From the Klinik für Herz- und Gefäßchirurgie
(Director: Prof. Dr. med. Jochen Cremer)
at the University Medical Center Schleswig-Holstein, Campus Kiel,
at Kiel University

ACUTE KIDNEY INJURY AFTER ASCENDING AORTA AND AORTIC ARCH REPLACEMENT SURGERY WITH MODERATE HYPOTHERMIA, CIRCULATORY ARREST AND CARDIOPULMONARY BYPASS

Inaugural dissertation to acquire the doctoral degree (Dr. med.)
at the Faculty of Medicine at Kiel

Presented by
MOSTAFA SALEM
from CAIRO / Egypt

Kiel 2019

1. Reviewer:	Prof. Dr. med. Assad Haneya, Klinik für Herz- und Gefäßchirurgie
2. Report by:	Priv.-Doz. Dr. Gunnar Elke, Klinik für Anästhesiologie und operative Intensivmedizin
Day of oral examination:	04.02.2020
Approved for printing, Kiel,	09.12.2019

Signed: Prof. Dr. Johann Roider

(Chairman of the Examination Committee)

Table of contents

Abbreviation

-AAR-	**-ascending aorta and aortic arch replacement-**
ACEI	**Angiotensin-converting enzyme inhibitors**
AKI	**Acute kidney injury**
AKIN	**Acute Kidney Injury Network**
ANP	**Atrial natriuretic peptide**
ARB	**Angiotensin II receptor blockers**
ARF	**Acute renal failure**
ADH	**Antidiuretic hormone**
ATN	**Acute tubular necrosis**
AVR	**Aortic valve replacement**
BNP	**B-type natriuretic peptide**
CABG	**Coronary artery bypass grafting**
CI-AKI	**Contrast-induced-acute kidney injury**
CKD	**Chronic kidney disease**
COPD	**Chronic obstructive pulmonary disease**
CPB	**Cardiopulmonary bypass**
CS	**Cardiogenic shock**
CSA-	**Cardiac surgery associated-**
CyC	**Cystatin C**
DM	**Diabetes mellitus**
EK	**Erythrocyte concentrate**
FDA	**US Food and Drugs Administrations**
GFR	**Glomerular filtration rate**
HCA	**Hypothermic circulatory arrest**
IABP	**Intra-aortic balloon pump**
LV-EF	**Left ventricle ejection fraction**
MI, AMI	**Myocardial infarct, acute myocardial infarct**
NYHA	**New York Heart Association**
PAD	**Peripheral arterial disease**
PCT	**Proximal convoluted Tubule**
PCS-	**Post cardiac surgery-**
POD	**Postoperative day**
RAAS	**Renin-Angiotensin-Aldosterone System**
-RRT	**-renal replacement therapies**
SCr	**Serum creatinine**
TAVI	**Transcatheter Aortic Valve Implantation**

1. Introduction

The gold standard for the treatment of ascending aortic and aortic arch aneurysms, dissection and advanced aortic calcification is still surgery. In the last 30 years, the mortality and morbidity of such operations have significantly decreased. However, according to most of the studies, the occurrence of postoperative acute kidney injury (AKI) is a frequent and severe postoperative complication of cardiac surgery, particularly when a hypothermic circulatory arrest (HCA) and cardiopulmonary bypass (CPB) are used.

HCA has been shown to have adverse effects on multiple organ systems[1]. Postoperative AKI is a common complication (40–50%) encountered in patients undergoing thoracic aorta replacement under HCA[2-3].

CPB was considered according to many studies to be the second most common cause of AKI in the intensive care unit after sepsis[4].

AKI represents a significant factor influencing 30 day and long-term outcome and is associated with a high incidence of morbidity and mortality as it places the patients at 5-times higher mortality risk during the hospital stay. The incidence of AKI varies with the causative aetiology, which differs according to the surgical techniques, perioperative management and pharmacological therapy used. However, we now understand better those different aetiologies of the underlying problem. Despite successful strategies to provide sufficient renal protection or strategies for 'rescue therapy', they are either unsubstantiated by randomised clinical trials or show no significant efficacy.

The early identification and therapeutic intervention for those individuals at high risk of developing post cardiac surgery – acute kidney injury (PCS-AKI) are critical to optimising the outcomes. In this analysis, we collected data for the last 15 years from approximately 1400 patients who underwent aortic ascending and aortic arch replacement using HCA and CPB.

In this study, we evaluate the correlation between outcome and AKI using serial preoperative, intraoperative and postoperative creatinine, urea and glomerular filtration rate (GFR) controls.

We also clear different surgical techniques as the HCA and CPB that were used and their influence on the perioperative kidney function. In addition to that we clear as well the various definitions, prevention strategies, early detection methods (novel markers and prediction scores before and after the operation), and risk factors, as well as causes of AKI.

1.1 Background of acute kidney injury

1.1.1 Definition of acute kidney injury

In the last few years, many studies and research papers have arisen with different definitions of acute kidney injury [5,6,7]; although they have defined AKI differently from each other, there was a general criterion to define AKI which is:
"A sudden loss or decrease in kidney function that is manifested clinically by signs including a rapid decline in the glomerular filtration rate (GFR), resulting in the dysregulation of extracellular fluid-, electrolyte- and acid-base balance, the retention and accumulation of urea and other nitrogenous waste products in the circulation (azotemia) and often low urine output (oliguria or anuria). In severe cases, this leads to metabolic acidosis, severe fluid retention, and electrolyte disturbance, as well as hypertension, and might require renal replacement therapy, traditionally in the form of intermittent haemodialysis."

There was confusion about the best way to evaluate and classify kidney functions, including which markers reflect them and which values of those markers indicate normal and abnormal kidney functions until the Acute Dialysis Quality Initiative (ADQI) created the RIFLE criteria[4] (an acronym for Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease). More recently, the AKIN criteria[5] (Acute Kidney Injury Network) and the KDIGO criteria[6] (Kidney Disease Improving Global Outcomes) were developed based on the RIFLE criteria. Therefore, the three classifications look similar at first sight. In all three classification systems, we can grade the AKI according to the increase in serum creatinine (SCr) or the duration of oliguria.

1.1.2 Aetiology of acute kidney injury

The aetiology of AKI has traditionally been classified into three categories **(A) post-renal, (B) intrinsic or renal** and **(C) pre-renal factors**. These classifications provide practical information about the different pathophysiological aetiologies that underlines AKI.

(A) **Post-renal AKI**

Post-renal failure is caused by clinical conditions which cause urine outflow obstruction due to:

- Bilateral renal tubule obstruction
- Bilateral ureteric obstruction.
- Unilateral ureteric or renal tubule obstruction with a non-functioning or missing another kidney.
- Urethral obstruction with subsequent blockage of the urine pathway.

Any factor that obstructs urine excretion may cause this type of renal injury by increasing the intra-tubular pressure and thus decreasing GFR[8]. Also, acute urinary tract obstruction can lead to impaired renal blood flow and inflammatory processes that also contribute to diminished GFR[9].

If the post-renal injury is not treated rapidly, it may result in either temporary or permanent actual nephron damage as well as resultant intrinsic renal injury.

(B) **Intrinsic AKI** (renal parenchymal disease)

This is caused by injury of the major structural components of the kidney, such as nephrons and renal parenchyma. Causes include:

- Acute tubular necrosis (ATN): Tubular damage is the most common underlying cause of intrinsic AKI occurring after surgery either because of ischaemic or nephrotoxic reasons [10].
- Acute interstitial nephritis.
- Acute severe pyelonephritis which leads to papillary necrosis, e.g. in Diabetes mellitus
- Rapidly progressive glomerulonephritis.
- Malignant hypertension or athero-embolic renal disease => Leading to vasculopathies which induce damage to the renal vasculature.

(C) **Pre-renal AKI** is caused by a significant reduction in kidney perfusion. The kidney, which has the highest tissue perfusion rate relative to organ weight, typically receives 15–20% of the total cardiac output [11]. This high perfusion rate makes the kidney vulnerable to haemodynamic injury. General causes that decrease kidney perfusion or alter the renal haemodynamics include:

- Hypovolemia as in blood, plasma or fluids loss.
- Shock with normal intravascular volume as in cardiogenic shock or Massive pulmonary embolism.

- Others: third spacing, e.g. pancreatitis, hepato-renal syndrome.
- Pre-renal AKI is reversible after correction of the underlying cause in the presence of normal kidney parenchyma and tubules, but when the duration of AKI induced by a prerenal cause is prolonged without rapid intervention, renal parenchymal damage occurs, eventually giving rise to intrinsic kidney injury[12], and in severe causes irreversible cortical necrosis happened[13].

Surgeries required CPB procedures were found to be one of the most common causes of postoperative prerenal AKI[13,14,16]. Other more controversial, but potentially significant modifiable risk factors are those specifically related to the performance of CPB, such as on-pump versus off-pump technique, pulsatile versus non-pulsatile flow, normothermic versus hypothermic CPB, haemodilution during CPB, and the duration of CPB[15]. These factors are discussed in more detail later in this review.

1.1.3 Classification of acute kidney injury

1.1.3.1 KDIGO Classification and definition of AKI (Figure 1)[17]

Recently, in 2012, the AKI study group called "Kidney Disease Improving Global Outcomes (KDIGO)" modified a new definition that combines the differences between the RIFLE and AKIN definitions; AKI is defined by the KDIGO as any of the following:

(A) increase in SCr by ≥0.3 mg/dl within 48 hours or

(B) increase in SCr to ≥1.5-times the baseline within seven days or

(C) Reduction in urine output <0.5 ml/kg/h for 6 hours.

(D) Treatment with renal replacement therapy (direct stage 3)

Stage	Serum Creatinine criteria	Urine output criteria
Stage 1	Increase in SCr by ≥0.3 mg/dl (≥26.5µmol/l) within 48 hours or Increase in SCr to ≥1.5- to 1.9-times the baseline within seven days	Urine output <0.5 ml/kg/h for 6–12 h
Stage 2	Increase of serum creatinine to 2.0 – 2.9 times from baseline	Urine output <0.5 ml/kg/h for ≥ 12 h
Stage 3	Increase of serum creatinine ≥3.0 times from baseline or serum creatinine ≥4.0 mg/dl (≥354 µmol/L) or treatment with RRT or in patients <18 years, a decrease in estimated GFR to <35 ml/min per 1.73 m²	Urine output <0.3 ml/kg/h for ≥24 h or anuria for ≥12 h

Figure 1: KDIGO Classification, GFR: glomerular filtration rate; SCr,: serum creatinine.

In the RIFLE and KDIGO, "acute on top of chronic AKI" is defined as a separate AKI stage (SCr ≥4 mg/dl ± a sharp rise of 0.5mg/dl) BUT; AKIN Classifies acute on chronic AKI as a part of stage 3.

1.1.4 Pathophysiology of PCS-AKI with moderate HCA and CPB

AKI is a common post cardiac surgery complication that affects up to 30% of patients [18], 3% of which require RRT [19,20,21].

Cardiac surgery with CPB is the second most common cause of AKI in ICU after sepsis and is independently associated with short- and long-term morbidity and mortality [22].

Many studies have demonstrated that the overall mortality after cardiac surgery ranges from 1% to 8%, but when AKI complicates surgery, a four-fold increase in the risk of death has been observed [23]. Moreover, the mortality of patients requiring RRT increases to 63%[24]. Furthermore, according to a recent retrospective study of 2973 patients, 45% of post-cardiac surgery patients surviving RRT remain dialysis-dependent, 33% may have partial renal recovery, and only 21% may have a complete renal recovery at the time of hospital discharge[25].

The commonest cause of postoperative AKI with HCA/CPB-surgery is ATN as a result of ischemic injury to nephrons in the medullary region of the kidney secondary to hypotension, hypovolaemia, and/or dehydration. However, several recent studies have identified some covariates affecting renal function in different pathways and proved that the underlying cause is multi-factorial rather than only being related to the kidney haemodynamic alterations[26].

Those predisposing factors are divided according to the time course of the operation into pre-, intra- and post-operative [27] summarised in Table 1.

Table 1: Factors Associated with postoperative AKI [27]

Preoperative	*Intraoperative*	*Postoperative*
- ***Nephrotoxic drugs***	- ***Cardiopulmonary bypass***	- ***Decreased cardiac function***
- ***Inflammation***	- ***Anaemia***	- ***Vasoactive drugs***
- ***Underlying CKD***	- ***Embolic events***	- ***Nephrotoxic drugs***
- ***Decreased effective volume***	- ***Haemodilution***	- ***Unstable hemodynamic state***
- ***Renovascular disease***	- ***Shock***	- ***Inflammation***
- ***Congestive heart failure***		

1.1.4.1 **The common associated risk factors and predictive scores**

- **Predictive scores**

The accurate prediction of postoperative-AKI provides clinicians with the chance to apply efficient prophylactic and therapeutic measures as early as possible. Several risk stratification systems exist for cardiac surgery patients.

The best-validated scores predict severe AKI requiring RRT (dialysis) after cardiac surgery include the (A) **Cleveland Clinic Score and (B) the Mehta Score [20,28] and more recently (c) the Simplified Renal Index (SRI) score**

(a) In 2005, Thakar et al.[28] published the Cleveland Clinic Score with a high level of precision in the calculation of the prevalence of PCS-RRT. After studying 33,217 patients who underwent open-heart surgery at the Cleveland Clinic Foundation between 1993 and 2002, the primary outcome was to identify high risk-AKI liable-patients who might require postoperative RRT (Figure 2).

(b) In 2006, Mehta et al.[20] suggested a bedside tool (Mehta score) for predicting the risk based on eight preoperative variables in 86,009 patients

(c) In 2007, Wijeysundera et al.[21] established the SRI model (SRI score, Toronto).

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 (reference to CABG)	1
CABG+ valve (reference to CABG)	2
Other cardiac surgery	2
Preoperative creatinine 1.2 to 2.1 mg/dl	2
Preoperative creatinine >2.1	5

Figure 2; The Thakar score[28]. (Minimum score 0; maximum score 17).

Table 2; Comparison between the three RRT prediction scores

Score (range)	Thakar (0-17)	Mehta (5-83)	Simplif (0-8)
Demographics			
-Age (12.0%)		**0-10 (12.0%)**	
-Female	**1 (5.9%)**		
-Race:		**2 (2.4%)**	
Preoperative history			
-Chronic lung disease	**1 (5.9%)**	**3 (3.6%)**	
-Diabetes controlled orally /diabetes insulin-dependent	**1 (5.9%)**	**2 (2.4%)** **5 (6.0%)**	**1 (12.5%)**
-Basal creatinine	**2-5 (29.4%)**	**5-40 (48.2%)**	
-eGFR			**1-2 (25%)**
Preoperative cardiac status			
-Congestive heart failure	**1 (5.9%)**		
-LVEF	**1 (5.9%)**		**1 (12.5%)**
-Myocardial infarction <3 wks		**3 (3.6%)**	
-Cardiogenic shock		**7 (8.4%)**	
-NYHA class IV		**3 (3.6%)**	
-Preoperative use of IABP 2	**2 (11.8%)**		**1 (12.5%)**
-Previous cardiac surgery	**1 (5.9%)**	**3 (3.6%)**	**1 (12.5%)**
Operative details			
-Surgery type (CABG/Valve)	**1-2 (11.8%)**	**2-7 (8.4%**	**1 (12.5%)**
-Emergent surgery	**2 (11.8%**		**1 (12.5%)**

These scores use similar risk factors to predict AKI. However, external validation studies have been performed [29,30], with findings that the Cleveland scoring system offered the best discriminative value for postoperative RRT. However, before using a model to estimate risk probabilities at a specific centre, recalibration may be needed.

The prediction of mild and moderate AKI is also essential [17]. That is why **Birnie et al.**[31] analysed data collected prospectively from over 30,000 subjects undergoing cardiac surgery at three British hospitals to develop the first prediction model for all stages of postoperative-AKI using the KDIGO criteria. The model's risk prediction score for any stage of AKI (AUC, 0.74 (95% CI: 0.72–0.76)) demonstrated better discrimination than the **Cleveland Clinic Score** and equivalent discrimination to the Mehta score.

The incorporation of novel markers into prediction scores may provide additional opportunities to identify patients at high risk. Until now, most studies have evaluated the ability of damage and functional markers to predict AKI compared with clinical risk factors. However, to date, they are not used in any prediction scores for postoperative AKI.

- **Risk factors:**

Some recent patient-related and surgery-related studies have emphasised the risk factors involved in cardiac-surgery and vascular-surgery-associated AKI (Table 3) [20,23,24,32-36].

Table 3: Risk factors for AKI after cardiac (I) and vascular-open (II) surgeries

- **Cardiac surgery [20,23,24,32-36]**
  - **Female sex**
  - **Cardiogenic shock**
  - **NYHA class IV**
  - **Reduced LV function**
  - **Congestive heart failure**
  - **Preoperative need for IABP**
  - **Diabetes mellitus**
  - **Peripheral vascular disease**
  - **COPD**
  - **Preoperative reduced renal function (eGFR<60 mL/min; Cr >2.1 mg/dL)**
  - **Anaemia (Hb <12.5 g/dL)**
  - **Emergent surgery**
  - **Re-intervention**
  - **Intraoperative use of aprotinin**
  - **CPB time**
  - **Cross-clamp time**
  - **Transfusions (PRBC)**
  - **Haemodilution**
  - **Valve or combined (Valve and CABG) surgery**
  - **Haemolysis**
  - **Recent exposure to nephrotoxic agents (such as radio-contrast dyes, bile pigments, aminoglycoside antibiotics, and NSAIDs)**
  - **Respiratory disease**
  - **Advanced age**
  - **African-American ethnicity**
  - **Increased body weight**
  - **Pulse pressure hypertension**
  - **Poor intraoperative blood pressure control**
  - **Aortic surgery**

- **Vascular surgery-open[37-39]**
  - **Renal ischaemia (aortic cross clamp time)**
  - **Double renal ischaemia vs. single ischaemia**
  - **Intraoperative hypotension**
  - **Age**
  - **Symptomatic AAA**
  - **Supra/iuxtrarenal AAA**
  - **Preoperative SCr >1.5 mg/dL**
  - **Hypertension**
  - **Respiratory disease**

AAA: abdominal aortic aneurysm; CABG: coronary artery bypass surgery; CAD: coronary artery disease; COPD: chronic obstructive pulmonary disease; CPB: cardiopulmonary bypass; Cr: creatinine; eGFR: estimated glomerular filtration rate; Hb: haemoglobin; ; IABP: intra-aortic balloon pump; LV: left ventricle; NYHA: New York Heart Association; PRBC: packed red blood cells; SCr: serum creatinine

In our discussion part, each of the previous risk factors, as well as each risk factor in the predicting score mentioned above, will be revised and analysed individually to determine whether they are correlated to postoperative AKI or not.

1.1.5 Postoperative Kidney functions tests

1.1.5.1 Kidney functions tests and "old" biomarkers (widely used until now)

Although there are different varieties of kidney function, clinically in the ICU, tubular metabolism, hormone production and the excretion of small peptides are rarely measured. The two physiological functions that are continuously measured in the ICU – and seen to be of clinical interest are (1) **the excretion of metabolic water-soluble wastes** like urea and creatinine and (2) **urine output**. Consequently, these are the aspects of renal function that clinicians have focused on to define the presence of acute kidney injury.

The excretion of metabolic water-soluble wastes is the result of glomerular filtration and the glomerular filtration rate (GFR). The standard way to evaluate renal function is measuring the clearance of those waste substances (i.e. creatinine clearance). However, GFR varies as a function of normal physiology as well as disease. For example, vegetarians may have a GFR of 45–50 ml/min, while non-vegetarians with high dietary protein levels may have a GFR of 140–150 ml/min, although both have a healthy kidney with the same renal mass[40].

The baseline glomerular filtration rate can be increased by either efferent arteriolar vasoconstriction or afferent arteriolar vasodilatation, or both. Angiotensin-converting enzyme (ACE) inhibitors induce the opposite effect and reduce GFR[41]. The maximum GFR is not yet recognised, but it can be approached with an acute high protein or amino acid intake.

The principle of a baseline and maximal GFR is defined as the "renal functional reserve". A hypothetical patient with a vegetarian diet and another patient with a unilateral nephrectomy may have the same baseline GFR, but their functional reserve may be different. Consequently, even accurate measurements of baseline GFR may not correspond to the full extent of functioning renal mass and will not allow the clinician to define the renal function.

In the intensive care unit and perioperative, routine measurements of renal clearance are taken; standard practice is to estimate the GFR using serum creatinine. Although creatinine clearance is known to be the best predictive marker of a change in renal function and the possible subsequent development of perioperative dysfunction, the test is not practical in the operating theatre, is too unreliable to indicate acute postoperative changes in kidney function[42] and is problematic for the following reasons:

- Serum creatinine levels are elevated after renal function has declined about 48 h after the initiating event and do not reflect injury, so a considerable proportion of patients with normal serum creatinine values may have a reduced GFR, and a reduction of 50% may even

be associated with a normal serum creatinine concentrations; therefore, using SCr results in a delayed diagnosis of postoperative AKI when in fact severe tubular injury has occurred and may be ongoing.

- It is subject to confounding factors such as age, sex, muscle mass, and diet.

Therefore, recent investigations have focused mainly on finding practical serum and urine biomarkers that could reveal early postoperative renal injury before profound functional damage occurs; those are called ***Novel Biomarkers.***

1.1.5.2 Novel biomarkers and identification of subclinical postoperative AKI

Changes in SCr develop late in cases of postoperative AKI, typically 48 h after the initial renal injury[43]. Haemodilution related to the pump prime is a factor in this. That results in a delayed diagnosis of postoperative AKI when in fact severe tubular injury has already occurred and may still be ongoing. Thus, one of the critical conditions that influence the successful treatment of postoperative AKI, the earlier detection and intervention[44,45], is not fulfilled here as interventional therapy would be initiated too late after the acute tubular necrosis is already established and ongoing.

Several research studies [46,47] have suggested that the lack of sensitive "troponin-like" kidney-biomarkers for the early detection of acute kidney injury has had a negative impact on clinical trials investigating promising interventional strategies for AKI[48,49]. Therefore, in the last few years, the attention of the researchers with regard to AKI was focused on finding novel AKI biomarkers. Luckily, it is an area of intense activity [50, 51].

