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RISK FACTORS ASSOCIATED WITH ACUTE KIDNEY INJURY IN PATIENTS WHO UNDERWENT CARDIAC SURGERY: A RETROSPECTIVE REVIEW

by

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DECLARATION

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I Sona Nuby, declare that "**Risk factors associated with acute kidney injury in patients who underwent cardiac surgery: a retrospective review"** is my own work. All sources that have been used or quoted have been indicated and acknowledged by means of complete references and this work has not been submitted for any other degree at any other institution.

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Sona Nuby Date

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Give thanks to Lord, for he is good; his love endures forever.

All thanks and glory to God, my Father and Creator, for the wisdom and grace to complete the study and being my refuge and strength.

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ABSTRACT

Background: Acute kidney injury occurs in one out of ten cardiac surgery patients. Cardiac surgery-associated acute kidney injury not only increases patients' mortality rate but the length of stay in intensive care unit and hospital. Cardiac surgery patients' long-term risk for chronic kidney disease and heart failure increases with the incidence of acute kidney injury. Various preoperative, intraoperative and postoperative risk factors are associated with the development of cardiac surgery-associated acute kidney injury.

Aim: The aim of the study was to identify the risk factors associated with acute kidney injury in patients who underwent cardiac surgery. The identified risk factors were categorized into modifiable, partially modifiable and non-modifiable risks. The frequency of acute kidney injury among cardiac surgery patients was also assessed.

Research design: The researcher chose a quantitative correlational retrospective design and conducted a retrospective chart review to assess the risk factors associated with AKI in patients that had undergone cardiac surgery.

Methods: Non-probability purposive sampling was used to select the records of patients that underwent cardiac surgery between January 2014 and December 2018. Data collection was done using a self-developed audit tool. Descriptive and inferential statistics were used for data analysis.

Significance: The study enabled the researcher to identify and categorize the risk factors into modifiable, partially modifiable and non-modifiable categories. Early recognition and mitigation of risk factors could prevent patients from developing cardiac surgery-associated acute kidney injury.

Research findings: The study found a 22.7% frequency of CSA-AKI. Anaemia, hypoalbuminemia, hyperglycaemia, use of N-acetylcysteine and fluid overload were identified as modifiable risk factors. Bicarbonate level <22mmol/L, use of diuretics, use of antibiotics, longer duration of surgery, fresh frozen plasma use >500ml on the day of surgery, red blood cell transfusion >1L on the day of surgery and prolonged use of mechanical ventilation were partially modifiable risk factors. No non-modifiable risk factors were identified.

Keywords: Cardiac surgery-associated acute kidney injury; risk factors; modifiable, partially modifiable and non-modifiable.

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LIST OF ABBREVIATIONS

AKI- acute kidney injury

BMI-body mass index

CABG- coronary artery bypass graft

CCS- Cleveland clinic score

COPD- chronic obstructive pulmonary disease

CPB- cardiopulmonary bypass

CSA-AKI- cardiac surgery associated acute kidney injury

CVP- central venous pressure

GFR- glomerular filtration rate

ICU- intensive care unit

KDIGO- kidney disease improving global outcome

NAC- N-acetylcysteine

RIFLE- risk, injury, failure, loss, end stage

RRT- renal replacement therapy

CHAPTER 1: ORIENTATION TO THE STUDY

1.1 INTRODUCTION

Acute kidney injury (AKI) is a sudden decrease in kidney function with or without kidney damage, occurring over a few hours or days. Acute kidney injury (AKI) is characterized by a rapid onset of renal impairment resulting in the accumulation of nitrogenous waste products, fluid and electrolyte imbalance and metabolic derangement (Bellomo, Kellum & Ronco 2012:756). In the United States of America, AKI is one of the major complications that occur in cardiac surgery patients (Alshaikh, Katz, Gani, Nagarajan, Canner, Kacker et al 2018:471). The severity of AKI among cardiac surgery patients varies from asymptomatic to a need for renal replacement therapy (Ortega-Loubon, Fernández-Molina, Carrascal-Hinojal & Fulquet-Carreras 2016:688). Cardiac surgery-associated acute kidney injury (CSA-AKI) has a high incidence rate and mortality rate (Meersch, Schmidt, Hoffmeier, Aken, Wempe, Gerss et al 2017:1553; Rao, Shenoy & Gopalakrishnan 2018:535). In the United States, Alshaikh et al (2018:471) found that the risk for in-hospital mortality among cardiac surgery patients increased by tenfold with the incidence of AKI. Furthermore, the length of hospital stay and hospitalization costs increased by twofold in patients with cardiac surgery-associated AKI (Alshaikh et al 2018:471).

