAC has been proven to ameliorate kidney injury in rats following a CPB-model.[224] However, while administrated before or during cardiac surgery NAC has not improved any outcomes. Six meta-analyses and systematic reviews publish between 2008 and 2011 concluded that NAC has no effect on renal function in cardiac surgery.[196,197,225-228] Wang et al. conducted a meta-analysis which included 1407 patients from 15 randomized trials, and writers could not detect differences in the incidence of over 25 % increase in serum creatinine above the baseline (OR = 0.86; 95% CI, 0.66-1.12; p=0.26) or need for RRT (OR = 1.05; 95% CI, 0.52-2.11, p = 0.90) in patients treated with NAC compared to the patients receiving placebo.[228] They could not find a significant difference in mortality, new onset of atrial fibrillation, acute myocardial infarction, or stroke between the NAC and placebo treated patients, either. Wijeysundera et al. performed a post-hoc analysis of

their randomized trial of 177 patients with preoperative renal insufficiency undergoing cardiac surgery, and discovered that NAC was associated with increased blood loss and blood product transfusion.[229] Naughton et al. had a similar finding in their meta-analysis, there was a small, but statistically significant increase in postoperative blood loss among patients treated with NAC. However, in a recent meta-analysis there was no difference in red blood cell transfusion requirements, re-exploration or postoperative drainage.[225,228]

Although the results of the single RCT studies on NAC are inconclusive, also the meta-analyses have similar conclusions. However, they have the limitations and strengths of the included trials. The limitations include heterogeneity of study populations, different definitions of AKI, different doses and administration routes of NAC, and different appraisal of preoperative renal dysfunction of the patients. The dose and the route of administration of NAC may conflict the results, because the antioxidant and anti-inflammatory effects of NAC are related to the dose.[230]

The pathophysiology of CSA-AKI involves multiple factors. Interestingly, there is experimental evidence from a few small studies to indicate, that NAC may protect kidneys by reducing oxidative stress, reperfusion injury, and systemic inflammatory response associated with cardiac surgery.[184,185,224] Metabolic factors, neurohumoral activation, and endogenous and exogenous toxins also contribute to the development of CSA-AKI. Moreover, the lack of evidence on the positive effect of NAC treatment as an anti-oxidant in diseases characterized with increased oxidative stress indicates our lack of knowledge of the role of reactive oxygen species in pathophysiology of disease.[231,232]

Low cardiac output syndrome is an extremely harmful event in cardiac surgery leading frequently to serious complications.[233] Moreover, the therapy of low output syndrome is the administration of inotropes, which has been found to be associated with increased mortality and postoperative morbidity.[234] Hypoperfusion may trigger a sympathoadrenergic response, hyperglycemia, and inflammation resulting in a cardiorenal syndrome, which can be part of CSA-AKI.[235] The exception is levosimendan, and its administration has spread to cardiac surgery during last decade. Levosimendan is characterized by triple mechanism of action; it acts via calcium-dependent binding to cardiac troponin C, and opens the K_{ATP} channels on smooth muscle cells in the vasculature, and in cardiac mitochondria, and this results in its inotorpic and vasodilatory effects, respectively.[236] The opening of K_{ATP} channels in cardiac mitochondria is believed to cause the cardioprotective effects of levosimendan.[237] In pigs levosimendan protected kidney against ischemia/reperfusion injury through antioxidant and NO-related mechanisms.[238] Harrison et al. conducted a meta-analysis to evaluate the effects of levosimendan in cardiac surgery patients with and without preoperative systolic dysfunction and discovered that mortality, postoperative AKI requiring RRT, new atrial fibrillation, and acute myocardial injury were reduced, especially in patients with low ejection fraction of the left ventricle.[239] Beneficial effects of levosimendan in the weaning from CPB were clearly shown in the main report of the current study IV, too.[219] Although there was no significant difference in the renal markers between the levosimendan group

and placebo group, there was a tendency towards preserved renal function in levosimendan group. Eight out of 30 patients (26.6%) had over 25 % postoperative increase in serum creatinine in patients treated with levosimendan, when 13 out of 30 patients (43.3 %) had this finding in placebo group. Niu et al. conducted a meta-analysis of five trials with 529 cardiac surgery patients and discovered that the use of levosimendan was associated with lower AKI incidence 9.5 % vs. 19.2 % in the control group, OR = 0.44 (0.22-0.85), p = 0.02.[213] The role of levosimendan regarding renal function in cardiac surgery is not yet determined, and adequately powered, randomized trials are needed to prove the beneficial effects.