Publications by Bagshaw, Bellomo, and Devarajan explain the ideal characteristics of AKI biomarkers[46,47]:

(1) They should be easy, quick and cheap, and use readily available specimens (i.e. urine, serum).
(2) They should be precise and reliable and use standardised assay methods applied merely at the bedside.
(3) They should be highly sensitive for AKI, thus permitting early detection.
(4) They should enable monitoring of the course of injury patterns and have some ability to predict the severity and trajectory of AKI (i.e. the need for RRT).
(5) They should be specific, allowing the clinician to discriminate between subtypes of AKI.

The detection of these novel biomarkers opened up a new era of early detection, intervention, and prognosis for AKI. They had a significant effect on enhancing monitoring, the early initiation of treatment measures, and improved patient counselling. Those markers are proteins released from the kidney in serum during injury and others filtered by them in the urine which reflect the glomerular filtration more accurately and offer several theoretical advantages over SCr. Concentrations of those biomarkers increase in the plasma and urine within a few hours from the injury. Some are more specific, while others are more sensitive.

Some markers **(A)** are still **under investigation** for renal damage (e.g., NGAL, KIM 1, IL-18, NAG, and GST) and function (cystatin C).

Others **(B)** have recently been **approved by the FDA** (TIMP-2 and IGFBP-7) and are now used as an assessment of the risk of moderate or severe AKI within 12 hours of cardiac surgery.

(A) and **(B)** will be explained later in the next part of the review.

(A) Novel biomarkers under investigation

Neutrophil gelatinase-associated lipocalin (NGAL)

NGAL is a protein found naturally in tissue and circulates at minimal concentrations in the blood plasma. It is released from neutrophils into the plasma at higher levels in response to inflammation and comprises a critical component of innate immunity to bacterial infection.

Studies prove that NGAL is one of the most up-regulated proteins in the kidney very early after acute injury[52,53], is a highly induced protein in the kidney after ischaemic or nephrotoxic AKI and reflects tubular injuries in animal models[54].

Haase et al.[55] validated these benefits for NGAL when they illustrated the plasma NGAL-positive but creatinine-negative AKI and correlated that with longer length hospital and ICU stays, and a higher risk of dialysis or death.

However, other studies proved that plasma NGAL was not a useful predictor of AKI within the first six hours after cardiac surgery, instead of reflecting systemic inflammation more than the extent of a renal injury inflicted[56]. However, urinary NGAL was shown to be a highly sensitive and specific predictor of cardiac surgery-associated acute kidney injury (PCS-AKI)[52]. It was demonstrated to be an early biomarker of AKI after CPB, increasing 25-fold within two hours and declining six hours after surgery[52]. This promoted the use of urine

NGAL as a predictive indicator of subclinical PCS-AKI; it was also superior to conventional markers and plasma NGAL in the early diagnosis of PCS-AKI[57].

Very recently, in a cohort of high-risk adult patients undergoing cardiac surgery, there was an increase in postoperative AKI and 1-year mortality from the first to the third tertile of preoperative serum NGAL. Those in the last tertile (>220ng/L) had an estimated two-fold increased risk of cardiovascular and all-cause mortality at one-year[58].

It is certain that once urinary and plasma NGAL are introduced into more clinical practice and observational studies, this novel biomarker test will outline their role in our investigational and diagnostic field more clearly. Meanwhile, it has excellent potential to be used in intervention trials as a way of enriching the study population for the randomisation of putative interventions.

Kidney injury molecule-1 (KIM-1)

KIM-1 is a type 1 transmembrane glycoprotein that is usually minimally expressed in the proximal tubule of the kidney. In cases of ischaemic or nephrotoxic AKI, it is markedly up-regulated in proximal renal tubular cells[59-61]. Although fewer cardiac surgery studies on KIM-1 have been published, several recent studies reported the sensitivity and increase in plasma KIM-1 levels within two days for non-cardiac surgical patients who would develop AKI; correspondingly, KIM-1 was suggested as a predictor biomarker for early AKI detection[62]. In one study that involved 103 adult patients who underwent an operation with cardiopulmonary bypass, KIM-1 levels increased markedly at both 2 and 24 hours postoperatively in patients who afterwards developed AKI[63]. In a recent review, KIM-1 was proved to be useful as a diagnostic assay for AKI after cardiac surgery but was less sensitive in predicting postoperative mortality or the need for renal replacement therapy (dialysis)[64].

Interleukin-18

IL-18 is a pro-inflammatory cytokine and possible mediator of tubular injury. It was shown to be significantly increased in a mouse model of ischaemic acute renal failure[66]. In humans, IL-18 was found in the urine of patients with established AKI when compared to urine from patients with urinary tract infection, chronic kidney disease (CKD), so-called pre-renal azotaemia and healthy controls[66]. A prospective observational study by Parikh et al. demonstrated that an increase in IL-18 (and NGAL) in the postoperative period after cardiac surgery was predictive of AKI in paediatric patients[67]. In a nested case-control study within the Acute Respiratory Distress Syndrome (ARDS) Network, IL-18 was demonstrated to

precede clinical evidence of AKI by an estimated 24-48 hours[68]. The performance of urine IL-18, as shown by the area under the receiver operating characteristics curve, for diagnosis of AKI at 4, 12, and 24 h after CPB was 61%, 75%, and 73%, respectively[67].

(B) Novel markers recently approved by the US Food and Drug Administration

-Tissue inhibitor of metalloproteinase-2 (TIMP-2)

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

Tissue inhibitor of metalloproteinase-2 (TIMP-2) and insulin-like growth factor binding protein 7 (IGFBP7) are cell-cycle arrest proteins. They are released in the urine during events of tubular injury due to toxin exposure, hypoxia, and inflammation[69].

Recently, the FDA has approved the measurement of those two biomarkers to aid in the risk assessment of moderate or severe AKI within 12 hours of cardiac surgery. Clinical use of these markers has been marketed as Nephrocheck®.

Recent studies reported the following:

The combination of urinary TIMP-2 and IGFBP7 4 hours after postoperative ICU admission identifies patients at risk of developing AKI, not just stage 2–3 AKI, following cardiac surgery[16].

Urinary [TIMP-2] × [IGFBP7] tests sufficiently detect patients with a risk of AKI after major high-risk surgery. Due to its rapid responsiveness, it extends the time frame for intervention to prevent the development of AKI[70].

The findings indicate that urinary [TIMP-2] [IGFBP7] may be a reliable biomarker for the early detection of AKI. However, given the significant heterogeneity among the included studies, clinicians should be aware of the utility and limitations of this biomarker in clinical practice. Additional high-quality studies examining a larger sample of patients are required[71].

1.2 Background about aortic diseases and aortic surgery

1.2.1 Anatomy of the Aorta [72] (Figure 3):

The anatomy of the ascending aorta, aortic root, and aortic arch:

The aortic root: is where the ascending aorta begins at the level of the aortic valve and the origins of the coronary arteries from the aortic root (sinuses of Valsalva)

The ascending aorta: is anatomically defined as the part of the aorta between the aortic valve and the origin of the brachiocephalic trunk.

The aortic arch: originates from the ascending aorta and continues as the descending aorta. It is anatomically defined as the part of the aorta between the brachiocephalic trunk until directly after the origin of the left subclavian artery, and gives rise to 3 main branches that supply the head, neck, and arms:

- Brachiocephalic trunk
- Left common carotid artery
- Left subclavian artery

The aortic arch continues as the descending aorta until the diaphragm then continues as the abdominal aorta until the 4th lumbar vertebrae, where the aorta is subdivided into right and left iliac arteries. The aortic root, ascending aorta, aortic arch and descending aorta together make up what is known as the thoracic aorta.

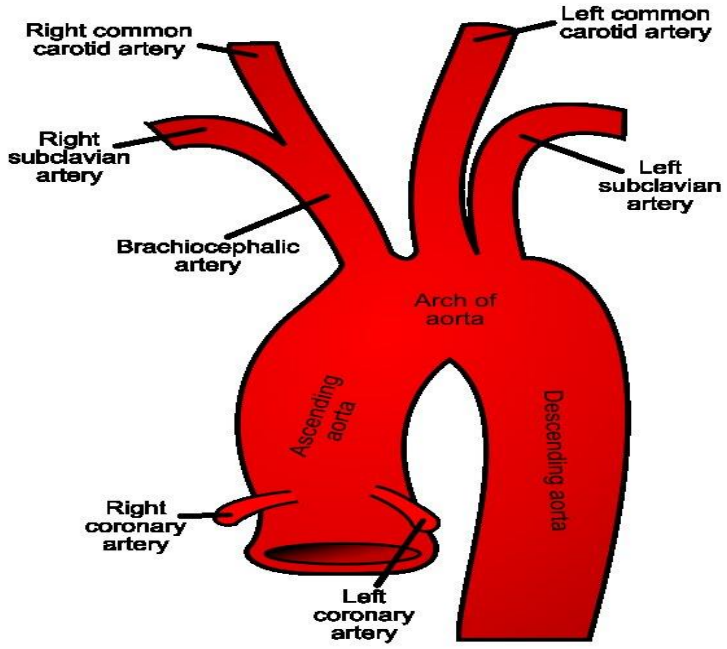

Figure 3; Anatomy of the Aorta

NORMAL SIZES OF THE AORTA

A healthy aorta is widest at the aortic root and narrows gradually until it divides into the pelvic arteries. Standard aortic diameter is <40mm. The aorta is typically larger in men than in women. The aorta transports about 200 million litres of blood over the course of an average lifespan and is continuously subjected to arterial blood pressure. To endure this constant strain, the aorta, like all organs, undergoes a continual adaptation and repair process.

THE HISTOLOGICAL OVERVIEW OF THE AORTIC WALL (Figure 4):

The aorta is an elastic artery formed of three layers.

The innermost layer is the tunica intima, followed by the tunica media, with the outermost being the tunica adventitia.

The intima is composed of the so-called endothelium, a single cohesive layer of flat cells. It controls, among other things, oxygen and gas exchanges between the blood and the vessel wall. Injury to the endothelium forms blood clots (thrombus). An embolism occurs when a thrombus is swept up into the bloodstream.

The media consists primarily of ring-shaped smooth muscle cells. They regulate the vessel width and ensure a steady blood flow through their elasticity.

The adventitia is a mesh of connective tissue fibres that anchor the vessel into its surroundings. The so-called **"vasa vasorum"** are tiny blood vessels that run through the adventitia to supply it with blood.

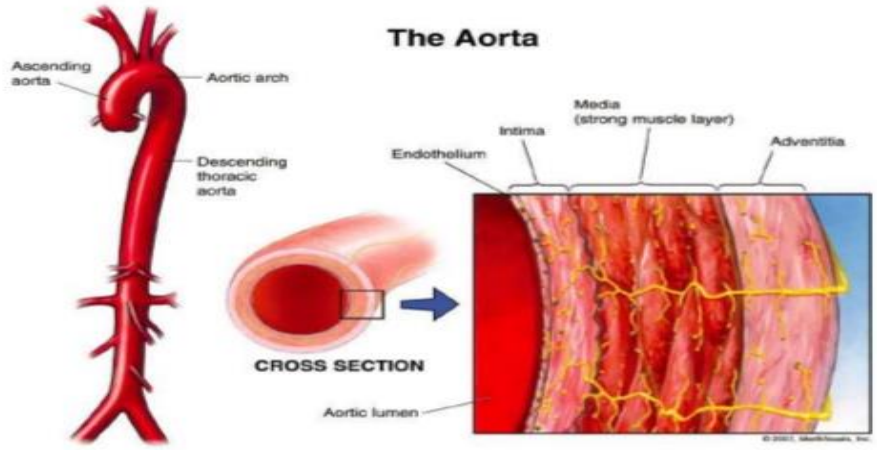

Figure 4; The histological overview of the aortic wall

1.2.2 Diseases of the ascending aorta and aortic arch with the surgical indication for each of them[72]

Aortic diseases can be divided into chronic aortic diseases and acute aortic syndromes. Chronic aortic diseases can trigger an acute event. Acute aortic syndromes typically lead to chronic aortic diseases.

Table 4; An overview of aortic diseases and the possible underlying causes

Chronic aortic diseases	Acute aortic diseases	Possible Causes

• **Aneurysm**
 	
• **Chronic dissection**
	• Aortic rupture
	  • Open rupture
	  • Closed rupture
	• PAU (aortic ulcer)
	• Aortic dissection
	  • Type A
	  o with malperfusion
	  o without malperfusion
	  • Type B ***(only in descending or abdominal aorta, not in A. Ar. or as.A)***
	  o with malperfusion
	  o without malperfusion
		• Atherosclerosis
		• Congenital connective tissue diseases (i.e. Marfan syndrome)
		• Inflammation of the aorta
		  – Infection
		  – Autoimmune diseases
		• Previous aortic dissection (chronic dissection)

1.2.2.1 Aortic aneurysms

An aortic aneurysm is the enlargement of the aorta to more than 1.5-times its standard size. As a general rule, this is a diameter of about 40 mm.

Thoracic aortic aneurysm risk factors include:

- **Age.** Thoracic aortic aneurysms occur most often in people aged 65 and older.
- **Tobacco use.** Tobacco use is a strong risk factor for the development of an aortic aneurysm.
- **High blood pressure.** Increased blood pressure damages the blood vessels in the body, raising the chance of developing an aneurysm.
- **The build-up of plaques in the arteries (atherosclerosis).** The build-up of fat, calcification and other substances that can damage the lining of a blood vessel (atherosclerosis) increases your risk of an aneurysm. This is a more common risk in older people.
- **Family history.** People who have a family history of aortic aneurysm are at increased risk of having one. People who have a family history of aneurysms tend to develop aneurysms

at a younger age and are at a higher risk of rupture. This is a primary risk factor for younger people.

- **Marfan syndrome and related disorders.** People who have Marfan syndrome or related disorders such as Loeys-Dietz syndrome or Ehlers-Danlos syndrome have a significantly higher risk of thoracic aortic aneurysm.

The clinical picture of ascending and aortic arch aneurysm:

Very often, neither ascending nor aortic arch aneurysms cause any complications or symptoms until a certain size is reached; they are both often detected by chance during routine investigations like echocardiography (ultrasound of the heart) and chest x-ray.

In the case of **ascending aortic aneurysm,** symptoms start to appear when the diameter of an aneurysm is so big that it causes dilatation of the aortic valve ring or the aortic root which leads to the symptoms of aortic valve insufficiency (e.g. reduced stamina, heart failure). Sometimes, those are the first symptoms for the patient. Other symptoms such as chronic persistent chest pain or upper body venous congestion can occur as a result of compression of the superior vena cava.

In the case of **aortic arch aneurysms**, these very often remain asymptomatic until rupture. Compression of the trachea or the main bronchus can lead to stridor or dyspnoea, along with compression of the oesophagus, which leads to swallowing difficulties. Occasionally, with the continued expansion of an aneurysm, compression of the left recurrent laryngeal nerve may cause hoarseness of the patient’s voice.

In general, an acute increase or severe persistent chest pain, "aortic pain", is a sign of a pending rupture (bursting) or dissection (tearing) of the aorta and requires emergency treatment. Some patients experience "aortic pain" connected to rapid enlargement of the aorta’s diameter. An unnoticed aortic aneurysm usually makes itself known through a sudden painful event. This event is known as **acute aortic syndrome**.

Irrespective of the location of an aneurysm, 85% of patients have arterial hypertension.

Indications of surgical interference in ascending and aortic arch aneurysm:

Aneurysms of the ascending aorta or the aortic root:

(1) When the diameter of the ascending aorta aneurysm reaches 55 mm, surgery should be performed

(2) If heart surgery is performed for any other reasons, the ascending aorta should be treated alongside if its diameter has reached 45 mm

There are various diseases, which have a high risk of an aortic complication. In these cases, the aorta should be operated upon earlier.

- patients with connective tissue diseases of the aorta, such as Marfan syndrome[17], without aortic valve replacement (AVR) => aortic diameter threshold diameter of 45 mm
- with aortic valve replacement => aortic diameter threshold of 40 mm

(3) Patients with bicuspid aortic valve[17]

- without aortic valve replacement => aortic diameter threshold diameter of 50 mm
- with aortic valve replacement => aortic diameter threshold of 45 mm

(4) Patients with a strongly positive family history of dissection/rupture/sudden death should receive a surgical replacement of the ascending aorta as soon as the diameter reaches 50mm.

(5) For other particular risk factors such as rapid growth (growth rate ≥1 cm/year), leaking of the aortic valve or with a planned pregnancy, surgery should be performed when the aorta diameter reaches 45 mm.

(6) Symptomatic patients should undergo aneurysm resection, regardless of aneurysm size. Acutely symptomatic patients require an emergency operation.

Aneurysm of the aortic arch

(1) When the diameter of the aorta arch aneurysm reaches 55 mm, surgery should be performed

(2) If an operation on a bordering section of the aorta is planned, the aortic arch can sometimes also be replaced, even if the diameter is smaller than 55mm

(3) Symptomatic patients should undergo aneurysm resection, regardless of aneurysm size.

1.2.2.2 Aortic dissection

An aortic dissection occurs in a weakened area of the aortic wall as cleavage in the aortic wall's three layers. In contrast to an aortic rupture, blood does not flow out of the aortic wall

but instead accumulates between the aortic wall layers, lifting the innermost layer, the intima, away from the aortic wall.

As the dissection advances, a new channel for blood flow is created. This is called a "false lumen". The original vascular channel is called the "true lumen". The "false lumen" usually develops in the direction of the blood flow.

Causes:

(1) **Aortic aneurysm**

(2) **Chronic high blood pressure** may stress the aortic tissue, making it more susceptible to tearing.

(3) Congenital conditions associated with a weakened and enlarged aorta, such as **Marfan syndrome**

(4) **Bicuspid aortic** valve or other rarer conditions related to the weakening of the walls of the blood vessels.

(5) Rarely, aortic dissections are caused by **traumatic injury to the chest** area, such as during motor vehicle accidents.

Aortic dissections are divided into two groups according to the **Stanford Classification**, depending on which part of the aorta is affected:

- **Type A.** Mainly affects the ascending aorta, which may extend more distally to affect other parts of the aorta, including the “arch, descending aorta, the abdominal aorta or even the pelvic and groin vessels”.

This is the more common (about more than 65% of aortic dissections) and more dangerous type; its risk arises from the possible involvement of the **aortic valve, coronary vessels and vessels to the head** which can cause sudden death through rupture and bleeding into the pericardium (**pericardial tamponade**) with subsequent heart failure and heart arrest. As a result of the potential for complications, an untreated "Type A dissection" has a high mortality rate of about 40–60% in the first 48 hours (around 1% per hour).

- **Type B.** This involves a tear in the lower aorta only (descending aorta), which may also extend into the abdomen.

Risk factors for aortic dissection include:

- Uncontrolled high blood pressure (hypertension)
- Hardening of the arteries (atherosclerosis)
- Weakened and bulging artery (pre-existing aortic aneurysm)
- An aortic valve defect (bicuspid aortic valve)
- A narrowing of the aorta at birth (aortic coarctation)

Certain genetic diseases increase the risk of having an aortic dissection, including:

- **Turner's syndrome.** High blood pressure, heart problems and some other health conditions may result from this disorder.
- **Marfan syndrome.** This is a condition in which connective tissue, which supports various structures in the body, is weak. People with this disorder often have a family history of aneurysms of the aorta and other blood vessels or family history of aortic dissections.
- **Other connective tissue disorders.** This includes Ehlers-Danlos syndrome, a group of connective tissue disorders characterised by skin that bruises or tears easily, loose joints and fragile blood vessels and Loeys-Dietz syndrome, with twisted arteries, especially in the neck.
- **Inflammatory or infectious conditions.** These may include giant cell arteritis, which is an inflammation of the arteries, and syphilis, a sexually transmitted infection.

Clinical picture

An acute aortic dissection is expressed in a sudden event of characteristically sudden (impending death) chest pain; as the dissection progresses distally, the pain location also migrates from the anterior chest to the throat, neck and subsequently between the scapulae.

Aortic dissection can block the vessels originating from the aorta, causing a heart attack, stroke, paraplegia, acute malperfusion syndrome (disturbance in the blood supply) of the arms or legs, or insufficient blood supply to the abdominal organs.

A sudden discrepancy in the blood pressure of the extremities in association with painful event points towards an aortic dissection. After an aortic dissection, the blood is contained only by the thin outer wall layer (adventitia). A complete aortic rupture becomes a possible complication.

A well-known history of hypertension, a well-known thoracic aortic aneurysm, or a diagnosis of Marfan syndrome should always be an alarm signal for a dissection.

Indication for surgery

Immediately on suspicion of an aortic dissection, aggressive drug therapy should be started immediately with the goal of setting pain control and blood pressure reduction. Preferably, intravenous beta-blockers are used, since they reduce aortic wall stress and thus reduce the possibility of rupture.

(1) Acute type A dissection and intramural haematoma of the ascending aorta should be considered surgical emergencies.

(2) All clinical symptoms of malperfusion of the myocardium, brain, spinal cord, visceral organs, and extremities are considered indicative of an emergency procedure.

(3) The aortic arch then has to be additionally surgically treated when intimal dissections are arched or when the dissection is on the floor of a pre-existing fusiform aneurysm.

(4) In cases of chronic dissection in the ascending aorta, immediate intervention for rupture and severe aortic valve regurgitation is indicated.

(5) Usually, patients with chronic type A dissection have a stable condition with a dilated ascending aorta and mild to severe aortic insufficiency. The risk of a rupture always exists, and the elective replacement of the aorta is indicated by a diameter of >5 cm. On the other hand, in patients with Marfan syndrome, elective replacement with a diameter of >4 cm should be considered.

1.3 Aims and Objective

The overall objective of this study was to evaluate the incidence surrounding acute renal failure after ascending and aortic arch replacement surgery that required moderate hypothermic circulatory arrest and cardiopulmonary bypass.