This chapter outlines the background to the problem and study; describes the conceptual framework, research design and methodology, and ethical considerations; defines key terms, and presents the layout of the chapters.

1.2 BACKGROUND TO THE PROBLEM

Acute kidney injury (AKI) indicates a sudden decrease in kidney function which has the potential to progress to chronic kidney disease (Palomba, Castro, Yu & Burdmann 2017:569; Lerma, Sparks & Topf 2019:45). Cardiac surgery patients' risk for long-term complications, such as heart failure, increases threefold with AKI onset (Ninni, Seunes, Ortmans, Mouton, Modine, Koussa et al 2018:55). Despite the risk for long-term complications, there is no single evidence-based intervention to prevent the occurrence

of AKI (Meyer 2015:7). Moreover, the use of some of the recommended drugs, such as steroids, high dose erythropoietin, N-acetylcysteine, sodium bicarbonate and statin, has been found to be less effective in preventing CSA-AKI (Chen, Huang, Cao & Xu 2018:52). In addition, if AKI progresses and patients become anuric, the only treatment option available is to provide supportive care with renal replacement therapy (Romagnoli, Ricci & Ronco 2018:108). The limitations in prevention and management of AKI emphasise that prevention of AKI in cardiac surgery patients should be focused on risk assessment and reversal of risk factors (Johnson, Feehally & Floege 2019:825).

Cardiac surgery-associated AKI is recognized as a global health concern. In 2017 and 2018, Australia had 20.4% and America had 24.8% post cardiac surgery patients who developed AKI (Grynberg, Polkinghorne, Ford, Stenning, Lew, Barrett et al 2017:93; Kindzelski, Corcoran, Siegenthaler & Horvath 2018:64). In a study in Canada, Wong, Onge, Korkola and Prasad (2015:37) reported that 5.4% of post-cardiac surgery patients had stage 3 AKI and among those, 60.8% required dialysis during hospital stay. In India, Karim, Yunus, Saikia, Kalita and Mandal (2017:23) reported AKI among 49% of post-cardiac surgery patients. In Cape Town, South Africa, Dlamini, Heering, Chivese and Rayner (2017:e0177460) found that 8.2% of patients admitted between July 2012 and July 2013 had developed AKI due to cardiovascular surgery with sepsis as the most common precipitating factor. The studies conducted in other African countries were focused on AKI in medical patients and there is shortage of statistical data on CSA-AKI from those countries (Halle, Chipekam, Beyiha, Fouda, Coulibaly, Hentchoya, et al. 2018:32; Yousif, Topping, Osman, Raimann, Osman, Kotanko et al. 2018:204).

Exposure to multiple pre-, intra- and postoperative risk factors enhances cardiac surgery patients' risk for developing AKI (Johnson, Feehally & Floege 2019:786). The recognized preoperative risk factors include age, diabetes mellitus, use of intra-aortic balloon pump, use of diuretics and increased preoperative serum creatinine level (Thakar, Arrigain, Worley, Yared & Paganini 2005:165; Yi, Li, Jian, Xiao, Chen, Zhang et al 2016:241). The type of cardiac surgery, cardio-pulmonary bypass time, aorta clamp time and type of anaesthetic medication (*sevoflurane*) used increase the intra-operative risk for AKI (Yoo, Shim, Song, Yang & Kwak 2014:415; Yi et al 2016:242; Saydy, Mazine, Stevens, Jeamart, Demers, Pagé et al 2018:261). Chang, Guo, Xu and Li (2017:16663) identified the use of extracorporeal membrane oxygenation as an individual risk factor for AKI. Massive

erythrocyte transfusion and low cardiac output syndrome along with the use of extracorporeal membrane oxygenation enhances the postoperative risk for AKI (Yoo et al 2014:415; Jiang, Teng, Xu, Shen, Wang, Fang et al 2016:e003754).