Prevention of AKI in cardiac surgery

There are no known drugs to prevent CSA-AKI at the present time. There may be several reasons for the variable efficacy of the pharmacological interventions.[240] Such as the small number of patients enrolled to the trials to significantly prove the effect of the studied drug. The studied patients are often at low risk of renal dysfunction to benefit from the therapy. The pathophysiology of CSA-AKI is complex and multi-factorial, thus focusing on one or two pathways may be insufficient to produce results. The measurement of renal function with creatinine may hide smaller benefits of the drug, and when creatinine level increases, patients may have already lost 50 % of kidney function. Currently known interventions to reduce the risk of CSA-AKI are to identify the patients at risk for AKI, avoid known nephrotoxic treatments, optimize hydration, avoid hemodilution and anemia, postpone surgery at least 24 hours after coronary angiography, shorten or avoid CPB, start statin therapy when feasible, and start RRT as soon as possible when needed.

6.3. Limitations of studies I-IV

Studies I and II were single center cohort studies with limited study population. They were also underpowered to detect the relationship between creatinine and cystatin C and severe renal failure requiring RRT or morbidity. The absolute changes in creatinine and cystatin C do not reveal the superiority of the other marker without the hard outcomes as RRT or morbidity, and that requires large multicenter cohorts.

Study III was statistically powered to detect the positive effect of NAC on tubular function. NAG values increased in both study groups indicating the change in tubular function after CBP, but in later studies NAG alone has not proved to be a very reliable marker of the kidney damage in cardiac surgery.[241] The study population should have been larger to insure assessing AKI with substantial increase of creatinine or need for RRT. Another limitation was the different types of cardiac surgeries increasing the heterogeneity of the study patients. However, the inclusion criterion of increased preoperative creatinine made the study population more homogenous compared to the studies carried out with high-risk patients without knowledge of the accurate preoperative renal function.

The limitation of study IV was its small size. It was a sub-study study to detect both positive and negative renal effects of a novel drug, levosimendan. It was not powered to

demonstrate its ability to reduce AKI after CABG surgery, but as a new inotrope it was associated with slight tendency to reduce kidney injury without harmful effects.

6.4. Future prospects

Due to the complex pathogenesis of CSA-AKI, it is unlikely that it can be influenced with only one intervention. The prevention of AKI requires multi-factorial approach where the co-morbidities of the patient and the specific characteristics of cardiac surgery are taken into consideration. Early recognition of AKI is required for timely intervention. Although NGAL and IL-18 may improve the detection of developing CSA-AKI, even more accurate diagnostic tools are needed. In a recent study regional renal oximetry was applied to the patients undergoing cardiac surgery with CPB.[242] The investigators discovered that patients who developed CSA-AKI appeared to have longer duration of low regional renal oxygenation, however, the treatment to this hypoperfusion is still not answered. The research of the pathophysiology of AKI may result in new treatments. Mitochondrial injury appears to be an early pathogenic event in multiple forms of AKI, and the treatment and prevention of kidney insult may include preventing mitochondrial injury, stimulating clearance of injured mitochondria, and mitochondrial biogenesis, thus a mitochondrial-based drug may ameliorate also CSA-AKI.[243]

7. CONCLUSIONS

The following conclusions can be made from the presented data:

1. Serum cystatin C and plasma creatinine detected AKI in a similar way after cardiac surgery with elderly patients. Serum cystatin C did not improve the detection of AKI.

2. Serum cystatin C and plasma creatinine changed similarly in patients with AKI after heart transplantation. Serum cystatin C increased postoperatively with patients without kidney injury while plasma creatinine did not change. Serum cystatin C was not beneficial in detection of AKI. Urine N-acetyl-β-D-glucosaminidase increased with all the heart transplant patients after cardiopulmonary bypass, and it was not able to identify patients with clinical kidney injury.

3. Prophylactic treatment with intravenously administrated N-acetylcysteine has no renoprotective effects in patients with minor kidney injury undergoing cardiac surgery.

4. Perioperatively administrated levosimendan has not significant effects on renal functions of coronary artery bypass patients with compromised left ventricle function.

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Veikkola November 2015, Anne Ristikankare

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