More specifically, we wanted to:

1.3.1 To determine the predictors of PCS-AKI from the different surgical techniques used in ascending aorta replacement vascular surgery as hypothermic circulatory arrest time (HCAT), CPB time and blood transfusion.

1.3.2 Investigate the incidence of AKI after ascending aorta and aortic arch replacement surgery with moderate HCA and CPB.

1.3.3 Evaluate the outcome of PCS-AKI by measuring the mortality and morbidity rate of the critically ill patients who underwent those surgeries

1.3.4 Evaluate the known renal replacement therapy prediction scores of the PCS and the other risk and predisposing factors of PCS-AKI not mentioned in those prediction scores. We measured those variant parameters and the risk factors involved in those prediction scores and correlated them with serial perioperative kidney function measurements by using the correct statistical evaluation for them. This will subsequently lead us to decrease the postoperative AKI by avoiding those risk factors; and when avoidance is not available, then by early therapeutic intervention.

2. Materials and Methods

2.1 Literature

Before starting the analyses, the previous literature was studied. Articles were found using PubMed and the following keywords in the different search engines: postoperative acute kidney injury, post-cardiac surgery AKI, hypothermic circulatory arrest, cardiopulmonary bypass, RIFLE, AKIN, KDIGO and ascending aorta replacement surgery.

References in the identified articles were also used. These articles were used in the introduction and discussion section of this thesis. An overview of the articles can be found under references. The references were compiled using “Endnote”.

2.2 Study population & design

General-patient population

In the presented retrospective cohort study, the database for Kiel University clinic was searched for patients with aortic arch and aortic ascending replacement surgeries with HCA and CPB techniques. Between January 1, 2001, and December 31, 2017. 1359 patients were found in our database with different causes for those operations such as ascending aortic and aortic arch -aneurysm, -dissections or -calcifications, who were operated upon. The patient records were abstracted, and the data were entered into a database and then revised for accuracy by randomly checking chart data with data on the computer.

Preoperative coexisting medical problems and variables, as well as operative technique variables and postoperative and follow-up complications, were recorded; all preoperative, operative and postoperative variables and data are presented in tables 5,6,7 and 8 in the result section.

Acute renal failure was measured based on the KDIGO criteria (Figure 1).

2.3 Inclusive and Exclusive Criteria

Inclusion criteria were that the patient underwent an ascending aorta replacement surgery, an aortic arch replacement surgery or both together, regardless of other additional operations performed simultaneously, with a minimum age of 18 years.

No general **exclusion criterion** existed, except for missing data.

2.4 Clinical Data collection and Ethical considerations

The basis of the analysis was the patient records of uni-clinic Kiel. These include the corresponding preclinical emergency physician protocol including the patient's first contact and any resuscitation protocol before arriving at the hospital as well as all the in-patient documentation in the clinic database.

The entry was made retrospectively by accessing the patients' archived files in the hospital's electronic database. For this purpose, pre-clinic emergency physician protocols, medical history sheets, operative and anaesthesia protocols and follow-up documentation in intensive care and intermediate care units, as well as normal station, serial laboratory and blood gas analysis results during the hospital stay, consultation findings, and medical reports were used and evaluated.

Seven-day and thirty-day mortality-rate follow-up was performed for all patients. House doctors (Hausärzte) were called for all patients who were released from the hospital before 30 days of their operation date, to ask whether they were still alive or not; in cases of death within the first 30 postoperative days after release from the hospital, the time and cause of death was recorded.

The patient data collected were subdivided into three main categories, pre-, intra- and post-operative (as mentioned before) using Microsoft Excel®, and included all study-related information. The patient registration and evaluation took place exclusively in the pseudonymised form using a sequential number. The collected data remained in a computer file in the hospital where it was only possible for the project team to access.

This retrospective study was conducted by and after receiving the positive opinion of the Ethics Committee of Kiel University as well as the hospital's Leaders.

2.5 Statistical analysis

All Statistical analyses were performed by ANALYSE-IT®, which is a statistical analysis add-on for Microsoft Excel. Analyse-it is the successor to Astute, developed in 1992 for Excel 4, and the first statistical analysis add-on for Microsoft Excel. The data collection took place

with Microsoft Excel, and the quantitative variables values are presented as the mean ± Standard deviation.

- **Paired t-test**

The paired t-test was used to compare related values (values for each patient were paired together) with each other. A probability level (p-value) of less than 0.05 has been considered to indicate statistical significance.

- **Spearman's correlations coefficient**

The correlation coefficient (Spearman's rank correlation) should generally be at least 0.3 to show a relationship; values up to 0.2 are considered as "very low correlation", values up to 0.5 as "low correlation", values up to 0.7 as "medium", up to 0.9 as "high" and >0.9 as "very high correlation"; this also applies to negative correlations.

2.6 Operation technique[72]

Short introduction

Medial sternotomy provides access to the ascending aorta or aortic arch

The surgical repair of an aneurysm and dissection of the aorta involves replacing the affected aortic segment with a vascular prosthesis, usually associated with an aortic valve replacement. The procedure is performed using the heart-lung machine and systemic hypothermia (24-28°C).

Operations on the aortic arch require the use of deeper hypothermic cardiac arrest (18-24°C) primarily to protect the brain. As additional protective measures, both antegrade (directly via right and left internal carotid artery) and retrograde perfusion (indirectly via superior vena cava) may be used.

2.6.1 Technical requirements for surgery

Circulatory arrest

Because of the location of the aortic arch and the vessels that originate here, it cannot be cross-clamped for replacement. For operations of the aortic arch, the heart-lung machine must be **turned off** for a short amount of time. Circulatory arrest then ensues. After removing the

aneurysms and suturing in the vascular prosthesis, circulation is again started via the heart-lung machine.

To avoid damage to the organs due to a lack of oxygen, various techniques are used to protect the organs (see the following techniques).

Hypothermia

Lowering the body temperature (hypothermia) reduces the cellular need for energy and, as a result, for oxygen. Cooling the body can, therefore, be used as a technique to protect organs from a lack of oxygen. This has been used since the 1960s in interventions in the aorta, in particular, to **protect the brain** (so-called **neuroprotection**), the least tolerant organ for oxygen shortage.

Cooling the **entire body** to temperatures **less than 20°C** is achieved indirectly with the heart-lung machine, which cools the circulating blood. After completing the aortic replacement under circulatory arrest and hypothermia, the body is again warmed with the heart-lung machine.

Cardiopulmonary bypass through the Heart-lung machine

Operations on the ascending aorta and aortic arch are carried out with a heart-lung machine which takes over the patient's **blood circulation** and the supply of oxygen. It is connected to the heart's right atrium and the aorta. Blood flows into the heart-lung machine, where it is enriched with oxygen, cooled or warmed and pumped back into the patient's aorta. The lungs and heart are thereby circumvented. In this way, operations on **"open", non-beating hearts** can be carried out.

The blood is thinned with the help of heparin so that it does not clot in the tubes of the heart-lung machine. In aortic surgery using a heart-lung machine, the surgeon tries to seal off the segment being replaced with clamps (cross-clamping). After suturing in a vascular prosthesis, the blood flow is again released into the treated segment.

Selective antegrade or retrograde cerebral perfusion

To support neuroprotection, the technique of selective antegrade cerebral perfusion was developed.

This means that **only the brain vessels** (directly via only right and left internal carotid artery (=selective) in the normal direction of the blood flow (=antegrade) are **supplied** (=perfusion)

with blood from the heart-lung machine during circulatory arrest, and retrograde perfusion (indirectly via superior vena cava) may be used.
In this way, a continual influx of nutrients and oxygen is maintained and an extension of the period of "safe circulatory arrest" is achieved. Because the abdominal organs react with less sensitivity than the brain to circulatory arrest, the **lower body temperature** under circulatory arrest can be raised (**25-28°C**) when cerebral perfusion is used.

Aortic prostheses

Aortic prostheses are made out of **polyester**. This is a high-quality synthetic fibre that is woven into tubular-shaped vascular prostheses. The prosthesis is designed with small pleats to provide flexibility to fit the patient's anatomy. Because the woven material is not leak proof, it is sealed with **collagen** or **gelatine**.
There are many sizes and variations of aortic prostheses. The simplest prostheses are straight grafts. Complex prostheses have side branches for attaching vessels, a portal for the heart-lung machine or a section with a stent graft (so-called hybrid prostheses).
The surgical team in Hanover, Germany, in collaboration with Vascutek, a producer of medical devices, has already developed an aortic prosthesis with all of these characteristics (Thoraflex Hybrid prosthesis, see aortic arch replacement).
Composite aortic prostheses are still produced **by hand**. Sometimes, several thousand stitches are necessary to suture an aortic prosthesis together. Production can take up to eight weeks.

2.6.2 Different Operations Types[72]

Aortic valve reconstruction "aortic root reconstruction"

By the end of the 1950s, techniques to reconstruct the aortic valve were already in use. The advantage over valve replacement using mechanical valves lies in the lack of a need for a long-term blood thinner (e.g. with warfarin) and the reduced vulnerability of valve infection. An aortic valve reconstruction is only possible when the valve cusps show no severe structural changes (e.g. calcification).
Aortic valve reconstruction is suited to treating enlargements of the aortic root that are associated with leaking of the aortic valve. The most commonly applied technique for aortic valve reconstruction is the so-called David procedure or aortic valve re-implantation. It was first introduced in 1992 by Prof Tirone David.

The entire ascending aorta is removed, apart from a small rim above the aortic valve. The coronary arteries are detached from the aorta as so-called buttons. Below the aortic valve, stabilising sutures are subsequently sewn through the aortic wall from inside to outside. With these sutures, an aortic prosthesis is pulled down over the outside of the aortic valve and secured deep into the aortic root. The aortic valve is now sutured into the aortic prosthesis. Finally, the two coronary arteries are reimplanted.

For several decades various techniques for aortic valve reconstruction have been employed. In 1982, a technique was described by Sir Magdy Yacoub in which the ascending aorta is removed to just above the aortic valve and replaced with an aortic prosthesis that is cut to the appropriate size.

This so-called aortic valve remodelling technique does not involve a root stabilisation procedure. To prevent a later enlargement in the root, this technique can be combined with various stabilising techniques.

Aortic valve replacement

Aortic valve replacement is necessary when structural changes in the valve (mostly calcification) lead to a severe narrowing (stenosis) or leaking (insufficiency) of the aortic valve. In many aortic operations of the ascending aorta, the aortic valve is also affected and must be replaced when it cannot be reconstructed.

The original, no longer functional heart valve is cut out of the aortic valve annulus (a fibrous ring). The calcified materials in the aortic valve annulus are removed with special forceps. The annulus is then measured, and an appropriate prosthetic valve is chosen. Following this, sutures are placed in the aortic valve annulus. These threads are then sewn through the sewing ring of the prosthetic valve. The prosthetic valve is guided down into the annulus. The sutures are tied off, and the prosthetic valve is checked for correct positioning.

Mechanical prostheses

Mechanical valves are heart valve prostheses made out of synthetic materials. Most consist of a valve annulus in which two leaflets or cusps are attached to the inside. On the outside, a sewing ring is affixed.

Mechanical valve prostheses have the advantage of being virtually unlimited durability. The disadvantage of this prosthesis is that the foreign surface of the prosthetic valve activates blood clotting. This drives clot formation on the prosthetic valve when coagulation is not

inhibited. This also leads to a risk of stroke. Therefore, patients who have a mechanical heart valve must take blood-thinning medication for the rest of their lives.
Most commonly, warfarin is given. A side effect is that warfarin can cause unwanted bleeding (e.g. gastrointestinal haemorrhage). Therapy requires the regular measurement of clotting parameters. This happens at intervals of several weeks by a general practitioner or can be performed by the patient with a measurement device.

Bio-prostheses

Biological prosthetic valves consist mostly of bovine pericardial tissue or porcine heart valves that are fixed to a sewing ring.
The main advantage of these prostheses is that they do not activate blood clotting, so the patient only needs to follow a blood-thinning therapy for a short time after surgery (about 2-3 months).
The disadvantage of bioprostheses is that they calcify and degenerate over time. In this way, a new narrowing of the valve or leaking can develop. The valve must be replaced again. The lifespan of biological prosthetic valves is 12-15 years on average.

Replacement of the ascending aorta with aortic root "conduit, Bentall-operation-valved conduit"[(72)]

If the aortic valve, aortic root, and ascending aorta all need to be replaced at once, composite grafts that consist of an aortic prosthesis and a prosthetic aortic valve are used.
So-called valved conduits are either sewn together at the factory or constructed by the surgeon during the operation.

Supra-coronary replacement of the ascending aorta

If only the ascending part of the supra-coronary aorta is affected by an aneurysm or dissection, this can be replaced as a rule with a simple, straight aortic prosthesis (so-called "tube graft").
For this, the ascending aorta is clamped - if possible - before the aortic arch, and during a short period of cardiac arrest, the aorta is wholly excised, both proximally just above the opening of the coronary arteries, and distally. A Dacron tube prosthesis of appropriate size is then anastomosed, first distally with the aorta, and finally by proximal anastomosis. The heart is again perfused with blood and begins to beat.

Partial aortic arch replacement

For many patients who undergo surgery due to an aneurysm of the ascending aorta, a small part of the aortic arch is also replaced under a short period of circulatory arrest. The replacement of the entire aortic arch is not necessary. It is often called "hemi-arch replacement", "partial aortic arch replacement" or more accurately "open anastomosis", because the aortic arch must be briefly opened, without it being completely replaced, for the suturing in of the ascending aortic prosthetic.

For a short period of circulatory arrest, patients must be cooled (24-28°C) to protect the organs. Also, the vessels to the head are sometimes supplied with blood via a special catheter (antegrade cerebral perfusion), in particular when the suturing of the aortic prosthesis is expected to take longer than ten minutes.

Total aortic arch replacement

Because of the anatomical characteristics, replacing the entire aortic arch is one of the most complex interventions in heart surgery.

The three arteries that supply the arms and head with blood begin at the aortic arch. After the aortic arch, the aorta transitions into the descending aorta, which supplies the lower part of the body with blood. The aortic arch can only be opened when the blood flow to these arteries is temporarily stopped. Thus, the operation takes place under circulatory arrest.

After opening the aortic arch during circulatory arrest (18-24°C), each vessel to the head is perfused (so-called selective antegrade cerebral perfusion) with a special catheter to supply the brain with oxygen. Initially, the lower part of the body remains in circulatory arrest. At a later point, it will again be supplied with blood via a prosthetic aortic arch. The circulatory arrest then ends.

The arteries that begin at the aortic arch are sewn into the aortic prosthesis either grouped as a combined "island" or separately.

There are special prostheses with four side arms (three for connecting the vessels and one for the heart-lung machine) available for the latter technique. It is casually called the "**four finger prosthesis**". In order to better suture it into the distal aortic arch (section of the aortic arch closest to the descending aorta), it has a "collar".

If the enlargement extends to the descending part of the aorta, this must usually be treated in a later, second operation via the left side of the chest. This can be facilitated by leaving a part of the prosthetic aortic arch "dangling" freely in the bloodstream in the first operation, which will serve as a starting point for the second operation. This technique is called the "**elephant**

trunk" technique. It was developed in Hanover, Germany by Professor Hans-Georg Borst and first introduced in 1983.

If the elephant trunk part of the prosthetic aortic arch is also equipped with a stent graft, it is called the **"frozen elephant trunk"** technique because the prosthesis no longer "dangles" freely but is fixed or "frozen". Because these prostheses are part "normal" aortic prosthesis and part "stented", they are called **hybrid prostheses**.

If only the beginning of the descending aorta is affected in addition to the aortic arch, a second operation can be skipped by using such hybrid prostheses. The first "**frozen elephant trunk**" prosthesis was developed in Hanover, Germany (Haverich-Chavan prosthesis) and has been continually improved since then. The Thoraflex™ Hybrid prosthesis by Vascutek now exists, which is an aortic arch prosthesis that combines all of the features mentioned above. It is, at the moment, the most complex aortic prosthesis available.

3. Results

3.1 General data:

Demographic and clinical characteristics of the study population (Table 5):

Preoperative coexisting medical problems and variables include sex, age, preoperative comorbidities and cardiopulmonary status.

The mean age of the patients was 66.7±11 years (range 16–88 years). Of these, 903 (66.5%) were male, and 465 (33.5%) were female. Solo acute aneurysm was present in 890 (65.4%) patients, while solo dissection was present in 256 (18.8%), combined acute aneurysm and dissection was present in 117 (8.6%) patients, and calcification in 143 (10.5%); some were overlapping with aneurysm and dissection.

The results are summarised in table 5.

Table 5; Preoperative variables and data

	Total	**Male**	**Female**	**P-value**
No. of patients	1359 (100%)	903 (66.5%)	464 (33.3%)	----
Age, years	66.7±11.1 69.2 (61.0;74.4)	65.8±11.6 68.3 (58.9;74.1)	68.4±9.9 70.2 (64.0;75.6)	**0.002**
Logistic EuroSCORE (%)	14.4 (9.0;25.1)	12.3 (7.4;22.6)	18.4 (11.7;29.2)	**<0.001**
EuroSCORE II (%)	4.12 (2.38;7.13)	3.7 (2.2;6.6)	4.7 (2.8;7.5)	**0.001**
EuroSCORE (%)	9.0 (7.0;11.0)	8 (7;10)	10 (8;11)	**<0.001**
Body mass index, kg/m2	26.5 (24.2;29.4)	26.8 (24.5;29.4)	25.7(23.0;29.1)	**0.001**
Arterial hypertension	687 (75.9%)	442 (73.2%)	245 (81.4%)	**0.006**
Pulmonary hypertension	55 (6.1%)	38 (6.3%)	17 (5.6%)	0.703
Type 1 Diabetes mellitus	1 (0.1%)	0 (0.0%)	1 (0.3%)	0.333
Type 2 Diabetes mellitus	108 (11.9%)	71 (11.7%)	37 (12.2%)	0.732
Oral medication	70 (7.7%)	47 (7.8%)	23 (7.6%)	----
Insulin dependent	28 (3.1%)	19 (3.1%)	9 (3.0%)	----
Dietary treatment	10 (1.1%)	5 (0.8%)	5 (1.7%)	----
Diabetic nephropathy	0 (0.0%)	0 (0.0%)	0 (0.0%)	----
Diabetic neuropathy	3 (0.3%)	3 (0.5%)	0 (0.0%)	0.555
Hyperlipoproteinaemia	367 (40.6%)	253 (41.9%)	114 (38.0%)	0.262
Chronic renal failure	99 (11.0%)	77 (12.8%)	22 (7.3%)	**0.013**
Decompensated renal insufficiency	13 (1.4%)	8 (1.3%)	5 (1.7%)	0.769
Renal replacement therapy	10 (1.1%)	8 (1.3%)	2 (0.7%)	0.510
COPD	104 (11.5%)	64 (10.6%)	40 (13.3%)	0.235
Smoking	176 (19.8%)	118 (19.7%)	58 (19.9%)	0.944
Previous smoking	270 (30.5%)	196 (32.9%)	74 (25.4%)	**0.023**
Coronary heart disease	350 (38.8%)	258 (42.9%)	92 (30.6%)	**<0.001**
One-vessel disease	175 (19.4%)	116 (19.3)	59 (19.6%)	----
Two-vessel disease	63 (7.0%)	46 (7.7%)	17 (5.6%)	----
Three-vessel disease	112 (12.4%)	96 (16.0%)	16 (5.3%)	----
Heart rhythm				
Sinus rhythm	707 (78.1%)	471 (78.0%)	236 (78.4%)	0.884
Atrial fibrillation	163 (18.0%)	110 (18.2%)	53 (17.6%)	0.824

Other	74 (8.2%)	50 (8.3%)	24 (8.0%)	0.869
Pacemaker patient	32 (3.5%)	20 (3.3%)	12 (4.0%)	0.604
Defi patient	5 (0.6%)	3 (0.5%)	2 (0.7%)	0.669
Previous PCI (+/-DES)	84 (9.3%)	66 (10.9%)	18 (6.0%)	**0.016**
Previous thoracic surgery	100 (11.0%)	70 (11.6%)	30 (10.0%)	0.463
Previous CABG	23 (2.5%)	19 (3.2%)	4 (1.3%)	0.101
Peripheral vascular disease	51 (5.6%)	34 (5.6%)	17 (5.6%)	0.991
LVEF (%)	64 (53;70)	62 (51;70)	65 (55;70)	**0.010**
LVEF				0.118
Good (≥55%)	634 (74.2%)	408 (72.0%)	226 (78.7%)	----
Slightly impaired (45-54%)	115 (13.5%)	81 (14.3%)	34 (11.8%)	----
Moderately impaired (30-44%)	82 (9.6%)	59 (10.4%)	23 (8.0%)	----
Severely impaired (<30%)	23 (2.7%)	19 (3.4%)	4 (1.4%)	----
Diagnostic imaging				
Computed tomography	506 (56.0%)	326 (54.1%)	180 (59.8%)	0.101
Coronary angiography	861 (95.1%)	578 (95.7%)	283 (94.0%)	0.270
Magnetic resonance imaging	33 (3.6%)	22 (3.6%)	11 (3.7%)	0.993
Marfan syndrome	9 (1.0%)	7 (1.2%)	2 (0.7%)	0.726
Aortic aneurysm	823 (90.9%)	552 (91.4%)	271 (90.0%)	0.503
Diameter of aneurysm, mm	52 (50;57)	52 (50;55)	53 (50;60)	**0.004**
Calcific aortic disease	113 (12.5%)	74 (12.3%)	39 (13.0%)	0.762
Bicuspid aortic valve	104 (23.5%)	85 (28.1%)	19 (13.5%)	**0.001**
Aortic valve vitium				**0.042**
Aortic valve stenosis	145 (16.9%)	108 (19.0%)	37 (12.8%)	----
Aortic valve insufficiency	329 (38.3%)	203 (35.7%)	126 (43.6%)	----
Neurological deficits	123 (13.6%)	73 (12.1%)	50 (16.6%)	0.063
Clinical presentation				
Acute myocardial infarction (48h)	10 (1.1%)	8 (1.3%)	2 (0.7%)	0.510
Cardiogenic shock	5 (0.6%)	5 (0.8%)	0 (0.0%)	0.176
CPR	6 (0.7%)	5 (0.8%)	1 (0.3%)	0.670
Intubated	7 (0.8%)	2 (0.3%)	5 (1.7%)	**0.044**
Urgency of admission				0.095
Elective	821 (90.9%)	553 (91.9%)	268 (89.0%)	----
Urgent	62 (6.9%)	34 (5.6%)	28 (9.3%)	----
Emergency	20 (2.2%)	15 (2.5%)	5 (1.7%)	----
Preoperative status				
Stable	892 (98.6%)	596 (98.7%)	296 (98.3%)	----
Stable with low dose catecholamine	11 (1.2%)	6 (1.0%)	5 (1.7%)	----
Stable with high dose catecholamine	2 (0.2%)	2 (0.3%)	0 (0.0%)	----

Preoperative medication (Table 6):

The preoperative cardiovascular medicines that were used by each of the patients before the surgery. The most three used drugs were beta-blocker, ACEI and acetylsalicylic acid with a percentage of 56.2%, 44.2% and 39.3%, respectively.