Since the late 1980s, several risk prediction tools have been developed to optimize high risk patients (O'Neal, Shaw & Billings 2016:187). Of these, the most popular risk prediction score is the Cleveland Clinic Score (CCS), which predicts cardiac surgery patients' risk for developing AKI (Thakar et al 2005:165). To date, none of the risk prediction scores have been validated in the South African population.

Even if the patient-related factors for operative risk remain the same, differences occur in the relative influence of each risk factor between populations (Soo-Hoo, Nemeth, Baser, Argenziano & Kurlansky 2018:e010995). Many cardiac surgery risk score systems have been available since the 1980s, but they have all employed commonly used "western" risk scoring methods (Hote 2018:e011017). Initially, scoring systems for cardiac surgery were intended to predict mortality rates after high-risk cardiac surgery. These 'western' scores were relatively less accurate in correctly predicting operative mortality in eastern populations (Hote, 2018:e011017). In the late 1980s, the spectrum of coronary artery bypass graft (CABG) patients changed rapidly and more parameters were needed in developing scoring systems. Scoring systems changed because their focus shifted from predicting mortality to predicting major morbidity too. However, all the scoring systems have been proposed from either North America or Europe. There have been no scoring systems for the assessment of these risk factors among large population sub-groups like Japan, South-east Asia or Africa (Hote 2018:e011017; Soo-Hoo, Nemeth, Baser, Argenziano & Kurlansky 2018:e010995).

1.3 PROBLEM STATEMENT

Globally, approximately 22.3% of cardiac surgery patients are affected with AKI (Hu, Chen, Liu, Yu, Zou & Ding 2016:84). However, little information is available on the risk factors associated with CSA-AKI among the South African population.

In the unit where the researcher worked, on average one in ten patients developed AKI post cardiac surgery. The development of AKI increases the risk of mortality, prolongs the

patient's length of stay in intensive care unit (ICU) as well as the long-term risk of developing chronic kidney disease (Xie, Wan, Ji, Chen, Liu, Chen et al 2017:277; Palomba, Castro, Yu & Burdmann 2017:570). Although considerable progress has been made in understanding the pathophysiology and poor prognosis related to CSA-AKI, it is still a potential challenge to prevent and manage these patients. Prevention of AKI needs a thorough knowledge of the modifiable and non-modifiable risk factors. Risk assessment could be beneficial if exposure to the risk factors were timed and could be predicted (Ronco, Bellomo, Kellum & Ricci 2019:94, 95, 251).

As an ICU nurse in an ICU in Gauteng Province, South Africa, the researcher observed that no systematic pre-operative risk assessment was done to identify cardiac surgery patients' risk for developing AKI and there was uncertainty about the potential risk factors. This motivated the researcher to conduct this study to determine the pre-operative risk and potential risk factors associated with AKI in patients that undergo cardiac surgery. The researcher wished to categorize identified risk factors as modifiable, partially modifiable and non-modifiable risk factors.

1.4 AIM AND OBJECTIVES OF THE STUDY

The aim of the study was to identify the risk factors associated with acute kidney injury (AKI) in patients who undergo cardiac surgery.

The objectives of the study were to

- Assess the frequency of acute kidney injury among cardiac surgery patients in the study context.
- Identify the risk factors associated with acute kidney injury in patients who undergo cardiac surgery.
- Determine the association between the identified risk factors and acute kidney injury in patients who undergo cardiac surgery.
- Categorize the identified risk factors into modifiable, partially modifiable and non-modifiable categories.

Two hypotheses were tested in the study:

i. **Null hypothesis (Ho):** The development of AKI in cardiac surgery patients is not associated with modifiable, partially modifiable and non-modifiable risk factors.
ii. **Alternate hypothesis (Ha)**: The development of AKI in cardiac surgery patients is associated with modifiable, partially modifiable and non-modifiable risk factors.

1.5 RESEARCH QUESTION

In order to achieve the aim, the study wished to answer the following question:

What are the risk factors associated with acute kidney injury in patients who undergo cardiac surgery?

1.6 SIGNIFICANCE OF THE STUDY

The study enabled the researcher to identify the risk factors associated with AKI and their frequency among South African cardiac surgery patients. The study provided an opportunity for the researcher to categorize the risk factors into modifiable, partially modifiable and non-modifiable categories. The identified risk factors could be implemented in early recognition of patients at risk for CSA-AKI. Mitigating the modifiable and partially modifiable risk factors could prevent cardiac surgery patients from developing AKI. Cardiac surgery patients could have a better outcome in terms of decreased length of stay in ICU and hospital, reduced need for renal replacement therapy, and mortality.