The results are summarised in table 6.

Table 6; Preoperative medication

	Total	**Male**	**Female**	**P-value**
ACE inhibitor	376 (44.2%)	264 (46.2%)	112 (40.1%)	0.097
AT1-receptor antagonist	159 (18.7%)	101 (17.7%)	58 (20.8%)	0.271
Aldosterone antagonist	16 (1.9%)	9 (1.6%)	7 (2.5%)	0.346
Acetylsalicylic acid	335 (39.3%)	243 (42.4%)	92 (32.9%)	**0.007**
Clopidogrel	55 (6.4%)	41 (7.2%)	14 (5.0%)	0.229
Ticagrelor	3 (0.4%)	3 (0.5%)	0 (0.0%)	0.555

Prasugrel	3 (0.4%)	1 (0.2%)	2 (0.7%)	0.252
Marcumar	88 (10.3%)	63 (11.0%)	25 (8.9%)	0.347
Beta-Blocker	479 (56.2%)	315 (55.1%)	164 (58.6%)	0.333
Statin	299 (35.3%)	211 (37.2%)	88 (31.5%)	0.105
NSAIDs	28 (3.5%)	18 (3.4%)	10 (3.8%)	0.786

Operative data (Table 7):

Intraoperative variables included operation urgency and time, hypothermic circulatory arrest time (HCAT), cardiopulmonary bypass (CPB) time, aortic cross-clamp time, blood transfusion and surgery type and procedure.

The results are summarised in table 7

Table 7; Intraoperative data

	Total	**Male**	**Female**	**P-value**
Urgency				
Elective	809 (89.5%)	550 (91.1%)	259 (86.3%)	----
Urgent	75 (8.3%)	43 (7.1%)	32 (10.7%)	----
Emergency	19 (2.1%)	10 (1.7%)	9 (3.0%)	----
Length of surgery, min	250 (203;308)	260 (210;320)	225 (195;285)	<**0.001**
Cardiopulmonary bypass time, min	142 (113;187)	150 (118;192)	132 (105;175)	<**0.001**
Cross-clamp time, min	92 (65;125)	97 (73; 129)	83 (56;110)	<**0.001**
Circulatory arrest time, min	14 (12;18)	14 (12;17)	15 (13;19)	**0.003**
Number of packed red blood cells	2 (0;4)	2 (0;3)	2.5 (2;4)	<**0.001**
Number of fresh frozen plasma	0 (0;0), max 18	0 (0;0), max 18	0 (0;3)	0.115
Number of platelet concentrate	1 (0;1)	1 (0;2)	1 (0;1)	0.871
Surgical procedure				
Ascending aorta	757 (83.6%)	488 (80.8%)	269 (89.4%)	**0.001**
Diameter of ascending aorta prostheses	30 (28;32) mm	30 (28;32) mm	30 (28;32) mm	0.075
Partial arch replacement	203 (22.4%)	137 (22.7%)	66 (21.9%)	0.797
Total arch replacement	29 (3.2%)	19 (3.1%)	10 (3.3%)	0.880
Conduit/Bentall Operation	149 (16.5%)	113 (18.7%)	36 (12.0%)	**0.010**
David operation	63 (7.0%)	38 (6.3%)	25 (8.3%)	0.262
Elephant-trunk	9 (1.0%)	6 (1.0%)	3 (1.0%)	1.000
CABG	222 (24.6%)	174 (28.8%)	48 (16.0%)	<**0.001**
Aortic valve replacement	462 (51.0%)	325 (53.8%)	137 (45.5%)	**0.019**
Number of distal anastomosis	0 (0;1)	0 (0;2)	0 (0;1)	<**0.001**
Number of arterial grafts	0 (0;1)	0 (0;1)	0 (0;0)	<**0.001**
Mitral valve reconstruction /replacement	27 (3.0%)	17 (2.8%)	10 (3.3%)	0.672
Tricuspid valve reconstruction / replacement	1 (0.1%)	1 (0.2%)	0 (0.0%)	1.000
PFO-closure	46 (5.1%)	38 (6.3%)	8 (2.7%)	**0.019**
MAZE procedure	26 (2.9%)	18 (3.0%)	8 (2.7%)	0.784
Carotid	10 (1.1%)	8 (1.3%)	2 (0.7%)	0.510
TEVAR(EVAR)	2 (0.2%)	0 (0.0%)	2 (0.7%)	0.110
Arterial cannulation				
Femoral artery	10 (1.2%)	9 (1.6%)	1 (0.4%)	----
Ascending aorta	680 (80.2%)	455 (80.4%)	224 (79.7%)	----
Aortic arch	107 (12.6%)	71 (12.5%)	36 (12.8%)	----
Apex	2 (0.2%)	2 (0.4%)	0 (0.0%)	----
Pulmonary vein	48 (5.7%)	28 (4.9%)	20 (7.1%)	----
Venous cannulation				
Right atrium	786 (92.8%)	520 (91.7%)	266 (95.0%)	----
Bicaval	55 (6.5%)	42 (7.4%)	13 (4.6%)	----
Femoral vein	5 (0.6%)	4 (0.7%)	1 (0.4%)	----

Postoperative data and outcomes (Table 8):

Postoperative variables including all possible complication, ICU time, Seven-day and thirty-day mortality-rate follow-up was performed for all patients as well as the cause of death for each of them.

The results are summarised in table 8.

Table 8; postoperative variables and data

	Total	**Male**	**Female**	**P-value**
AKI KDIGO	48 (5.3%)	30 (5.0%)	18 (6.0%)	0.518
AKI KDIGO stages				
1	1 (2.1%)	0 (0.0%)	1 (5.6%)	----
2	0 (0.0%)	0 (0.0%)	0 (0.0%)	----
3	47 (97.9%)	30 (100.0%)	17 (94.4%)	----
New –onset of Hemodialysis	48 (5.3%)	30 (5.0%)	18 (6.0%)	0.518
Temporary dialysis, d	5.0 (2.0;15.0)	5.0 (1.8;14.5)	5.0 (2;16)	0.686
48 h-drainage loss, ml	600 (400;950)	600 (400;950)	550 (330;1000)	**0.011**
24 h-Number of packed red blood cells,	0 (0;2)	0 (0;2)	0 (0;2)	0.409
24 h-Number of fresh frozen plasma	0 (0;1)	0 (0;1)	0 (0;2)	0.595
24 h-Number of platelet concentrate	0 (0;0), max 16	0 (0;0), max. 16	0 (0;0), max 9	0.766
Total number of packed red blood cells,	1 (0;2)	0 (0;2)	1 (0;3)	0.148
Total number of fresh frozen plasma	0 (0;2)	0 (0;2)	0 (0;2)	0.581
Total number of platelet concentrate	0 (0;0), max. 18	0 (0;0), max. 16	0(0;0),max. 18	0.240
Postoperative status				
Stable	325 (36.0%)	221 (36.7%)	104 (34.8%)	----
Stable with low dose catecholamine	533 (59.1%)	353 (58.5%)	180 (60.2%)	----
Stable with high dose catecholamine	33 (3.7%)	23 (3.8%)	10 (3.3%)	----
IABP/ECLS	10 (1.1%)	6 (1.0%)	4 (1.3%)	----
Reintubation	76 (8.4%)	54 (9.0%)	22 (7.3%)	0.408
Tracheotomy	69 (7.6%)	50 (8.3%)	19 (6.3%)	0.300
Re-admission to the ICU	53 (5.9%)	33 (5.5%)	20 (6.6%)	0.480
Postoperative delirium	112 (12.4%)	90 (14.9%)	22 (7.3%)	0.**001**
Postoperative myocardial Infarction	3 (0.3%)	2 (0.3%)	1 (0.3%)	1.000
TIA/Stroke,… (CT-proofed)	52 (5.7%)	42 (7.0%)	10 (3.3%)	**0.027**
Electrical cardioversion	57 (6.3%)	42 (7.0%)	15 (5.0%)	0.248
CPR	26 (2.9%)	14 (2.3%)	12 (4.0%)	0.157
Bronchomulmonary infection	58 (6.4%)	46 (7.6%)	12 (4.0%)	0.**036**
Bacteriaemia/sepsis	31 (3.4%)	23 (3.8%)	8 (2.7%)	0.370
Rethoracotomy	59 (6.5%)	34 (5.6%)	25 (8.3%)	0.123
Sternal wound infection/VAC revision	12 (1.3%)	8 (1.3%)	4 (1.3%)	1.000
Sinus rhythm	697 (78.0%)	467 (78.4%)	230 (77.2%)	0.690
Atrial fibrillation	140 (15.7%)	90 (15.1%)	50 (16.8%)	0.515
Other Rhythm	47 (5.3%)	32 (5.4%)	15 (5.0%)	0.832
Pacemaker patient	59 (6.5%)	42 (7.0%)	17 (5.7%)	0.457
Ventilation time, h	17 (12;31)	17 (12;30)	18 (13;31)	0.109
ICU time, d	2 (1;4)	2 (1;4)	2 (1;4)	0.905
Postoperative days	9 (7;13)	9 (7;13)	9 (7;13)	0.750
7 d-Mortality	20 (2.3%)	12 (2.0%)	8 (2.7%)	0.527
30 d-Mortality	36 (4.2%)	22 (3.9%)	14 (4.9%)	0.476
Mortality POD	8 (2.0;19.5)	8.0 (2.5;18.5)	8.0 (2.0;25.0)	0.968
Hospital Mortality	38 (4.3%)	22 (3.7%)	16 (5.4%)	0.239
Cardiac death	13 (32.5%)	7 (30.4%)	6 (35.3%)	----
Cerebral death	6 (15.0%)	6 (26.1%)	0 (0.0%)	----
Sepsis	4 (10.0%)	3 (13.0%)	1 (5.9%)	----
MOF	17 (42.5%)	7 (30.4%)	10 (58.8%)	----

3.2 First aim results:

"To determine the predictors of PCS-AKI from the different surgical techniques used in ascending aorta replacement vascular surgery as moderate HCA, CPB and blood transfusion."

3.2.1 Hypothermic circulatory arrest time (HCAT)

- The patients with PCS-AKI had a mean HCAT of 37.7 (±34.4) min

The minimal HCAT was 9 min, and the maximum HCAT was 276 min (4 hours 36 min)

- Patients without PCS-AKI had a mean HCAT of 22.5 min

The minimal HCAT was 2 min, and the maximum HCAT was 182 min (3 hours 2 min)

To measure the effect of HCAT on the kidney function, we had correlated it with the postoperative serial change in serum creatinine and glomerular filtration rate using Spearman's correlation coefficient and Student's t-test

The Spearman's correlation coefficient and P value between HCAT and (1) serial postoperative creatinine value increase from a preoperative baseline creatinine value; (2) the percent value of these increased from the baseline creatinine value and (3) the percent decrease in GFR from the preoperative baseline GFR at 6-12 and 12-20 hours after surgery and the 1st, 2nd, 3rd and 8th postoperative days (Tables 9, 10 and 11). The highest correlation coefficient for the three renal function deterioration parameters with HCAT was at 12-20 hours after the surgery, with results of 0.268, 0.269 and 0.218, respectively, and the P values were less than 0.0001 for all of them.

The more time that passed from the operation day, the lower the correlation coefficient. The correlation coefficients for the parameter on the 8th postoperative day were 0.052, 0.051 and 0.042, respectively, with a P value less than 0.001 for all of them.

The results are summarised in tables 9, 10 and 11

Table 9; The relation between HCAT and the serial postoperative creatinine value change from the baseline creatinine just before surgery

	Correlation coefficient	**P-value**
Creatinine 6-12 h postoperative	0.212	less than 0.0001
Creatinine 12-20 h postoperative	0.268	less than 0.0001
Creatinine 1. POD	0.236	less than 0.0001
Creatinine 2. POD	0.202	less than 0.0001
Creatinine 3. POD	0.185	0.0216
Creatinine 8. POD (± 1 d)	0.052	less than 0.0001

Table 10; The relation between HCAT and percentage change in creatinine value from the baseline creatinine just before surgery		
	Correlation coefficient	**P-value**
Creatinine 6-12 h postoperative	0.214	less than 0.0001
Creatinine 12-20 h postoperative	0.269	less than 0.0001
Creatinine 1. POD	0.24	less than 0.0001
Creatinine 2. POD	0.214	less than 0.0001
Creatinine 3. POD	0.198	0.1287
Creatinine 8. POD (± 1 d)	0.051	less than 0.0001

Table 11; The relation between HCAT and the percentage decrease in GFR value from the baseline just before surgery		
	Correlation coefficient	**P-value**
GFR 6-12 h postoperative	0.174	less than 0.0001
GFR 12-20 h postoperative	0.218	less than 0.0001
GFR 1. POD	0.215	less than 0.0001
GFR 2. POD	0.182	less than 0.0001
GFR 3. POD	0.151	less than 0.0001
GFR 8. POD (± 1 d)	0.042	less than 0.0001

3.2.2 Cardiopulmonary bypass time:

- Patients with PCS-AKI had a mean CPB time of 195 (± 67.5) min (3 hours 15 min)
- The lowest CPB time was 86 min (1 hour 56 min), while the highest CPB time was 466 min (7 hours 46 min)
- Patients without PCS-AKI had a mean CPB time of 158 (±59.7) min (2 hours 38 min)
- The lowest CPB time was 49 min, while the highest CPB time was 467 min (6 hours 47 min)

To measure the effect of CPB time on kidney function, we correlated CPB time with the postoperative serial change in serum creatinine and glomerular filtration rate using Spearman's correlation coefficient and Student's t-test

The Spearman's correlation coefficient and the P-value between the CPB duration and (1) serial postoperative creatinine value increased from a preoperative baseline creatinine value; (2) the percent value of those increased from the baseline creatinine value and (3) the percent decrease in GFR from the preoperative baseline GFR at 6-12 and 12-20 hours after the surgery, and on the 1st, 2nd, 3rd and 8th postoperative days (Tables 12, 13 and 14). The highest correlation coefficient for the three renal function deterioration parameters with CPB duration was at 6-12 hours after surgery, with results of 0.306, 0.308, and 0.288, respectively; the P values were less than 0.0001 for all of them.

The more time that passed from the operation day, the lower the correlation coefficient. The correlation coefficient for the parameters on the 8th postoperative day were -0.022, -0.014, and -0.014, respectively, with a P value of less than 0.001 for all of them.

The results are summarised in tables 12, 13 and 14

Table 12; The relation between CPB time and the serial postoperative creatinine value change from the baseline creatinine just before the surgery

	Correlation coefficient	**P-value**
Creatinine 6-12 h postoperative	0.306	less than 0.0001
Creatinine 12-20 h postoperative	0.285	less than 0.0001
Creatinine 1. POD	0.271	less than 0.0001
Creatinine 2. POD	0.240	less than 0.0001
Creatinine 3. POD	0.186	less than 0.0001
Creatinine 8. POD (± 1 d)	-0.022	less than 0.0001

Table 13; The relation between CPB time and percentage change in creatinine value from the baseline creatinine just before surgery

	Correlation coefficient	**P-value**
Creatinine 6-12 h postoperative	0.308	less than 0.0001
Creatinine 12-20 h postoperative	0.288	less than 0.0001
Creatinine 1. POD	0.278	less than 0.0001
Creatinine 2. POD	0.265	less than 0.0001
Creatinine 3. POD	0.210	less than 0.0001
Creatinine 8. POD (± 1 d)	-0.014	less than 0.0001

Table 14; Relation between CPB time and the percentage decrease in GFR value from the baseline just before surgery

	Correlation coefficient	**P-value**
GFR 6-12 h postoperative	0.218	less than 0.0001
GFR 12-20 h postoperative	0.198	less than 0.0001
GFR 1. POD	0.202	less than 0.0001
GFR 2. POD	0.167	less than 0.0001
GFR 3. POD	0.133	less than 0.0001
GFR 8. POD (± 1 d)	-0.014	less than 0.0001

3.2.3 Transfusion:

Patients who had PCS-AKI had received a mean erythrocyte concentrate (EC) of 4.73 units. However, the patient who did not have PCS-AKI had received a mean of 2.42 units.

To measure the effect of perioperative blood transfusion on the kidney function, we correlated the number of erythrocyte concentrates transferred perioperatively for each patient with the postoperative serial change in serum creatinine and glomerular filtration rate using Spearman's correlation coefficient and Student’s t-Test

The Spearman's correlation coefficient and P value between the number of EC-units transfused and (1) serial postoperative creatinine values increase from a preoperative baseline creatinine value and (2) serial percent value of the increase from the baseline creatinine value at 6-12 and 12-20 hours after surgery, and on the 1st, 2nd, 3rd and 8th postoperative days (Tables 15 and 16). The highest correlation coefficient for the two renal function deterioration parameters with the EC-units number was at 12-20 hours after the surgery, with results of 0.28 and 0.286, respectively, the P values were 0,0064 and 0.0001, respectively. This indicates that the more time passed from the operation, the lower the correlation coefficient, which indicates a better kidney function as we move from the blood transfusion and the OP procedures. The correlation coefficient for the parameter on the 8th postoperative day was 0.098 and 0.094, respectively, with a P value of 0.0365 and 0.001, respectively.

The results are summarised in tables 15 and 16.

Table 15; The relation between No. of perioperative EC-units and the serial postoperative creatinine value change from the baseline creatinine just before surgery

	Correlation coefficient	**P-value**
Creatinine 6-12 h postoperative	0.244	0.1514
Creatinine 12-20 h postoperative	0.280	0.0064
Creatinine 1. POD	0.267	0.0107
Creatinine 2. POD	0.228	0.7664
Creatinine 3. POD	0.217	0.5746
Creatinine 8. POD (± 1 d)	0.098	0.0365

Table 16; The relation between the No. of perioperative EC-units and percentage change creatinine value from the baseline creatinine just before the surgery

	Correlation coefficient	**P-value**
Creatinine 6-12 h postoperative	0.249	0.0001
Creatinine 12-20 h postoperative	0.286	0.0001
Creatinine 1. POD	0.275	0.0001
Creatinine 2. POD	0.235	0.0096
Creatinine 3. POD	0.224	0.0001
Creatinine 8. POD (± 1 d)	0.094	0.0001

3.3 Second aim results

"The incidence of AKI after ascending aorta and aortic arch replacement surgery with moderate HCA and CPB."

- Of the 1351 patients who underwent those surgeries, 206 patients (15.2%) developed PCS-AKI according to KDIGO criteria.
- Incidence in females: of the 1351 patients, 453 were female, and 55 (12.1%) had PCS-AKI

- The incidence of RRT in females: of the 55 females with PCS-AKI, 42 patients required RRT (76.4%)
- Incidence in males: of the 1351 patients, 898 were male, and 151 (16.8%) had PCS-AKI.
- The incidence of RRT in males: of the 151 males with PCS-AKI, 81 patients required RRT (53.64%)

3.4 Third aim results

"The outcome of PCS-AKI was measured using (A) the mortality and (B) ICU duration of the critically ill patients who underwent those surgeries."

(A) Mortality rate

- 206 Patients with PCS-AKI; of them:
  - 57 (27.6%) patients died within 50 postoperative days
  - 52 died within 30 postoperative days (**25.2%** of total AKI patients)
  - 32 died within seven postoperative days (**15.5%** of the total AKI patients)
- Of the 1145 patients without PCS-AKI, 46 were dead within 30 postoperative days (**4%)**, **showing that PCS-AKI increases the mortality rate by more than six times.**
- Of the 57 Patients who died PCS-AKI, 51 **(89.5%)** had a new postoperative RRT
- The mortality rate in women with PCS-AKI was **43.6%** (24 women of the 55 with PCS-AKI died)
- The mortality rate in men with PCS-AKI was **21.8%** (33 men of the 151 with PCS-AKI died)

(B) Intensive care unit (ICU) stay by patients with and without PCS-AKI:

- Patients with PCS-AKI in general (with RRT and without RRT) had an average ICU stay of **13.2 (± 13.3) days**, whereas PCS-AKI patients who required RRT have an average ICU stay of **16.8 (± 14.9) days**. However, the PCS-AKI patients who did not require RRT had an average ICU stay of **7.8 (± 7.8) days.**
- Patients without PCS-AKI had an average ICU stay of **4 (±5.3) days.**

3.5 Fourth aim results

The (A) PCS-RRT prediction methods and (B) the risk factors were evaluated by serial measurement of the different parameters and risk factors involved in those prediction modes using the right statistical evaluation for them; this subsequently leads to early prediction and intervention as well as the avoidance of them when possible, resulting in decreasing the incidence of postoperative AKI by trying to avoid those risk factors and in patients with unavoidable risk factors by early intervention using the early prediction methods.

(A) Evaluation of the PCS-RRT predictions score items (Table 2):

- **Gender:**
  - Incidence in females: of the 1351 patients, 453 were female, and 55 had PCS-AKI (12.1%).
  - The incidence of RRT in females: of the 55 females with PCS-AKI, 42 required RRT (76.4%).
  - Incidence in males: of the 1351 patients, 898 were male; of them, 151 had PCS-AKI (16.8%).
  - The incidence of RRT in males: of the 151 males with PCS-AKI, 81 required RRT (53.64%).

- **Chronic obstructive lung disease (COPD) :**
  - Of the 1203 patients without COPD, 175 (14.5%) had PCS-AKI.
  - Of the 137 patients with COPD, 24 (17.5%) had PCS-AKI.

- **Diabetes mellitus (DM):**
  - Of the 1199 patients without (DM), 166 (13.8%) had PCS-AKI.
  - Of the 84 patients with DM on oral therapy, 15 (17.8%) had PCS-AKI. However, those on insulin therapy showed a marked increase in PCS-AKI, where 13 of the 37 patients with insulin-dependent DM (35%) had PCS-AKI.

- **Chronic kidney insufficiency (CKD) (basal creatinine - eGFR):**
  - Of the 285 patients with CKD, 102 (35.8%) have PCS-AKI.
  - Of the 1062 patients without CKD, 101 (9.5%) had PCS-AKI.

- **Left ventricle ejection fraction (LV-EF):**
  - Of the 873 patients with good LV-EF (LV-EF equal to or more than 55%), 103 (11.8%) had developed PCS-AKI.
  - Of the 140 patients with light restricted LV-EF (LV-EF between 45% and 54%), 12 (8.57%) developed PCS-AKI.
  - Of the 110 patients with middle restricted LV-EF (LV-EF between 30% and 44%), 26 (23.6%) had PCS-AKI.
  - Of the 33 patients with high restricted LV-EF (LV-EF less than 30), 5 (15.15%) had PCS-AKI.

- **Myocardial infarction (MI) (within 2 days):**
  - Of the 25 patients with preoperative MI (within two days before the surgery), 7 (28%) had PCS-AKI.
  - Of the 1316 patients without preoperative MI, 195 (15%) had PCS-AKI.

- **Cardiogenic shock (CS):**
  - Of the 32 patients with preoperative CS, 16 (50%) had PCS-AKI.
  - Of the 1306 patients without preoperative CS, 186 (14.2%) had PCS-AKI.

- **Preoperative use of intra-aortic balloon pump (IABP) 2 (pre-operative cardiopulmonary status):**
  - There were 1253 who were stable without circulatory system medication; of them, 164 (13%) had PCS-AKI.
  - In total, 50 patients were stable with a minimal dose of circulatory system medication; of them, 16 (32%) had PCS-AKI.
  - Of the 34 patients who were stable with a high dose of circulatory system medication, 19 (55%) had PCS-AKI.
  - There were 5 patients with IABP, 4 (80%) of which had PCS-AKI.

- **Previous cardiac surgery:**
  - Of the 134 patients with previous cardiac surgery, 34 (25.4%) had PCS-AKI.
  - Of the 1193 patients without previous cardiac surgery, 166 (14%) had PCS-AKI.

- **Emergent surgery:**

- Elective operation: of the 930 patients, 88 (9.46%) had PCS-AKI.
- Urgent operation: of the 103 patients, 15 (14.56%) had PCS-AKI.
- Emergency operation: of the 316 patients, 103 (32.6%) had PCS-AKI.

- **Surgery type (CABG / valve replacement)**
- With CABG surgery:
  - Of the 319 patients who underwent a superimposed bypass operation simultaneously, 55 (17.2%) had PCS-AKI.
  - Of the 540 patients without a bypass operation, 92 (17.03%) had PCS-AKI.
- Aortic valve replacement surgery:
  - Of the 791 patients who did not undergo a superimposed aortic valve replacement surgery simultaneously, 143 (18.07%) had PCS-AKI.
  - Of the 559 patients with a superimposed aortic valve replacement surgery simultaneously, 63 (11.27%) had PCS-AKI.

(B) Other Risk factors (Table 3):

⇨ Peripheral arterial disease (PAD):

- Of the 1268 patients without **PAD**, 187 **(14.7%)** had PCS-AKI.
- Of the 69 Patients with **PAD**, 11 **(16%)** had PCS-AKI.

4. Discussion

4.1 First aim discussion:

To determine predictors of PCS-AKI from the different surgical techniques, and to assess which surgical procedures increase the risk of developing a PCS-AKI and considering those techniques as an adjustable risk factor that could be modulated or when they are necessary for the surgery without modulation then to be used in our early prediction scores for PCS-AKI. From those adjustable surgical techniques are (1) HCAT, (2) CPB time and (3) Blood transfusion.

In our study, we measured the effect of the three surgical techniques on kidney function by correlating them to the postoperative kidney function using Spearman's Correlation coefficient and the t-test P-value.

The kidney function deterioration parameters were taken principally from the basic items in the KDIGO criteria (Table 1) which are:

- The increase in SCr (Postoperative SCr at X – Preoperative SCr);
- The percent increase in SCr ($\frac{(\text{Postoperative SCr at X} - \text{Preoperative SCr})}{\text{Preoperative SCr}}$ x 100);
- The percent decrease in GFR ($\frac{(\text{Preoperative GFR} - \text{Postoperative GFR at X})}{\text{Preoperative GFR}}$ x 100).

(X is the postoperative time when the SCr and the GFR were measured. Those include 6-12 hours and 12-20 hours postoperatively and the 1st, 2nd, 3rd and 8th postoperative days)

4.1.1 Hypothermic circulatory arrest time (HCAT)

Most cardiac surgical procedures can be accomplished using cardioplegia-induced cardiac arrest and cardiopulmonary bypass (CPB) to maintain perfusion of other organs. In some situations, however, the underlying pathology or the nature of the surgery proposed necessitates complete cessation of the circulation as in aortic arch replacement surgeries. The use of profound systemic hypothermia to preserve organ function during cessation of the circulation is termed deep/moderate hypothermic circulatory arrest (HCA). The technique provides excellent operating conditions while reducing the consequences of organ ischemia and injury when blood flow is inadequate.

In renal transplantation, hypothermia is the dominant treatment to reduce metabolic rate and oxygen demand in donor's kidneys, to prolong ischemic tolerance, and to preserve organ viability[147]. Renal hypothermia prolongs ischemic tolerance during aortic occlusion by the same mechanism[148] and is an established adjunct to reduce kidney injury in aortic surgery. In addition to moderate systemic hypothermia, all patients had one-time renal perfusion with 4 C solution to rapidly cool the kidneys when the visceral segment of the aneurysm was opened. Renal perfusion also reduced systemic temperature 1 to 2 C. Hypothermia does not reliably protect if renal ischemia times are prolonged (>75 minutes), at least with cross-clamp technique, unless kidneys are perfused at intervals to keep the temperature shallow [148].

HCA is typically undertaken at mild to moderate systemic hypothermia (typically a nasopharyngeal temperature of 25–36°C), and more challenging operations may require more profound hypothermia (15-24°C) to allow periods of low blood flow or circulatory arrest. Most patients tolerate 30 min of HCA without significant neurological dysfunction, but when this is extended to longer than 40 min, there is a marked increase in the incidence of brain injury. Above 60 min, the majority of patients will suffer irreversible brain damage, although a small number of patients can still tolerate this. More extended periods of HCA could be tolerated in neonates and infants compared with adults. It should be borne in mind that neurological injury may occur as a result of prolonged CPB and rewarming.

However, regarding PCS-AKI, we found in this analysis that the average HCAT for patients who developed PCS-AKI was 37.7 (± 34.4) min, which is nearly 15 min more than the average of patients who did not develop PCS-AKI, with an average of 22 min.

The Spearman's correlation coefficient between HCAT and the three renal function deterioration parameters of KDIGO criteria show a weak relation postoperatively, however, this relation was decreasing progrediently as time passed from the operation day which indicates an apparent recovery from PCS-AKI as we proceed further from the HCA, in addition to that the P values between them were 0.0001 which are extremely significant. (data are summarised in tables 9,10, 11 in the result section). With these results the effect of HCA on PSC-AKI could not be declined; however, more clinical trials are needed to clear the different pathophysiology.

Some studies have found that HCA is not an independent risk factor for PSC-AKI as in Englberger et al.[146] who stated that thoracic aortic surgery could be performed with low rates of AKI, comparable to other cardiac surgery procedures. They stated as well that HCA and

preoperative SCr are not independent risk factors for PCS-AKI, rather the risk estimation for PCS-AKI require multivariable prediction.

Other many studies have agreed with our finding that HCA influences PSC-AKI; however, they have different pathophysiological reasons that lead to this insult where some blame the Hypothermia and its degree, while others blame the rewarming mechanism itself rather than the hypothermia.

In a recent randomised trial by Boodahwani et al.[74] stated in data from two controlled trials, with more than 450 patients, demonstrate that in a routine CABG population, PCS-AKI occurred commonly (16%). Sustained mild intraoperative hypothermia did not appear to have a nephroprotective effect, as determined by postoperative SCr levels. On the other hand, rewarming from 32° to 37°C during a period of 10 to 15 minutes resulted in elevated postoperative SCr levels and a higher incidence of PCS-AKI compared with control patients rewarmed to 34°C. In addition to rewarming, CPB time and the presence of diabetes were predictors of renal dysfunction after CABG. In study 2, postoperative serum creatinine levels were similar between the hypothermic and normothermic groups (p 0.44), and there was no difference in the incidence of PCS-AKI between groups (hypothermic, 20% vs normothermic, 15%; p 0.28), suggesting that rewarming, rather than cooling, is responsible for PCS-AKI.

Based on such data, the rewarming rate may be a critical factor regarding suitable equilibrium of oxygen supply and demand in cardiac surgery with hypothermia.
This was also confirmed by an experimental model in which during the restoration of normothermia, hypoperfusion of the outer part of the kidney cortex may happen with possible damage to these nephrons during the increased metabolic demands of rewarming. Moreover, the high perfusion of the kidney could amplify the harmful effects of rewarming.

Nussmeier et al.[73] found aswell that rewarming, and the rate of rewarming, rather than the degree of temperature achieved may also be involved in the pathogenesis of organ injury; this rewarming is related to ischaemia-reperfusion injury.

Although many studies had and are still investigating this topic, some cardiac surgeries are also performed in normothermic conditions, and there are still significant conflicting results of hypothermia versus normothermia regarding PCS-AKI.
A possible reason for this discrepancy is how body temperature is measured. Monitoring nasopharyngeal, bladder or rectal temperature has a limited pathophysiological significance, since such measurements are reliant on factors such as body habitus, the percentage of body

fat, and ambient temperature, and may not provide a realistic assessment of the temperature of the blood which directly interacts with organs.

Nussmeier et al.[73] found that the arterial temperature rather than core temperature gives a better estimation of jugular bulb temperature, which reflects the temperature of the central nervous system.

Furthermore, in AORTA-study by Sansone et al.[149], the population was subdivided into various groups according to the HCAT. The outcomes are emphasized in figure 5, a group of five patients with HCA less than 15 min (30-day mortality 0%, AKI 0%), another group (13 patients) with HCA between 15-30 min (30-day mortality 15.3%, AKI 30.7%) and the last group (19 pat.) with HCA greater than 30 min (30-day mortality 42%, OR 5.8 p = 0.038; AKI 52.6% OR 2.8 p = 0.05). These data emphasise the benefits of as short as possible HCA in terms of short-term survival and renal outcomes (Figure 5).

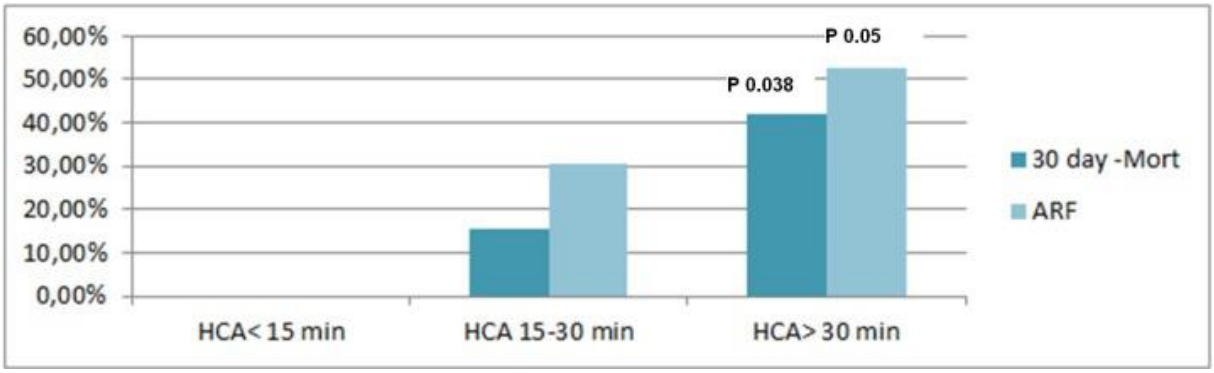

Figure 5; Thirty-day mortality and AKI by hypothermic circulatory arrest times; ARF = acute renal failure; HCA = hypothermic circulatory arrest.

In addition according to degrees of HCA, as illustrated in figure 6, they identified 12 patients who underwent HCA less than 21°C (30-day mortality 33.3%; AKI 50%, p = ns), another group of 23 patients in whom we performed HCA between 21–25°C (30-day mort 26%; AKI 34,7%, p = ns), and a last group of two patients with HCA greater than 25°C (30-day mortality 0%; AKI 0%). These data seem to suggest a better 30-day survival and better renal outcomes with lesser hypothermia.

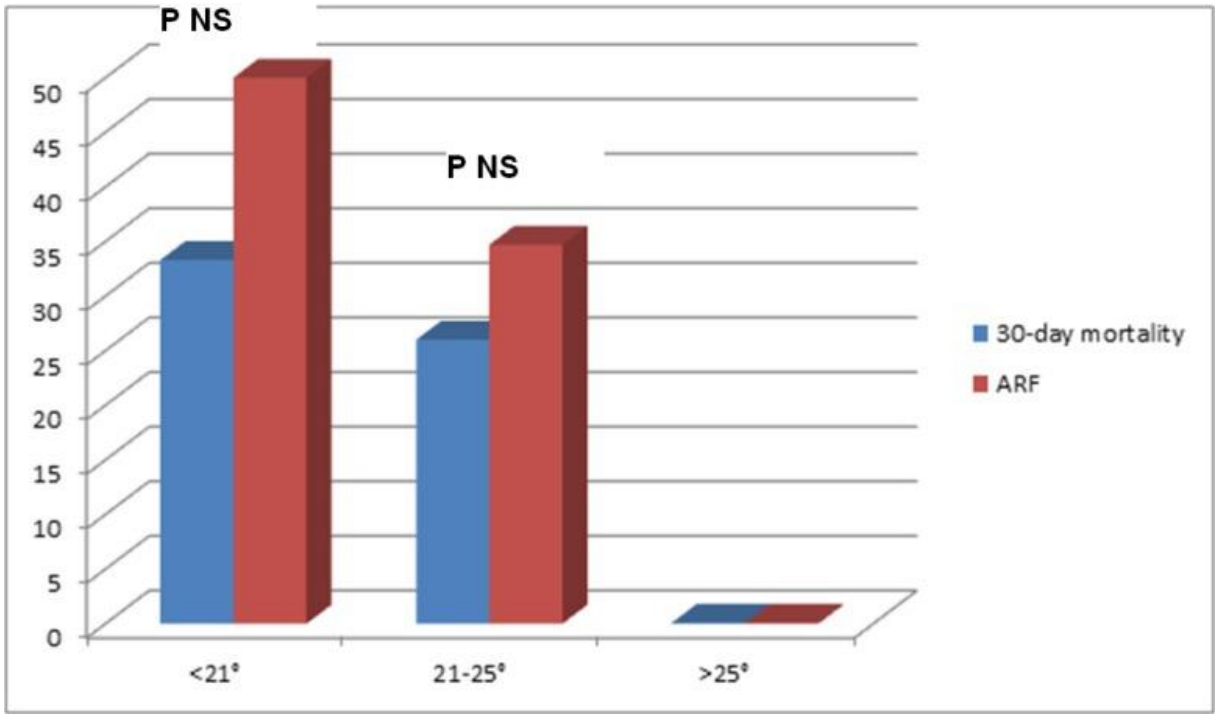

Figure 6; Thirty-day mortality and AKI by hypothermic circulatory arrest temperature, C°. ARF = acute renal failure; NS = non-significant.

The AORTA-Study bring out a better 30-day survival and better renal outcomes in case of shorter HCA and a lesser degree of hypothermia. The option of lesser and shorter hypothermia may be beneficial.

Nota H. et al. [150] was trying in his analysis to find out the risk factors related to PCS-AKI with selective cerebral perfusion (SCP) and mild HCA. The AKI group had a significantly longer mean operation time, CPB time, cardiac arrest time, mild HCA time and SCP time compared with the non-AKI group (Figure 7). The logistic regression analysis identified CKD and mild HCA >60 min as independent risk factors for PSC-AKI (Figure 8)

	AKI (*n* = 50)	**Non-AKI (*n* = 66)**	***P*-value**
Operation time (min)	293.0 ± 73.4	253.6 ± 67.5	0.005*
CPB time (min)	164.9 ± 46.9	140.4 ± 43.5	0.002*
Cardiac arrest time (min)	93.8 ± 29.8	78.5 ± 26.5	0.003*
Mild HCA time (min)	59.2 ± 21.5	48.5 ± 17.8	0.004*
SCP time (min)	105.3 ± 31.0	94.3 ± 25.5	0.040*
Tympanic temperature at initiation of mild HLBCA (°C)	24.8 ± 1.4	25.1 ± 1.5	0.171
Lowest tympanic temperature (°C)	23.7 ± 1.2	23.6 ± 1.1	0.421
Bladder temperature at initiation of mild HLBCA (°C)	29.6 ± 2.6	29.7 ± 2.7	0.701
Lowest bladder temperature (°C)	27.7 ± 2.1	27.7 ± 2.1	0.959
Operation time >360 min	9 (18.0%)	4 (6.0%)	0.044*
Mild HLBCA time >60 min	23 (46.0%)	13 (19.6%)	0.002*

Figure 7; perfusion data; AKI: acute kidney injury; CPB: cardiopulmonary bypass; HCA: hypothermic circulatory arrest.

Variable	*P*-value	Odds ratio	95% Confidence Intervall
CKD (eGFR <60 ml/min/1.73 m^2)	0.014*	2.949	1.24–7.01
Mild HCA >60 min	0.028*	2.937	1.12–7.65
Tympanic temperature at initiation of mild HCA (°C)	0.225		
Lowest tympanic temperature (°C)	0.581		
Bladder temperature at initiation of mild HCA (°C)	0.747		
Lowest bladder temperature (°C)	0.958		

Figure 8; Multivariate analysis for PCS-AKI; AKI: acute kidney injury; CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate; HCA: hypothermic circulatory arrest.

4.1.2 Cardiopulmonary bypass (CPB) time

More than 60 years ago, the cardiopulmonary bypass machine was introduced to the medical field. This introduction made complicated cardiac surgery possible without high risk; however, already in the 1960s, the association between CPB and AKI became apparent[75]. The materials and techniques have improved, but CPB is still considered to have a massive influence on PCS-AKI.

CPB time was mentioned in many studies as a directly proportional modulated risk factor (or surgical technique) to the incidence of PCS-AKI.

In our study, the average CPB duration for patients who developed PCS-AKI was 3 hours 15 min (195 ± 67.5 min), 35 min longer than the average of patients who did not develop PCS-AKI, with an average of 2 hours 38 min (158 ±59.7 min).

Although that the Spearman's correlation coefficient showed weak relations between the CPB time and the three kidney deterioration variable of KDIGO criteria postoperatively, There was a sequential decrease in the Spearman's correlation as more time passed from the operation day, which indicates an improvement in kidney function as we move away from the CPB. In addition to that the P values between them showed extremely significant relations (0.0001 for all relations; data are summarised in tables 12,13 and 14). Those results showed a clear proof that the CPB time has a direct effect on the postoperative kidney functions deterioration.

The Pathophysiology PSC-AKI after CPB is multivariable. The generation of SIRS, activation of the immune system, as well as hypotension and other adverse physiologic processes caused by CPB exposure explain why the incidence of PCS-AKI correlates with the duration of CPB. A recent meta-analysis of 9 studies reported that 756 of the 12,466 patients (6.06%) who underwent CPB developed PCS-AKI by AKIN definition and had longer CPB

times. The average CPB time for patients who developed PCS-AKI compared to those who did not was significantly longer[76] (23.18 min, 95% CI 16.7–29.66; P < 0.0001).
Other studies indicate that longer CPB and cross-clamp times are strongly associated with an increased incidence of PCS-AKI. A safe cut-off time has not been determined[76].

Pump flow during CPB

The goal of CPB is to maintain regional perfusion at a level that supports optimal organ function[77]. The CPB flow rate recommendation of 1.8-2.2 l/min/m^2 is based on experimental calculations of global oxygen consumption at different perfusion rates[78]. However, it is not known what the regional flow rates are with this recommendation, and generally, flow rates are maintained at the level of the standard cardiac index, 2.2-2.4 l/min/m^2.
There is debate as to whether a pulsatile flow preserves kidney function better than a non-pulsatile flow in CPB. In one prominent study, pulsatile flow demonstrated no protection to the kidneys compared with the non-pulsatile flow[79]. 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[80].
It was also shown that pulsatile flow lowers peripheral vascular resistance, maintaining better microcirculation and tissue metabolism, and decreasing tissue oedema[81].
Despite the theoretical benefits of the pulsatile flow, almost all centres perform CPB using non-pulsatile pumps.

Perfusion pressure during CPB

CPB is associated with significant clinical haemodynamic changes that are related to the unique pressure and flow characteristics of CPB systems. Maintaining regional perfusion is the ultimate goal of non-pulsatile CPB flow. This perfusion is required for the support of optimal cellular and organ function.
The flow rate and perfusion pressure determine regional blood flow in CPB. The ideal perfusion pressure to support adequate local oxygen transfer to the kidneys is unknown, and in general, an average perfusion pressure of 50 to 70 mmHg with normal cardiac output is maintained to ensure sufficient renal protection[15].
Also, it is unknown whether these recommended flow rates and pressure limits are sufficient to ensure an optimal renal blood flow in patients with preoperative kidney injury, or in patients with pre-existing ATN and the possible loss of autoregulation[15].
One study looked at CPB mean arterial pressure (MAP) ranges of 40 to 80 mmHg in elderly

patients and found no correlation with postoperative renal dysfunction[82].