1.7 CONCEPTUAL FRAMEWORK

The researcher adapted the input-process-output model (Dulebohn & Hoch 2017:571) as the conceptual framework for the study (see figure 1.1). The researcher adapted the model by including a feedback component. The input-process-output-feedback model provided a general structure for the phenomenon under study and guided the direction of the study. The influence of the preoperative CSA-AKI risk score and association between the pre-, intra- and post-operative risk factors in developing CSA-AKI can be better

illustrated with the input-process-output-feedback model. Furthermore, the model helped the researcher to relate the impact of AKI on cardiac surgery patients' outcomes.

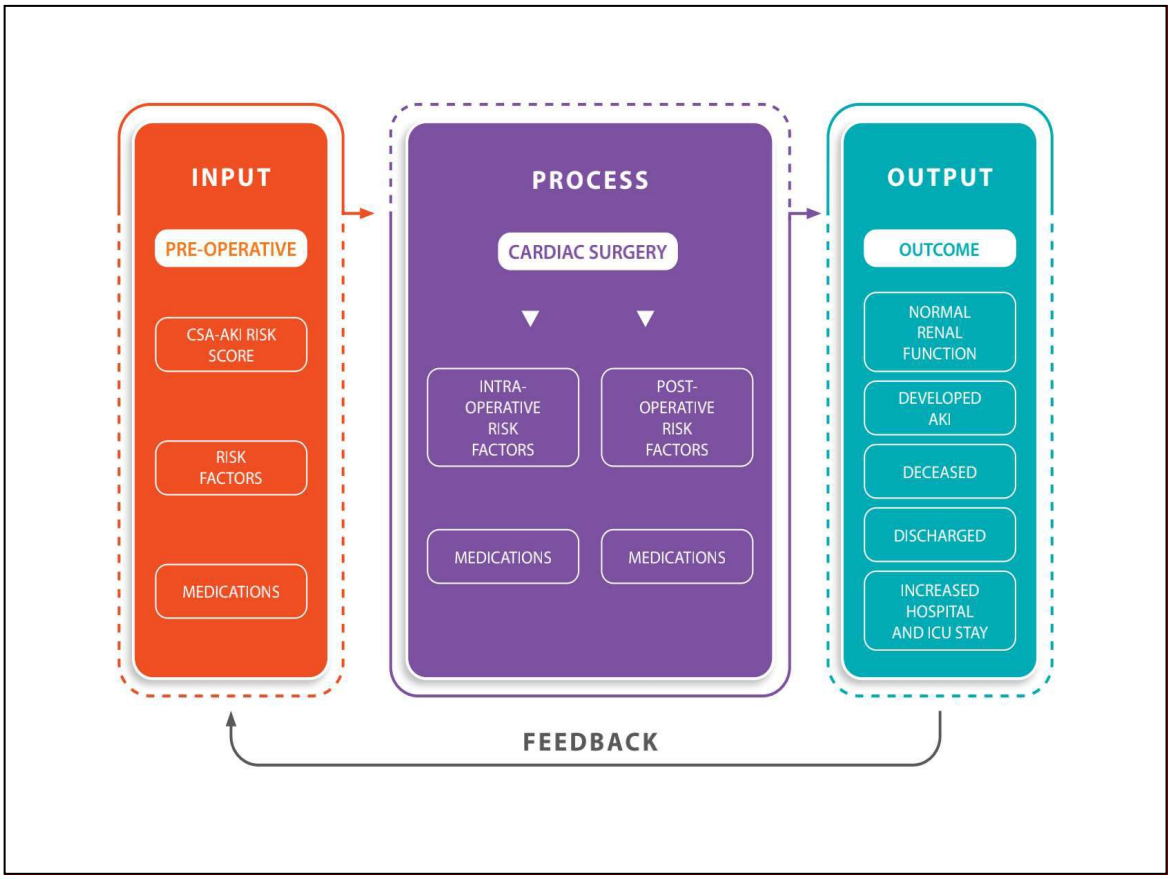

Figure 1.1 Conceptual framework for risk factors associated with AKI in patients who undergo cardiac surgery

Adapted from: Dulebohn and Hoch (2017:571)

- ***Input*** in the conceptual framework indicates the preoperative phase: the risk with which patients undergo cardiac surgery. The preoperative risk for CSA-AKI arises from comorbidities, diagnostic studies or from medications administered to the patient. During the preoperative phase, cardiac surgery patients should be screened to assess the risk for CSA-AKI.