A study in patients with normal preoperative renal function showed an association between postoperative AKI and longer CPB time, lower perfusion flow, and extended periods on CPB at pressures below 60 mmHg[83].

Ono et al. measured the excursions of MAP during CPB 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 related to AKI, although the absolute MAP did not differ between patients with AKI and those without kidney injury[84].

Moreover, it was proved that a MAP change (preoperative minus intraoperative MAP) more than 26 mmHg was independently related to AKI in high-risk patients[85].

Embolism during CPB

During macroscopic and microscopic CPB, both gaseous and particulate emboli are generated and may lead to organ injury. The importance of embolism during CPB is confirmed by the fact that post-mortem studies have documented atheroemboli in the brain, heart, gastrointestinal tract, kidney, and lower extremity tissues of patients who had undergone CPB[86].

Another in vivo method was applied to correlate between the number of cerebral emboli and postoperative stroke, and kidney injury was demonstrated[87]. 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[87].

Air is another source of emboli. It may enter the left side of heart when the left side of the heart is open, for example during valve surgery, or enter from the right side through an open foramen ovale. “De-airing” manoeuvres 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[88]. Echocardiography is helpful to detect and to aid the removal of residual air[89].

Inflammatory system

CPB activates a systemic inflammatory response, which in some patients clinically manifests as a syndrome (SIRS)[90].

Cardiac surgery with a CPB pump elevates more systemic inflammatory factors than off-pump operations, indicating that CPB itself aggravates SIRS[91].

The main triggers of CPB-associated SIRS are the direct contact of blood with the artificial

surface of the bypass circuit, the development of ischaemia-reperfusion injury, and the presence of endotoxaemia[92-94].

Other possible provoking factors are operative trauma, non-pulsatile blood flow, mediastinal shed blood during CPB, and pre-existing left ventricular dysfunction[15].

The increased level of circulating inflammatory mediators may elicit endothelial dysfunction and the initiation of AKI amplified by alterations in renal perfusion[95].

Ultrafiltration during CPB

Ultrafiltration is a standard method to remove fluid overload during CPB. It is frequently used in paediatric cardiac surgery and is progressively being used more in adult cardiac surgery, both perioperatively and postoperatively. There are no data, however, on whether this procedure improves renal outcome in adult cardiac surgery, but it is known that ultrafiltration reduces the adverse effects of haemodilution, and therefore reduces the need for transfusion and also may decrease inflammation[96].

Haemodilution during CPB

During CPB, haemodilution decreases blood viscosity, improving regional blood flow in the setting of hypoperfusion and hypothermia, and minimises the need for blood transfusion. Increases in regional blood flow are expected to compensate for the decreased oxygen-carrying capacity of the blood. The impairment of oxygen transport to the hypoxic kidney medulla or the increase in systemic inflammatory mediators caused by ischaemia is thought to play a vital role in the pathogenesis of PCS-AKI[15,77].

In a retrospective study of 1,760 CPB surgery patients, it was found that intraoperative anaemia of haematocrit less than 24% was significantly related to an increased occurrence of PCS-AKI[97].

AKI risk seemed to increase when both anaemia and hypotension occurred during CPB, compared with anaemia alone[81].

Karkouti et al.[98] showed that moderate haemodilution (haematocrit concentration 21–25%) was associated with the lowest risk of PCS-RRT, and the risk increased as the haematocrit concentration deviated from this range in both directions.

In a recent prospective study, in the low-haematocrit group, <24% presented an increase in PCS-AKI and tissue hypoxemia (lactate) markers[99].

These studies suggest that a higher risk of PCS-AKI accompanies a haematocrit level of <24%. The need for randomised controlled studies remains.

Haemolysis during CPB

Intravascular haemolysis is a typical result of CPB[100]. In haemolysis, there are several contributing factors to kidney injury, such as the loss of red blood cell (RBC) mass, impaired endothelial function, oxidative damage, and cytotoxic tubular damage[101].

Haptoglobin scavenges circulating free haemoglobin (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[102].

In a recent study of cardiac surgery patients, there was a significant correlation between haemolysis, NO consumption, and kidney tissue damage after CPB and surgery[101].

Also, the structure of RBCs can be damaged, which diminishes their ability to enter small vessels and reduces their contact with vessel walls, leading to organ ischaemia[100].

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 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[104].

CPB time is also directly related to the degree of hemolysis[105].

There is no evidence of the advantage of the rollers over the centrifugal pumps concerning haemolysis[100].

The suggested strategies to prevent haemolysis during CPB are to avoid the excessive use of suction, use a separate cardiotomy reservoir to avoid damaged RBCs and fHb, administer haptoglobin or NO-donors to compensate for the enhanced NO consumption, and apply a super high-flux haemofilter to remove fHb[101].

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 devices retain RBCs and remove fHb, inflammatory mediators, fat emboli, and heparin, as well as plasma and platelets, as mentioned before.

At present, there is no proof that this cell saving technique has an effect on renal outcome after cardiac surgery[101].

4.1.3 Blood transfusion

Perioperative RBC transfusion is considered to be a risk factor for PCS-AKI in susceptible patients, such as those with preoperative kidney disease or anaemia[106]; in our study, we

found that patients who received more EC-units via transfusion perioperatively have a higher risk of developing PCS-AKI, as patients who had PCS-AKI received a mean of 4.73 EC-units while those who did not have PCS-AKI received a mean of 2.42 EC-units perioperatively.

The Spearman's correlation coefficient and P value for the number of EC-units transfused and serial postoperative creatinine values increase from a preoperative baseline creatinine value and serial percent value of these increase from the baseline creatinine value at 6-12 and 12-20 hours after surgery, and on the 1st, 2nd, 3rd and 8th postoperative days (Tables 15 and 16). The highest correlation coefficient for the two renal function deterioration parameters with the EC-units number was at 12-20 hours after the surgery, with results of 0.28 and 0.286, respectively, the P values were 0,0064 and 0.0001, respectively. This indicates that the more time passed from the operation, the lower the correlation coefficient, which shows a better kidney function as we move from the blood transfusion and the OP procedures. The correlation coefficient for the parameter on the 8th postoperative day was 0.098 and 0.094, respectively, with a P value of 0.0365 and 0.001, respectively.

There is a big discussion here over whether the development of PCS-AKI is because of the transferred blood itself or as a result of the tissue hypoxia result from blood loss during the operation or a predisposing anaemia; many studies have been working in this field trying to clear it as much as possible.

The PCS-AKI relation to the blood transfusion was explained in other studies by the long duration blood concentrate could be stored when it is proved; the stored RBCs in these blood concentrates after 14 days 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, free iron and haemoglobin. Hence, instead of improving oxygen delivery, they may cause organ injury[107-110].

The transfusion of stored RBCs may elicit harmful effects, such as inflammation, renal hypoxia, and oxidative stress[106].

Patients with preoperative anaemia are especially more susceptible to transfusion-related AKI than non-anaemic patients[77].

In a recent study, prophylactic RBC transfusion reduced perioperative anaemia and RBC transfusions and possibly reduced plasma iron levels[111].

Interventions to avoid perioperative blood transfusion are recommended, such as drugs that increase preoperative blood volume or decrease postoperative bleeding, the use of devices that

conserve blood, and interventions that protect the patient's blood from the stress of operation[111].

Anaemia

Studies have shown that perioperative anaemia in cardiac surgery is independently associated with various adverse outcomes, including PCS-AKI[112,113].

Anaemia may contribute to kidney injury by reducing renal oxygen delivery, worsening oxidative stress, and impairing haemostasis.

Tissue oxygen delivery is directly related to arterial oxygen content, which is primarily dependent on the haemoglobin concentration[114].

The adverse consequences of anaemia are likely increased more in the course of cardiac surgery, as, for reasons outlined earlier, the kidney is more prone to renal hypoperfusion[115].

Anaemia decreases oxygen delivery to kidneys and particularly the outer part of the renal medulla, where the normal partial pressure of oxygen in the renal tissue is very low[114].

Anaemia may enhance renal oxidative stress because RBCs serve essential antioxidant functions[114].

Anaemia leads to haemostasis disequilibrium, as the normal platelet role is dependent on the presence of sufficient (but as yet undetermined) haemoglobin concentrations[116,117].

In cardiac surgery, during which patients are already at an increased risk of bleeding due to CPB-related haemostatic defects[118], the added burden of anaemia-induced platelet dysfunction may lead to excessive bleeding, which in turn may require several RBC transfusions and re-exploration surgery, both associated with AKI.

4.2 Second Aim discussion

In the present study, out of 1351 patients, who underwent aortic surgery with moderate HCA and CPB, 205 (15.2%), according to the KDIGO criteria for AKI, showed either an increase in the serum creatinine value to more than 0.3 mg/dl (26.5μM) from the preoperative serum creatinine value within 48 hours or more than 1.5 times the preoperative serum creatinine value within 7 days; required a new postoperative RRT; or decreased their urine volume to less than 0.5 ml/kg/h for more than 6 hours and thus to an acute kidney injury.

Male patients showed a slightly higher incidence of developing PCS-AKI than female patients with a ratio of 16.8%:12.1%.

Of the 205 patients who developed PCS-AKI, 123 (60%) had to be dialysed in the further course; females with PCS-AKI showed a higher incidence of RRT than males with the same PCS complication in a ratio of **76.4%:53.64%**.

Previous studies report a different PCS-AKI incidence ranging between 8.9% and 50% after cardiac surgeries, or a dialysis incidence rate ranging from 1–5% of patients who established PCS-AKI[7]. The following table provides an overview of the incidence of AKI and mortality according to cardiac surgery from several studies.

Table 17 Various studies showing the incidence of PCS-AKI according to RIFLE, AKIN or KDIGO criteria

Study	Year published	Patient Numbers	Surgery type	Incidence	Diagnosis criteria	In-hospital mortality rates of AKI vs non-AKI
Karkouti et al. [119]	2009	3,500	CS	three thresholds of AKI: 24, 7, and 3%, respectively	AKIN: 25, 50, and 75% decrease in eGFR within 1 week	three thresholds of AKI: 10, 25, vs non-AKI
Bagur et al. [120]	2010	213	TAVI	11.7%	RIFLE: reduction of 25% in eGFR within 48 h	28 vs.7.4%
D'Onofrio et al. [121]	2010	2,488	CS	23.5%	RIFLE: using peak postoperative SCr in the ICU	5.5 vs 1.5%
Swaminathan et al. [122]	2010	10,275	CABG	10.8%	AKIN: a peak SCr ≥50% above baseline within five days postoperatively	n.k.
Englberger et al. [123]	2011	4,836	CS with CPB	diagnosed by AKIN: 26.3%; by RIFLE: 18.9%	defined by RIFLE and AKIN within seven days postoperatively	RIFLE: 3.8 (R), 18.3 (I), 19.4 (F) vs. 0.53% AKIN: 2.6 (I), 12.3 (II), 44.6 (III) vs. 0.64%
Robert et al. [124]	2010	25,086	CS	diagnosed by AKIN: 30%; by RIFLE: 31%	AKIN and RIFLE	AKIN: 4.1 (I), 14.2 (II), 36.8 (III) vs. 1.3% RIFLE: 3.3 (R), 11.1 (I), 36.4 (F) vs. 1.4%
Brown et al. [125]	2010	4,987	CS	39%	AKIN	HR: 1.54–6.13 (non-AKI HR: 1)
Li et al. [126]	2011	964	Elective CABG	19.8% (7.9% in stage 1, 3.5% in stage 2, and 8.4% in stage 3)	AKIN	in-hospital mortality rate [15, 16]: OR 4.07; p<0.001(overall in-hospital mortality rate 5.1%)
Parolari et al. [127]	2012	3,219	CS with CPB	8.9%	AKIN	n.k.
Englberger et al. [128]	2012	951	TV	30%	RIFLE class (R, I, or F) within the	6.5 (R), 17.2 (I), 54.4 (F) vs. 1.5%

					first seven days postoperatively	
Lagny et al. [129]	2015	443	CAPG or MVR/AVR or both with CPB	49.9%	RIFLE: Elevated serum creatinine (AKI SCr) and oliguria (AKIUO) was observed in 9.7 % and 40.2 %,	2.37 % vs. 0.04

CS = Cardiac surgery; eGFR = estimated glomerular filtration rate; HR = adjusted hazard ratio from Cox proportional hazard model; n.k. = not known; TAVI = trans-catheter aortic valve implantation; TV = tricuspid valve surgery.

It is evident that there are significant differences in the reported incidence of PCS-AKI as well as the need for RRT.

Isolated CABG surgery was reported with the lowest incidence of AKI, followed by valvular surgery and combined CABG with valvular surgery[135].

D'Onofrio et al. described a PCS-AKI incidence of nearly 23.5% in the mixed patient population of cardiac surgery with CPB[121]. Yamamoto et al. reported only 15% of 415 TF-TAVI patients[131]. Bagur et al. reported an AKI incidence of only 11.7%[120]. A significantly higher incidence rate is described by the work of Lagny et al.,[129]at 49.9%.

The significant differences in the incidence of PCS-AKI according to different studies can be explained by the different comorbidities of the patients studied, the type of cardiac surgical interference performed and the lack of a uniform definition of AKI, which has complicated the research in this field and made the results of comparisons confusing as there are various definition criteria used to identify patients with AKI (RIFLE, AKIN or KDIGO). Previous studies defined an AKI according to RIFLE criteria, while the more recent studies define the AKI according to the modified RIFLE criteria AKIN and later by KDIGO. In our study, an AKI diagnosis was based strictly on the renal function parameters according to the KDIGO AKI-Criteria (Figure 1).

Further reasons for the different incidence of postoperative AKI can be explained by different perioperative and postoperative management as well as different times for the collection of renal function parameters.

4.3 Third aim discussion

"The outcome of PCS-AKI by measuring (A) the mortality and (B) ICU duration of those critically ill patients who underwent those surgeries."

(A) Mortality rate

AKI is an independent predictor of mortality after cardiac surgery [119,132]. Prior studies proved that the AKIN and RIFLE criteria are accurate early predictors of death,[123,124] along with KDIGO in our analysis.

According to our study, we found that PCS-AKI increases the postoperative 30-day mortality rate by 6.3 times, where the 30-day mortality rate percent ratio in patients with PCS-AKI and patients without was 25.2%:4%.

Also, the seven-day mortality rate for patients with PCS-AKI was 15.5%, and the woman to man ratio with PCS-AKI mortality rate was 43.6%:21.8%.

Applying AKIN, RIFLE or KDIGO criteria, the mortality rate (hospital discharge or 30-day mortality) is between 3.8 and 54.4% in patients who develop PCS-AKI and increases progressively with the degree of renal impairment (Table 17)[4]. Recent studies reported that after cardiac surgery, even a slight increase in serum creatinine level has a significant effect on the postoperative mortality rates[132,133]. Furthermore, long-term survival was significantly related to the duration of AKI[125], and the early recovery of renal function was associated with improved long-term survival after PCS-AKI[122].

Older studies have demonstrated that the overall mortality after cardiac surgery ranges between 1% and 8%, but when PCS-AKI exists, a four-fold increase (up to 36%) in mortality rates were recorded[119].

Furthermore, 45% of PCS patients surviving RRT, according to a recent retrospective study of 2973 patients, remain dialysis-dependent, 33% may have partial renal recovery, and only 21% may have a complete renal recovery at the time of hospital discharge[25].

Some studies have been performed to modulate the dialysis technique, as in Schiffl et al.,[134] who stated that the high frequency of haemodialysis of 5 times per week instead of 3 times increases the rapid recovery from AKI from 17 days ±6 to 9 days ±2, and decreases the mortality rate from 46% to 28%.

Nuromohamed et al.[135] stated that an inadequate CRRT-Dose is directly associated with the high mortality rate, while KDIGO states that the recommended RRT dose by AKI is 20-25 ml/kg KG/h.

Other studies have been performed to indicate the early criteria for starting dialysis and compared and defined the early and late start times when there is no absolute indication for dialysis present. In the study by Zarbock et al.,[136] the signs to an early start of RRT were: KDIGO stage 2; plasma neutrophil gelatinase-associated lipocalin (NGAL) >150 ng/mL; and one of the following: severe sepsis, use of vasopressors or catecholamines, refractory fluid overload, or the development or progression of non-renal organ dysfunction [Sequential Organ Failure Assessment (SOFA) score ≥ 2].

The "early" initiation of RRT, according to Zarbock et al., was done to patients treated by RRT within 8 hours from stage 2 AKI; the "delayed" initiation implied that RRT started within 12 hours of the diagnosis of stage 3 or any absolute indication for RRT, including the following: serum urea level >100 mg/dL; hyperkalaemia (>6 mEq/L) and/or with electrocardiography abnormalities; serum magnesium level >8 mEq/L; UO <200 mL/12 hours or anuria; and organ oedema in the presence of AKI resistant to diuretic treatment (one attempt with loop diuretics prior to randomisation).

Zarbock et al. concluded that the "early" initiation of RRT for critically ill patients with AKI reduced mortality over the first 90 days over "delayed" initiation.

(B) Intensive care unit duration for patients with and without AKI

In our analysis, patients with PCS-AKI had a mean stay in the intensive care unit of 13.2 (± 13.3) days, whereas patients who required RRT had an average ICU stay of 16.8 (± 14.9) days, however, the patients with PCS-AKI who did not require RRT had an average ICU stay of 7.8 (± 7.8) days

Patients without PCS-AKI had a mean ICU stay of 4 (±5.3) days.

Therefore, PCS-AKI increases the hospital stay by twice, up to 4 times (in case of RRT), the duration required without AKI, which has an immediate and economic effect on the hospital, patients and cost of stay.

Another previous study[54] stated that the risk-adjusted average cost of care for patients undergoing surgery was $42,600 for patients with any AKI compared to $26,700 for patients without AKI. Also, patients with AKI were more likely to have other postoperative complications which increased the length of stay in ICUs and the hospital overall.

4.4 Fourth aim discussion

In our study, we mentioned a scoring RRT prediction mode that used certain risk factors as an indication for early dialysis; on the other hand, we also mentioned other studies which identified some risk factors to be predictive risk factors for PCS-AKI.

Postoperative RRT is closely related to the high mortality rate. Moreover, death is the most prominent fear of any patient who undergoes an operation. Patients who require RRT postoperatively have -according to our study- a high mortality rate more than 50%, Therefore, we consider it vital to re-evaluate the RRT prediction scores and use them for the early prediction of PCS-AKI and -RRT in our patients and to initiate the required therapy as soon as possible, trying to avoid as many complications as possible.

In 2005, Thakar et al.[28], in 2006, Mehta et al.[20] and in 2007, Wijeysundera et al.[21] stated that some risk factors (and operations techniques will be discussed in Aim 1 results) mentioned in table 2 could predict the postoperative requirement of RRT.
Also, other studies have identified some risk factors to be predictive of PCS-AKI (Table 3).
Out of those risk factors, we have checked the following:

(1) Gender:

Female sex was only mentioned in the Thakar prediction score and some studies[20,23,24,32-36] as a risk factor.
In our study, we found that it is an insignificant risk factor as the percentage of females who were operated on and developed PCS-AKI is lower than the male percentage, with a female to male ratio of 12.1%:16.8%.
Therefore, the percentage of men who postoperatively suffer from AKI is higher than that of females.
Hashemzadeh et al.[137] confirmed that male gender is a risk factor for PCS-AKI.
Different studies have contradicting results about the gender; due to the insignificant difference between males and females who developed PCS-AKI (only 4%), we believe that gender is not a significant risk factor for PCS-AKI.

(2) COPD was mentioned in the prediction scores of Thakar el at., Metha el at. and some studies[20,23,24,32-36] as a risk factor.

In our analysis, we found that there is a slight increase in PCS-AKI in COPD patients, where the incidence of PCS-AKI in patients who have COPD and those without was 17.5% and 14.5%, respectively.

Hashemzadeh et al.[137] stated that COPD is not a risk factor, as the risk of developing a PCS-AKI in patients with COPD and those without was 7.8% and 8.8%, respectively.

(3) Diabetes mellitus (DM) was mentioned in Thakar et al., Metha et al. and Wijeysundera et al. prediction scores, as well as some other studies[20,23,24,32-36] as a risk factor. Hashemzadeh et al.[137] found that the ratio of patients with DM and those without who developed PCS-AKI was 29.7%:18.5%.

Moreover, in our study, the level of IDDM patients showed a marked increase in PCS-AKI, with a percent of 35%, whereas DM patients on oral therapy and no DM showed a significantly lower value of 17.8% and 13.8%, respectively.

(4) Chronic kidney disease (**CKD) or preoperative renal injury.** With the application of CKD classification, most studies and prediction scores demonstrated that the degree of preoperative renal dysfunction, either with a high creatinine or low GFR value, parallel a proportionally increased risk of PCS-AKI and the requirement of RRT[20,23,24,32-36,126].

In our study, the preoperative CRF or renal injury were very significant risk factors for PCS-AKI and PCS-RRT. In the present study, patients with preoperative CRF showed an increase in PCS-AKI incidence with a percentage of 35.8% in comparison with patients without preoperative CRF who had a percentage of 9.5%.

The focus of some studies was an assessment of the probability of PCS-AKI superimposed on CKD, while another focus was avoiding subclinical or silent AKI preceding surgery, in which the drugs used, especially contrast media-induced kidney injuries. When cardiac catheterisation and cardiac surgery occurred during the same hospitalisation period, there was an increased risk of postoperative AKI. This is likely due to the time needed for renal cell recovery before new insults to renal cells from the surgery itself[138].

(5) Left ventricular ejection fraction (LV-EF). During the perioperative period, the volume status of the patients is of vital importance; according to different studies, cardiac output before, during or after surgery, is directly related to PCS-AKI incidence. This can be explained by the hyperactivity of the sympathetic nervous system, with the corresponding

activation of the renin-angiotensin-aldosterone (RAA) system, which increases renal vasoconstriction[32].

LV-EF was mentioned in Thakar et al., and in the Wijeysundera et al. prediction scores as well as in the following studies [20,23,24,32-36] as a risk factor for PCS-AKI.

Hashemzadeh et al.[137] mentioned that patients with LV-EF less than 30% have evidently a higher risk of developing PCS-AKI (14.1%) than patients with a higher LV-EF (5.5%).

Pieri et al.[139] confirmed that patients with low LV-EF (≤40%) undergoing cardiac surgery are at a higher risk of postoperative complications, and the incidence of those complications was higher in patients with LV-EF (≤30%). Among those complications is PCS-AKI.

However, in our study, patients with LV-EF ≤30 showed a slight increase in the development of PCS-AKI than those with a higher LV-EF, with a percentage of 15.15% and 12.5%, respectively.

This was not a marked difference to the previous studies; our explanation for this was that not all our patients had undergone recent echocardiography as many were emergency patients. Therefore, we had to use the most recent echocardiograph to register their LV-EF, which in many patients was few months before the surgery and did not reflect the preoperative LV-EF, which could have deteriorated more before the surgery in those critically ill patients.

(6) Myocardial infarction (**MI)** in less than three weeks was mentioned in 2006 by Mehta et al. and the following studies [20,23,24,32-36] as a risk factor for PCS-AKI.

In our study, we found a marked increase in the incidence of PCS-AKI in patients with recent MI within 48 hours before surgery, with a percent of 28%, while patients without MI had a PCS-AKI percent of 15%.

However, acute myocardial infarction (AMI) is well known to be a risk factor for AKI, with or without any operation, as in the study by Sun et al.[140]. Here, a total of 1371 adult inpatients with AMI were studied, of which 410 (29.9%) developed AKI after the injury. They also stated that decreased baseline renal function, increased fasting plasma glucose (FPG) and the use of diuretics were common independent risk factors of AKI after AMI.

(7) Cardiogenic shock (CS) was mentioned in 2006 by Mehta et al. as a risk factor for PCS-AKI. In our study, we found a marked increase in the percentage of PCS-AKI when a patient had suffered a cardiogenic shock before the operation, where the incidence of PCS-AKI for patients with cardiogenic shock and those without was 50% and 14.2%, respectively, which is significantly higher by more than three and a half times.

According to other studies, CS is a well-known risk factor for AKI with or without operation, as in the study by Tarvasmäki et al.,[141] where 154 patients with cardiogenic shock without any operation were studied in a prospective multicentre CardShock study analysis. AKI was defined and staged according to the KDIGO criteria by creatinine (AKI SCr) and/or urine output (AKI UO). CysC-based AKI (AKI CysC) was defined similarly to AKI SCr. Changes in haemodynamic parameters were assessed over time from baseline until 96 h. The incidence of AKI was: AKI SCr 31%, AKI UO 50%, and AKI Cysc 33%. Moreover, the 90-day mortality was 38%.

Zhongguo et al. [142] investigated 172 patients admitted to the general hospital of PLA from 1993 to 2003 with the diagnosis of AMI or unstable angina in a state of CS to study the relationship between early AKI and the prognosis of patients with CS after MI. In total, 31% (51 patients) developed AKI within 24 hours after the onset of shock. In-hospital mortality in patients with and without AKI was 90% (46/51 cases) and 56% (68/121 cases), respectively.

(8) IABP was mentioned in both Thakar et al., Wijeysundera et al. RRT prediction scores as a risk factor. In our study, we found that 80% percent of patients who needed IABP preoperatively had developed PCS-AKI, which is a significant high percent.

Our patients were divided into four levels according to the preoperative cardiopulmonary stability condition and the measures required to stabilise them; those four levels were: stable without circulatory system medication; stable with a minimal dose of circulatory system medication; stable with a high dose of circulatory system medication; and stable with IABP. The percent of developing PCS-AKI was as follows: 13%, 32%, 55% and 80%, respectively.

That means that the more a patient is preoperative cardiopulmonary unstable, the more likely to develop PCS-AKI.

However, in our study, and those of Thakar and Wijeysundera, IABP use showed that patients were haemodynamically unstable preoperatively rather than the use of IABP itself being a risk factor.

In many recent as well as old studies, there was marked evidence that preoperative prophylactic use of IABP was a successful measure to reduce the risk of PCS-AKI, as in the study by Wang et al.[143] in 2016 by The Society of Thoracic Surgeons. This was the first meta-analysis to demonstrate significant beneficial effects of preoperative prophylactic IABP on renal function in high-risk patients undergoing CABG.

In this meta-analysis, they investigated the effects of preoperative prophylactic IABP on postoperative renal function and short-term death of high-risk patients, and They found that

preoperative prophylactic IABP use decreased the incidence of PCS-AKI and short-term mortality and significantly reduced the need for PCS-RRT by up to 82% compared with high-risk patients without the procedure.

(9) Previous cardiac surgery was mentioned as a PCS-AKI risk factor in all prediction scores by Thakar et al., Mehta et al. and Wijeysundera et al. as well as the following studies[20,23,24,32-36]. In our study, we found that previous cardiac surgery is a risk factor for PCS-AKI, as patients who underwent previous cardiac surgery have a higher incidence of developing PCS-AKI than those without, with an incidence ratio of 25.4%:14%.

(10) Emergency surgery showed a higher incidence of PCS-AKI of 32.6% in our study in comparison with the urgent operation indication of 14.56% and elective operation indication of 9.46%; we explained that by the smaller time available to bring those critically ill patients to a haemodynamically stable state before the surgery.

In the RRT prediction scores of Thakar et al. and Wijeysundera et al., an emergency indication for cardiac surgery was considered to be a risk factor for PCS-AKI.

In the Thakar study, those patients who had an emergent indication for surgery showed a higher incidence of the requirement of PCS-RRT (11.2%) than those without, who showed an incidence of 2.9%.

(11) Surgery type (CABG/ valve replacement surgeries) was considered to be a PCS-AKI risk factor by the three different RRT prediction scores, as well as in other studies[20,23,24,32-36].

In our study, the primary operation was ascending aorta and aortic arch replacement surgery. However, we studied whether a superimposed CABG or valve surgery is a risk factor for PCS-AKI or not.

In case of a superimposed **CABG** surgery, there was no marked difference on the influence of PCS-AKI in patients who had an additional CAPG surgery and those who did not, with results of 17.2 % and 13.03%, respectively.

However, in case of a superimposed **valve surgery** (especially aortic valve), in contrast to what has been published in the aforementioned studies and prediction scores, we found that superimposed valve surgery reduced the incidence of PCS-AKI, where the level of PCS-AKI being reduced from 18.07% without any valvular surgery to 11.27% with valvular surgery.

This regression in PCS-AKI after the superimposed valvular surgery (especially the aorta valve) can be hypothetically explained by the improvement in LV-EF and cardiac output after the surgery with increasing organ as well as kidney perfusion, resulting in reduced prerenal causes of AKI.

Chaliki et al. [144] stated that patients with severe aortic regurgitation (AR) and significantly lower LV-EF had a marked LV-EF improvement postoperatively and that most patients who survived the surgery enjoy a long postoperative survival without the recurrence of heart failure after aortic valve replacement (AVR); thus they should not be denied the benefits of AVR.

(12) Peripheral arterial disease (PAD) was not involved in the RRT prediction scores but other studies such as in Kheterpal et al.[145] and in almost all studies [20,23,24,32-36] that analysed risk factors of PCS-AKI. However, we found only a slightly higher incidence in patients with PAD who developed PCS-AKI than patients who did not, with a percentage ratio of 16%:14.7%.

We explain that slight increase by a gap of missed data during the history taking as not all patients know whether they have PAD or not as it is not a clinically evident disease like hypertension or DM where every patient knows about them.

Therefore, in our retrospective study, where we had no personal contact with patients, but only contact with their folder and data, we could not collect enough information about PAD.

5. Conclusion :

1. The data obtained from our analysis outlined the predictive role of longer moderate HCA and CPB times and perioperative blood transfusion for AKI after ascending aorta and aortic arch replacement surgery. The complex multifactorial pathophysiology plays an underlying prognostic role regarding the outcome for this life-threatening complication and requires more focused clinical trials to illustrate the contradicting results from the previous analyses regarding the causing pathophysiology.

2. The incidence of AKI after ascending aorta and aortic arch replacement surgery using moderate HCA and CPB is approximately 15 %.

3. AKI after ascending aorta and aortic arch replacement surgery increases the mortality rate more than six times, and the ICU stay more than three times.

4. Gender, COPD and superimposed CABG surgery are insignificant risk factors for PCS-AKI. DM (specially insulin dependent), preoperative chronic kidney disease, recent myocardial infarct, preoperative cardiogenic shock, cardiopulmonary instability condition, previous cardiac surgery, emergent surgery and superimposed aortic valve surgery (indirectly proportion) are all significant risk factor for PCS-AKI and can be used as predictive variables in the future postoperative AKI prediction scores. LV-EF and PAD need more focused clinical trials to determine their significance to PCS-AKI

6. Reference :

1. Griepp RB, Stinson EB, Hollingsworth JF, Buehler D. Prosthetic replacement of the aortic arch. JThorac CardiovascSurg 1975;70:1051–63
2. Augoustides JG, Floyd TF, McGarvey ML, Ochroch EA, Pochettino A, Fulford S et al. Major clinical outcomes in adults undergoing thoracic aortic surgery requiring deep hypothermic circulatory arrest: quantification of organ-based perioperative outcome and detection of opportunities for perioperative intervention. J Cardiothorac Vasc Anesth 2005;19: 446–52.
3. Arnaoutakis GJ, Bihorac A, Martin TD, Hess PJ Jr, Klodell CT, Ejaz AA et al. RIFLE criteria for acute kidney injury in aortic arch surgery. J Thorac Cardiovasc Surg 2007;134:1554–61.
4. Mao et al., Claudio Ronco: Cardiac Surgery-Associated Acute Kidney Injury. Cardiorenal Med 2013;3:178–199.
5. Chertow, G.M., et al.: Independent association between acute renal failure and mortality following cardiac surgery. Am J Med 1998; 104:343-8.
6. de Mendonca, A., et al.: Acute renal failure in the ICU: risk factors and outcome evaluated by the SOFA score. Intensive Care Med 2000; 26:915-21.
7. Vivino, G., et al.: Risk factors for acute renal failure in trauma patients. Intensive Care Med 1998; 24:808-14.
8. Basile DP, Anderson MD, Sutton TA. Pathophysiology of acute kidney injury. Compr Physiol 2012;2:1303-53.
9. Hegarty NJ, Young LS, Kirwan CN, O'Neill AJ, Bouchier-Hayes DM, Sweeney P, et al. Nitric oxide in unilateral ureteral obstruction: effect on regional renal blood flow. Kidney Int 2001;59:1059-65.
10. Section 2: AKI Definition. Kidney Int Suppl (2011) 2012; 2: 19-36.
11. Sear JW. Kidney dysfunction in the postoperative period. Br J Anaesth 2005; 95: 20-32.
12. Bellomo R, Kellum JA, Ronco C. Acute kidney injury. Lancet 2012; 380: 756-66.
13. T. Bove, A. Zangrillo: Acute renal failure and cardiac surgery. HSR proceeding in intensive care and cardiovascular anaesthesia
14. Hix JK, Thakar CV, Katz EM, Yared JP, Sabik J, Paganini EP. Effect of off-pump coronary artery bypass graft surgery on postoperative acute kidney injury and mortality. Crit Care Med 2006; 34: 2979-83.
15. Rosner MH, Portilla D, Okusa MD: Cardiac surgery as a cause of acute kidney injury: pathogenesis and potential therapies. J Intensive Care Med 2008; 23: 3–18.

16. Wang et al., Xiaoqiang Ding. Urinary TIMP-2 and IGFBP7 for the prediction of acute kidney injury following cardiac surgery. BMC Nephrology(2017)18:177
17. Machado MN, et al., Lilia Nigro Maia - Acute kidney injury based on KDIGO (Kidney Disease Improving Global Outcomes) criteria in patients with elevated baseline serum creatinine undergoing cardiac surgery. Rev Bras Cir Cardiovasc 2014;29(3):299-307
18. Hoste EA, Cruz DN, Davenport A, Mehta RL, Piccinni P, Tetta C et al. The epidemiology of cardiac surgery-associated acute kidney injury. Int J Artif Organs 2008;31:158-65.
19. Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group. KDIGO Clinical Practice Guideline for Acute Kidney Injury (www.kdigo.org). Kidney Int Suppl 2012; 2:1-138.
20. Mehta RH, Grab JD, O'Brien SM, Bridges CR, Gammie JS, Haan CK et al. Bedside tool for predicting the risk of postoperative dialysis in patients undergoing cardiac surgery. Circulation 2006;114:2208-16.
21. Wijeysundera DN, Karkouti K, Dupuis Jy, Rao V, Chan CT, Granton JT et al. Derivation and validation of a simplified predictive index for renal replacement therapy after cardiac surgery. JAMA 2007;297:1801-9.
22. Uchino S, Kellum JA, Bellomo R, Doig GS, Morimatsu H, Morgera S et al. Beginning and Ending Supportive Therapy for the Kidney (BEST Kidney) Investigators. Acute renal failure in critically ill patients: a multinational, multicenter study. JAMA 2005;17:813-8.
23. Karkouti K, Wijeysundera DN, yau TM, Callum JL, Cheng DC, Crowther M et al. Acute kidney injury after cardiac surgery: focus on modifiable risk factors. Circulation 2009;119:495-502.
24. Thakar CV, Worley S, Arrigain S, yared JP, Paganini EP. Influence of renal dysfunction on mortality after cardiac surgery: modifying effect of preoperative renal function. Kidney Int 2005;67:1112-9.
25. Hobson CE, yavas S, Segal MS, Schold JD, Tribble CG, Layon AJ et al. Acute kidney injury is associated with increased long-term mortality after cardiothoracic surgery. Circulation 2009;119:2444-53.
26. Ostermann ME, Taube D, Morgan CJ, Evans TW. Acute renal failure following cardiopulmonary bypass: a changing picture. Intensive Care Med 2000;26:565-71.
27. Jung Tak Park. : Postoperative acute kidney injury Korean J Anesthesiol 2017 June 70(3): 258-266

28. Thakar CV, Arrigain S, Worley S, Yared JP, Paganini EP. A clinical score to predict acute renal failure after cardiac surgery. J Am Soc Nephrol. 2005; 16: 162–168.
29. Candela-Toha A, Elias-Martin E, Abraira V, Tenorio MT, Parise D, de Pablo A, Centella T, Liano F: Predicting acute renal failure after cardiac surgery: External validation of two new clinical scores. Clin J Am Soc Nephrol 2008; 3: 1260–1265.
30. Englberger L, Suri RM, Li Z, Dearani JA, Park SJ, Sundt TM 3rd, Schaff HV: Validation of clinical scores predicting severe acute kidney injury after cardiac surgery. Am J Kidney D is 2010; 56: 623–631.
31. Birnie K, Verheyden V, Pagano D, Bhabra M, Tilling K, Sterne JA, et al.Predictive models for kidney disease: improving global outcomes (KDIGO) defined acute kidney injury in UK cardiac surgery. Crit Care. 2014;18(6):606.
32. Bellomo R, Auriemma S, Fabbri A, D'Onofrio A, Katz N, McCullough PA et al. The pathophysiology of cardiac surgery-associated acute kidney injury (CSA-AKI). Int J Artif Organs 2008;31:166-178.
33. Vercaemst L. Hemolysis in cardiac surgery patients undergoing cardiopulmonary bypass: a review in search of a treatment algorithm. J Extracorp Thecnol 2008;40:257-67.
34. Perez-Valdivieso JR, Monedero P, Vives M, Garcia-Fern-andez N, Bes-Rastrollo M; GEDRCC (Grupo Español de Disfunción Renal en Cirugía Cardiaca). Cardiac-surgery associated acute kidney injury requiring renal replacement therapy. A Spanish retrospective case-cohort study. BMC Nephrol 2009 22;10:27.
35. Society of Thoracic Surgeons Blood Conservation Guideline Task Force, Ferraris VA, Ferraris SP, Saha SP, Hessel EA II, Haan CK, Royston BD et al. Perioperative blood transfusion and blood conservation in cardiac surgery: the Society of Thoracic Surgeons and The Society of Cardiovascular Anesthesiologists clinical practice guideline. Ann Thorac Surg 2007;83:S27-86.
36. Karkouti K, Wijeysundera DN, yau TM, McCluskey SA, Chan CT, Wong Py et al. Influence of erythrocyte transfusion on the risk of acute kidney injury after cardiac surgery differs in anemic and nonanemic patients. Anesthesiology 2011;115:523-30.
37. Grant SW, Grayson AD, Grant MJ, Purkayastha D, Mc Collum CN. What are the risk factors for renal failure following open elective abdominal aortic aneurysm repair? Eur J Vasc Endovasc Surg 2012;43:182-7.

38. Marrocco-Trischitta MM, Melissano G, Kahlberg A, Vezzoli G, Calori G, Chiesa R. The impact of aortic clamping site on glomerular filtration rate after juxtarenal aneurysm repair. Ann Vasc Surg 2009;23:770-7.
39. Dubois L, Durant C, Harrington DM, Forbes TL, Derose G, Harris JR. Technical factors are strongest predictors of postoperative renal dysfunction after open transperitoneal juxtarenal abdominal aortic aneurysm repair. J Vasc Surg 2013;57:648-54.
40. Bosch, J.P., A. Lauer, and S. Glabman: Short-term protein loading in assessment of patients with renal disease. Am J Med 1984; 77:873-9.
41. Bosch, J.P., et al.: Renal functional reserve in humans. Effect of protein intake on glomerular filtration rate. Am J Med 1983; 75:943-50.
42. Bellomo, R., J.A. Kellum, and C. Ronco: Defining acute renal failure: physiological principles. Intensive Care Med 2004; 30:33-7.
43. Mishra J, Dent C, Tarabishi R, Mitsnefes MM, Ma Q, Kelly C, Ruff SM, Zahedi K, Shao M, Bean J, Mori K, Barasch J, Devarajan P: Neutrophil gelatinase-associated lipocalin (NGAL) as a biomarker for acute renal injury after cardiac surgery. Lancet 2005; 365: 1231–1238.
44. Jo, S.K., et al.: Delayed DMSO administration protects the kidney from mercuric chloride-induced injury. J Am Soc Nephrol 2004; 15:2648-54.
45. Schrier, R.W.: Need to intervene in established acute renal failure. J Am Soc Nephrol 2004; 15:2756-8.
46. Devarajan, P.: Emerging biomarkers of acute kidney injury. Contrib Nephrol 2007; 156:203-12.
47. Bagshaw, S.M. and R. Bellomo: Early diagnosis of acute kidney injury. Curr Opin Crit Care 2007; 13:638-44.
48. Allgren, R.L., et al.: Anaritide in acute tubular necrosis. Auriculin Anaritide Acute Renal Failure Study Group. N Engl J Med 1997; 336:828-34.
49. Hirschberg, R., et al.: Multicenter clinical trial of recombinant human insulin-like growth factor I in patients with acute renal failure. Kidney Int 1999; 55:2423-32.
50. Devarajan, P., et al.: Gene expression in early ischemic renal injury: clues towards pathogenesis, biomarker discovery, and novel therapeutics. Mol Genet Metab 2003; 80:365-76.
51. Han, W.K. and J.V. Bonventre: Biologic markers for the early detection of acute kidney injury. Curr Opin Crit Care 2004; 10:476-82.

52. Mishra J, Dent C, Tarabishi R, et al. Neutrophil gelatinase-associated lipocalin (NGAL) as a biomarker for acute renal injury after cardiac surgery.Lancet. 2005; 365:1231-8.
53. Bennett M, Dent CL, Ma Q, et al. Urine NGAL predicts severity of acute kidney injury after cardiac surgery: a prospective study. Clin J Am Soc Nephrol. 2008;3: 665-73.
54. Nickolas TL, O'Rourke MJ, Yang J, et al. Sensitivity and specificity of a single emergency department measurement of urinary neutrophil gelatinase-associated lipocalin for diagnosing acute kidney injury.Ann Intern Med. 2008;148:810-9.
55. Haase M, Devarajan P, Haase-Fielitz A, Bellomo R, Cruz DN, Wagener G, et al. The outcome of neutrophil gelatinase-associated lipocalin-positive subclinical acute kidney injury: a multicenter pooled analysis of prospective studies. J Am Coll Cardiol. 2011;57(17):1752–61.
56. Martensson J, Bell M, Oldner A, Xu S, Venge P, Martling CR. Neutrophil gelatinase-associated lipocalin in adult septic patients with and without acute kidney injury. Intensive Care Med. 2010;36:1333-40.
57. Koyner JL, Bennett MR, Worcester EM, Ma Q, Raman J, Jeevanandam V, Kasza KE, O'Connor MF, Konczal DJ, Trevino S, Devarajan P, Murray PT: Urinary cystatin C as an early biomarker of acute kidney injury following adult cardiothoracic surgery. Kidney Int 2008; 74: 1059–1069.
58. Cruz et. Al., Nevin Katz, MD.: Neutrophil gelatinase-associated lipocalin: A promising biomarker for detecting cardiac surgery-associated acute kidney injury. J Thorac Cardiovasc Surg 2010;139:1101-6
59. Ichimura, T. et al.: Kidney injury molecule-1 (KIM-1), a putative epithelial cell adhesion molecule containing a novel immunoglobulin domain, is up-regulated in renal cells after injury. J Biol Chem 1998; 273:4135-42.
60. Ichimura, T., et al.: Kidney injury molecule-1: a tissue and urinary biomarker for nephrotoxicant-induced renal injury. Am J Physiol Renal Physiol 2004; 286:F552-63.
61. Vaidya, V.S., et al.: Urinary kidney injury molecule-1: a sensitive quantitative biomarker for early detection of kidney tubular injury. Am J Physiol Renal Physiol 2006; 290:F517-29.
62. Sabbisetti VS, Waikar SS, Antoine DJ, Smiles A, Wang C, Ravisankar A, et al. Blood kidney injury molecule-1 is a biomarker of acute and chronic kidney injury and predicts progression to ESRD in type I diabetes. J Am Soc Nephrol 2014; 25: 2177-86.

63. Liangos O, Tighiouart H, Perianayagam MC, et al. Comparative analysis of urinary biomarkers for early detection of acute kidney injury following cardiopulmonary bypass. Biomarkers. 2009;14:423-31.
64. Huang Y, Don-Wauchope AC. The clinical utility of kidney injury molecule 1 in the prediction, diagnosis and prognosis of acute kidney injury: A systematic review. Inflamm Allergy Drug Targets. 2011;10:260-71.
65. Melnikov, V.Y. et al.: Impaired IL-18 processing protects caspase-1-deficient mice from ischemic acute renal failure. J Clin Invest 2001; 107:1145-52.
66. Parikh, C.R., et al.: Urinary interleukin-18 is a marker of human acute tubular necrosis. Am J Kidney Dis 2004; 43:405-14.
67. Parikh, C.R., et al.: Urinary IL-18 is an early predictive biomarker of acute kidney injury after cardiac surgery. Kidney Int 2006; 70:199-203.
68. Parikh, C.R., et al.: Urine IL-18 is an early diagnostic marker for acute kidney injury and predicts mortality in the intensive care unit. J Am Soc Nephrol 2005; 16:3046-52.
69. Gocze I, Koch M, Renner P, Zeman F, Graf BM, Dahlke MH, et al. Urinary biomarkers TIMP-2 and IGFBP7 early predict acute kidney injury after major surgery. PLoS One 2015; 10: e0120863.
70. Gocze I, Koch M, Renner P, Zeman F, Graf BM, Dahlke MH, et al. (2015) Urinary Biomarkers TIMP-2 and IGFBP7 Early Predict Acute Kidney Injury after Major Surgery. PLoS ONE 10(3):e0120863. doi:10.1371/journal.pone.0120863
71. S. ROMAGNOLI, Z. RICCI. Postoperative acute kidney injury. Minerva Anestesiol 2015;81:684-96
72. Dr. T. Kaufeld, J. Umminger, H. Krueger, Dr. E. Beckmann, Prof. M. Shrestha, Dr. A. Martens: A Simple Guide to Thoracic Aortic Surgery. Department of Cardiothoracic, Transplantation and Vascular Surgery, Hannover medical school.
73. Nussmeier NA, Cheng W, Marino M, Spata T, Li S, Daniels G, Clark T, Vaughn WK: Temperature during cardiopulmonary bypass: the discrepancies between monitored sites. Anesth Analg 2006; 103: 1373–1379.
74. Boodhwani M, Rubens FD, Wozny D, Nathan HJ: Effects of mild hypothermia and rewarming on renal function after coronary artery bypass grafting. Ann Thorac Surg 2009; 87: 489–495.
75. Murphy GS, Hessel EA, 2nd, Groom RC. Optimal perfusion during cardiopulmonary bypass: an evidence-based approach. Anesth Analg 108: 1394-417; 2009.

76. Kumar AB, Suneja M, Bayman EO, Weide GD, Tarasi M: Association between postoperative acute kidney injury and duration of cardiopulmonary bypass: a meta-analysis. J Cardiothorac Vasc Anesth 2012; 26: 64–69.
77. Rosner MH, Okusa MD. Acute kidney injury associated with cardiac surgery. Clin J Am Soc Nephrol 1: 19-32; 2006.
78. Parolari A, Alamanni F, Gherli T, Bertera A, Dainese L, Costa C, Schena M, Sisillo E, Spirito R, Porqueddu M, Rona P, Biglioli P. Cardiopulmonary bypass and oxygen consumption: oxygen delivery and hemodynamics. Ann Thorac Surg 67: 1320-7; 1999.
79. Abramov D, Tamariz M, Serrick CI, Sharp E, Noel D, Harwood S, Christakis GT, Goldman BS. The influence of cardiopulmonary bypass flow characteristics on the clinical outcome of 1820 coronary bypass patients. Can J Cardiol 19: 237-43; 2003.
80. Onorati F, Santarpino G, Presta P, Caroleo S, Abdalla K, Santangelo E, Gulletta E, Fuiano G, Costanzo FS, Renzulli A. Pulsatile perfusion with intra-aortic balloon pumping ameliorates whole body response to cardiopulmonary bypass in the elderly. Crit Care Med 37: 902-11; 2009.
81. Haase M, Bellomo R, Story D, Letis A, Klemz K, Matalanis G, Seevanayagam S, Dragun D, Seeliger E, Mertens PR, Haase-Fielitz A: Effect of mean arterial pressure, haemoglobin and blood transfusion during cardiopulmonary bypass on postoperative acute kidney injury. Nephrol Dial Transplant 2012; 27: 153–160.
82. Sirvinskas E, Benetis R, Raliene L, Andrejaitiene J. The influence of mean arterial blood pressure during cardiopulmonary bypass on postoperative renal dysfunction in elderly patients. Perfusion 27: 193-8; 2012.
83. Fischer UM, Weissenberger WK, Warters RD, Geissler HJ, Allen SJ, Mehlhorn U. Impact of cardiopulmonary bypass management on postcardiac surgery renal function. Perfusion 17: 401-6; 2002.
84. Ono M, Arnaoutakis GJ, Fine DM, Brady K, Easley RB, Zheng Y, Brown C, Katz NM, Grams ME, Hogue CW. Blood pressure excursions below the cerebral autoregulation threshold during cardiac surgery are associated with acute kidney injury. Crit Care Med 41: 464-71; 2013.
85. Kanji HD, Schulze CJ, Hervas-Malo M, Wang P, Ross DB, Zibdawi M, Bagshaw SM. Difference between pre-operative and cardiopulmonary bypass mean arterial pressure is independently associated with early cardiac surgery-associated acute kidney injury. J Cardiothorac Surg 5: 71; 2010.

86. Doty JR, Wilentz RE, Salazar JD, Hruban RH, Cameron DE: Atheroembolism in cardiac surgery. Ann Thorac Surg 2003; 75: 1221–1226.
87. Sreeram GM, Grocott HP, White WD, Newman MF, Stafford-Smith M. Transcranial Doppler emboli count predicts rise in creatinine after coronary artery bypass graft surgery. J Cardiothorac Vasc Anesth 18: 548-51; 2004.
88. Kalpokas MV, Nixon IK, Kluger R, Beilby DS, Silbert BS. Carbon dioxide field flooding versus mechanical de-airing during open-heart surgery: a prospective randomized controlled trial. Perfusion 18: 291-4; 2003.
89. Dalmas JP, Eker A, Girard C, Flamens C, Neidecker J, Obadia JF, Montagna P, Lehot JJ, Jegaden O, Mikaeloff P. Intracardiac air clearing in valvular surgery guided by transesophageal echocardiography. J Heart Valve Dis 5: 553-7; 1996.
90. Taylor KM. SIRS--the systemic inflammatory response syndrome after cardiac operations. Ann Thorac Surg 61: 1607-8; 1996.
91. Menasche P. The systemic factor: the comparative roles of cardiopulmonary bypass and off-pump surgery in the genesis of patient injury during and following cardiac surgery. Ann Thorac Surg 72: S2260-5; S5-6, S7-70; 2001.
92. Kharazmi A, Andersen LW, Baek L, Valerius NH, Laub M, Rasmussen JP. Endotoxemia and enhanced generation of oxygen radicals by neutrophils from patients undergoing cardiopulmonary bypass. J Thorac Cardiovasc Surg 98: 381-5; 1989.
93. Kirklin JK, Westaby S, Blackstone EH, Kirklin JW, Chenoweth DE, Pacifico AD. Complement and the damaging effects of cardiopulmonary bypass. J Thorac Cardiovasc Surg 86: 845-57; 1983.
94. Sawa Y, Shimazaki Y, Kadoba K, Masai T, Fukuda H, Ohata T, Taniguchi K, Matsuda H. Attenuation of cardiopulmonary bypass-derived inflammatory reactions reduces myocardial reperfusion injury in cardiac operations. J Thorac Cardiovasc Surg 111: 29-35; 1996.
95. Laffey JG, Boylan JF, Cheng DC. The systemic inflammatory response to cardiac surgery: implications for the anesthesiologist. Anesthesiology 97: 215-52; 2002.
96. Wang S, Palanzo D, Undar A. Current ultrafiltration techniques before, during and after pediatric cardiopulmonary bypass procedures. Perfusion 27: 438-46; 2012
97. Habib RH, Zacharias A, Schwann TA, Riordan CJ, Engoren M, Durham SJ, Shah A: Role of hemodilutional anaemia and transfusion during cardiopulmonary bypass in renal injury after coronary revascularization: implications on operative outcome. Crit Care Med 2005; 33: 1749–1756.

98. Karkouti K, Beattie WS, Wijeysundera DN, Rao V, Chan C, Dattilo KM, Djaiani G, Ivanov J, Karski J, David TE: Hemodilution during cardiopulmonary bypass is an independent risk factor for acute renal failure in adult cardiac surgery. J Thorac Cardiovasc Surg 2005; 129: 391–400.
99. Huybregts RA, de Vroege R, Jansen EK, van Schijndel AW, Christiaans HM, van Oeveren W: The association of hemodilution and transfusion of red blood cells with biochemical markers of splanchnic and renal injury during cardiopulmonary bypass. Anesth Analg 2009; 109: 331–339.
100. Haase M, Haase-Fielitz A, Bellomo R, Devarajan P, Story D, Matalanis G, Reade MC, Bagshaw SM, Seevanayagam N, Seevanayagam S, Doolan L, Buxton B, Dragun D: Sodium bicarbonate to prevent increases in serum creatinine after cardiac surgery: a pilot double-blind, randomized controlled trial. Crit Care Med 2009; 37: 39–47.
101. Heringlake M, Heinze H, Schubert M, Nowak Y, Guder J, Kleinebrahm M, Paarmann H, Hanke T, Schon J: A peri-operative infusion of sodium bicarbonate does not improve renal function in cardiac surgery patients: a prospective observational cohort study. Crit Care 2012; 16:R156.
102. Welten GM, Chonchol M, Schouten O, Hoeks S, Bax JJ, van Domburg RT, van Sambeek M, Poldermans D: Statin use is associated with early recovery of kidney injury after vascular surgery and improved long-term outcome. Nephrol Dial Transplant 2008; 23: 3867–3873.
103. 97 Billings FT, Pretorius M, Siew ED, Yu C, Brown NJ: Early postoperative statin therapy is associated with a lower incidence of acute kidney injury after cardiac surgery. J Cardiothorac Vasc Anesth 2010; 24: 913–920.
104. Argalious M, Xu M, Sun Z, Smedira N, Koch CG: Preoperative statin therapy is not associated with a reduced incidence of postoperative acute kidney injury after cardiac surgery. Anesth Analg 2010; 111: 324–330.
105. Prowle JR, Calzavacca P, Licari E, Ligabo EV, Echeverri JE, Haase M, Haase-Fielitz A, Bagshaw SM, Devarajan P, Bellomo R: Pilot double-blind, randomized controlled trial of short-term atorvastatin for prevention of acute kidney injury after cardiac surgery. Nephrology (Carlton) 2012; 17: 215–224.
106. Karkouti K. Transfusion and risk of acute kidney injury in cardiac surgery. Br J Anaesth 109 Suppl 1: i29-i38; 2012.
107. Almac E, Ince C. The impact of storage on red cell function in blood transfusion. Best Pract Res Clin Anaesthesiol 21: 195-208; 2007.

108. Cardo LJ, Hmel P, Wilder D. Stored packed red blood cells contain a procoagulant phospholipid reducible by leukodepletion filters and washing. Transfus Apher Sci 38: 141-7; 2008.
109. Comporti M, Signorini C, Buonocore G, Ciccoli L. Iron release, oxidative stress and erythrocyte ageing. Free Radic Biol Med 32: 568-76; 2002.
110. Koch CG, Li L, Sessler DI, Figueroa P, Hoeltge GA, Mihaljevic T, Blackstone EH. Duration of red-cell storage and complications after cardiac surgery. N Engl J Med 358: 1229-39; 2008.
111. Karkouti K, Wijeysundera DN, Yau TM, McCluskey SA, Chan CT, Wong PY, Crowther MA, Hozhabri S, Beattie WS. Advance targeted transfusion in anaemic cardiac surgical patients for kidney protection: an unblinded randomized pilot clinical trial. Anesthesiology 116: 613-21; 2012.
112. Karkouti K, Wijeysundera DN, Beattie WS; RBC Investigators. Risk associated with preoperative anemia in cardiac surgery: a multicenter cohort study. Circulation. 2008;117:478–484.
113. Kulier A, Levin J, Moser R, Rumpold-Seitlinger G, Tudor IC, Snyder-Ramos SA, Moehnle P, Mangano DT. Impact of preoperative anemia on outcome in patients undergoing coronary artery bypass graft surgery. Circulation. 2007;116:471–479.
114. Nangaku M. Chronic hypoxia and tubulointerstitial injury: a final common pathway to end-stage renal failure. J Am Soc Nephrol. 2006;17:17–25.
115. Abuelo JG. Normotensive ischemic acute renal failure. N Engl J Med. 2007;357:797–805.
116. Valeri CR, Khuri S, Ragno G. Nonsurgical bleeding diathesis in anemic thrombocytopenic patients: role of temperature, red blood cells, platelets, and plasma-clotting proteins. Transfusion. 2007;47(suppl):206S–248S.
117. Valeri CR, Cassidy G, Pivacek LE, Ragno G, Lieberthal W, Crowley JP, Khuri SF, Loscalzo J. Anemia-induced increase in the bleeding time: implications for treatment of nonsurgical blood loss. Transfusion. 2001; 41:977–983.
118. Despotis G, Eby C, Lublin DM. A review of transfusion risks and optimal management of perioperative bleeding with cardiac surgery. Transfusion. 2008;48:2S–30S.
119. Karkouti K, Wijeysundera DN, Yau TM, Callum JL, Cheng DC, Crowther M, Dupuis JY, Fremes SE, Kent B, Laflamme C, Lamy A, Legare JF, Mazer CD, McCluskey SA,

Rubens FD, Sawchuk C, Beattie WS: Acute kidney injury after cardiac surgery: focus on modifiable risk factors. Circulation 2009; 119: 495–502.

120. Bagur R, Webb JG, Nietlispach F, Dumont E, De Larochelliere R, Doyle D, Masson JB, Gutierrez MJ, Clavel MA, Bertrand OF, Pibarot P, Rodes-Cabau J: Acute kidney injury following transcatheter aortic valve implantation: predictive factors, prognostic value, and comparison with surgical aortic valve replacement. Eur Heart J 2010; 31: 865–874.
121. D'Onofrio A, Cruz D, Bolgan I, Auriemma S, Cresce GD, Fabbri A, Ronco C: RIFLE criteria for cardiac surgery-associated acute kidney injury: risk factors and outcomes. Congest Heart Fail 2010; 16(suppl 1):S32–S36.
122. Swaminathan M, Hudson CC, Phillips-Bute BG, Patel UD, Mathew JP, Newman MF, Milano CA, Shaw AD, Stafford-Smith M: Impact of early renal recovery on survival after cardiac surgery-associated acute kidney injury. Ann Thorac Surg 2010; 89: 1098–1104.
123. Englberger L, Suri RM, Li Z, Casey ET, Daly RC, Dearani JA, Schaff HV: Clinical accuracy of RIFLE and acute kidney injury network (AKIN) criteria for acute kidney injury in patients undergoing cardiac surgery. Crit Care 2011; 15:R16.
124. Robert AM, Kramer RS, Dacey LJ, Charlesworth DC, Leavitt BJ, Helm RE, Hernandez F, Sardella GL, Frumiento C, Likosky DS, Brown JR; Northern New England Cardiovascular Disease Study G: Cardiac surgery-associated acute kidney injury: a comparison of two consensus criteria. Ann Thorac Surg 2010; 90: 1939–1943.
125. Brown JR, Kramer RS, Coca SG, Parikh CR: Duration of acute kidney injury impacts long-term survival after cardiac surgery. Ann Thorac Surg 2010; 90: 1142–1148.
126. Li SY, Chen JY, Yang WC, Chuang CL: Acute kidney injury network classification predicts in-hospital and long-term mortality in patients undergoing elective coronary artery bypass grafting surgery. Eur J Cardiothorac Surg 2011; 39: 323–328.
127. Parolari A, Pesce LL, Pacini D, Mazzanti V, Salis S, Sciacovelli C, Rossi F, Alamanni F; Monzino Research Group on Cardiac Surgery Outcomes: Risk factors for perioperative acute kidney injury after adult cardiac surgery: the role of perioperative management. Ann Thorac Surg 2012; 93: 584–591.
128. Englberger L, Suri RM, Connolly HM, Li Z, Abel MD, Greason KL, Dearani JA, Schaff HV: Increased risk of acute kidney injury in patients undergoing tricuspid valve surgery. Eur J Cardiothorac Surg 2013; 43: 993–999.

129. Lagny et al. Jean-Olivier Defraigne; Incidence and outcomes of acute kidney injury after cardiac surgery using either criteria of the RIFLE classification.BMC Nephrology (2015)16:76
130. Grayson AD, Khater M, Jackson M, Fox MA: Valvular heart operation is an independent risk factor for acute renal failure. Ann Thorac Surg 2003; 75: 1829–1835.
131. Yamamoto et al. Renal Function–Based Contrast Dosing Predicts Acute Kidney Injury Following Transcatheter Aortic Valve Implantation. JACC Cardiovasc Interv. 2013 May;6(5):479-86.
132. Lassnigg A, Schmidlin D, Mouhieddine M, Bachmann LM, Druml W, Bauer P, Hiesmayr M: Minimal changes of serum creatinine predict prognosis in patients after cardiothoracic surgery: a prospective cohort study. J Am Soc Nephrol 2004; 15: 1597–1605.
133. Kolli H, Rajagopalam S, Patel N, Ranjan R, Venuto R, Lohr J, Arora P: Mild acute kidney injury is associated with increased mortality after cardiac surgery in patients with EGFR <60 ml/min/1.73 m(2). Ren Fail 2010; 32: 1066–1072.
134. schiffl el al., Lang SM, Fischer R: Daily hemodialysis and the outcome of acute renal failure. N Engl J Med (2002) 31;346(5):305-10
135. Nuromohamed, SA et al.journal of critical care 2011; 26:213
136. Alexander Zarbock, MelanieMeersch; Effect of Early vs Delayed Initiation of Renal Replacement Therapy on Mortality in Critically Ill Patients With Acute Kidney Injury. JAMA.2016;315(20):2190-2199
137. Hashemzadeh K, Hashemzadeh S, Dehdilani M; Risk factors and outcomes of acute renal failure after open cardiac surgery. Asian Cardiovasc Thorac Ann. 2012 Jun;20(3):275-80
138. Kramer RS, Quinn RD, Groom RC, Braxton JH, Malenka DJ, Kellett MA, Brown JR; Northern New England Cardiovascular Disease Study Group: Same admission cardiac catheterization and cardiac surgery: is there an increased incidence of acute kidney injury? Ann Thorac Surg 2010; 90: 1418–1423; discussion 1423–1424.
139. Pieri et al., Giovanni Landoni; Outcome of cardiac surgery in patients with low preoperative ejection fraction. BMC Anesthesiology (2016) 16:97
140. Yan-Bei Sun, Bi-Cheng Liu, Yun Zou, Jia-Rong Pan, Yuan Tao & Min Yang (2016) Risk factors of acute kidney injury after acute myocardial infarction, Renal Failure, 38:9, 1353-1358, DOI: 10.3109/0886022X.2016.1148558

141. T. Tarvasmäki et al. ,Piotr Góral; Acute kidney injury in cardiogenic shock: in search of early detection and clinical certainty. https://doi.org/10.1002/ejhf.958
142. Zhongguo Wei Zhong Bing Ji Jiu Yi Xue.; Prognostic significance of early acute renal failure in patients with cardiogenic shock after acute myocardial infarction. 2004 Sep; 16(9):520-2.
143. WANG ET AL., Yang Yu; Preoperative Prophylactic Intraaortic Balloon Pump Reduces the Incidence of Postoperative Acute Kidney Injury and Short-Term Death of High-Risk Patients Undergoing Coronary Artery Bypass Grafting: A Meta-Analysis of 17 Studies. Ann Thorac Surg .2016;101:2007–19
144. Chaliki HP, Mohty D, Avierinos JF, Scott CG, Schaff HV, Tajik AJ, Enriquez-Sarano M; Outcomes After Aortic Valve Replacement in Patients With Severe Aortic Regurgitation and Markedly Reduced Left Ventricular Function. 2002 American Heart Association, Inc. 2002; 106:2687-2693.
145. Kheterpal S, Tremper KK, Heung M, Rosenberg AL, Englesbe M, Shanks AM, Campbell DA Jr.; Predictors of postoperative acute renal failure after noncardiac surgery DOI:10.1097 / ALN.0b013e3181979440
146. J Thorac Cardiovasc Surg. 2011 Feb;141(2):552-8. doi: 10.1016/j.jtcvs.2010.02.045. Epub 2010 Apr 14.
147. Toledo-Pereyra LH. Organ preservation. J Surg Res 1981;30:156-80.
148. Koksoy C, LeMaire SA, Curling PE, Raskin ZC, Conklin LD, Coselli JS. Renal perfusion during thoracoabdominal aortic operations: cold crystalloid is superior to normothermic blood. Ann Thorac Surg 2002;73:730-8.
149. Fabrizio Sansone, MD*†, Alessandro Morgante, MD†, Fabrizio Ceresa, MD, Giovanni Salamone, MD, Francesco Patanè, MD; Prognostic Implications of Acute Renal Failure after Surgery for Type A Acute Aortic Dissection; AORTA, June 2015, Volume 3, Issue 3: 91-97 DOI: http://dx.doi.org/10.12945/j.aorta.2015.14.022
150. Hiromitsu Nota; Risk factors for acute kidney injury in aortic arch surgery with selective cerebral perfusion and mild hypothermic lower body circulatory arrest ; interactive CardioVascular and Thoracic Surgery, Volume 19, Issue 6, 1 December 2014, Pages 955–961, https://doi.org/10.1093/icvts/ivu241