- ***Process*** reflects cardiac surgery (intra-operative) and postoperative phases. During the intra-operative phase, the patient's exposure to risk factors, such

as anaesthetic medications, cardio-pulmonary bypass pump, aorta cross clamp as well as the type of cardiac surgery, contributes to the AKI risk (Yoo et al 2014:415; Yi et al 2016:242; Saydy et al 2018:261). Postoperative use of extracorporeal membrane oxygenation, massive erythrocyte transfusion and low cardiac output syndrome also increase the patient's risk for developing AKI (Yoo et al 2014:415; Jiang et al 2016:e003754).

- ***Output*** depicts the patient's outcome after cardiac surgery. The patient's outcome will be measured in terms of normal renal function, development of AKI, deceased, discharged, increased length of stay in the hospital and the ICU.

- ***Feedback*** indicates the retrospective analysis of the cardiac surgery patients' documents. The researcher conducted a retrospective review of the cardiac surgery patients' documents to assess the frequency of CSA-AKI, identify possible risk factors associated with the development of CSA-AKI, and categorize the risk factors into modifiable, partially modifiable and non-modifiable categories.

1.8 DELINEATION

Delineation refers to setting boundaries for a study within manageable limits (Basavanthappa 2011:98, 99). The study was limited to one selected private hospital in Gauteng and included medical records only of patients who had undergone cardiac surgery between January 2014 and December 2018.

1.9 RESEARCH DESIGN AND METHODOLOGY

Polit and Beck (2017:41) describe a research design as "the overall plan for addressing a research question, including the specifications for enhancing the integrity of the study". The nature of research questions guides researchers to choose appropriate research designs to collect data to answer the research questions (Ellis 2016:15; Polit & Beck 2017:41). In this study, the researcher chose a quantitative correlational retrospective design to answer the research questions. Quantitative designs enable the collection of

numerical information by means of formal measurements which need statistical analysis (Polit & Beck 2017:41). According to Creswell (2014:4), quantitative research deals with numbers and statistics that are collected by a structured instrument, analysed and structured into an organised report to examine relationships between phenomena. The researcher considered a quantitative correlational design appropriate to examine the relationship between the variables (risk factors and AKI) in patients that had undergone cardiac surgery. As illustrated in the feedback component of the conceptual framework, the researcher conducted a retrospective chart review to assess the risk factors associated with AKI in patients that underwent cardiac surgery. A retrospective chart review involves collecting information that is available from data sources. The data sources include case notes, inpatient case files, attendance registers, nursing records, pharmacy records, disease registries, and laboratory records (Sarkar & Seshadri. 2014:JG01). The quantitative correlational retrospective chart review enabled the researcher to identify risk factors and statistically assess the association between risk factors and AKI in patients that underwent cardiac surgery (Sarkar & Seshadri 2014:JG01; Polit & Beck 2017:51, 61). Table 1.1 summarises the research methodology (see chapter 3 for full discussion).

Table 1.1 Research methodology of the study

Description	Application
The s*etting* refers to the location and conditions in which data collection occurs in a study (Polit & Beck 2017:744).	The setting consisted of ➢ A 323-bed private hospital with 4 ICUs, 2 high care units and 10 wards; An 11-bed cardiothoracic ICU; ➢ 2 cardiothoracic surgeons and 5 cardiologists worked permanently in this hospital; 10 Critical care specialized nurses, 16 Professional nurses and 4 Enrolled nurses worked permanently in the ICU; ➢ Additional specialist consultation was only available on referral by the primary doctor; ➢ Patient details were maintained in the admission book and electronic billing system called 'Impilo'.
The *unit of analysis* refers to the entire cases on which the researcher focuses in the study (Polit & Beck 2017:249).	➢ In this study, the unit of analysis referred to patients' documents, including admission assessment documents, doctors' notes, ward prescription charts,

	ICU charts and laboratory results. ➢ The inclusion criteria were ✓ Documents of all patients aged 18 years and older. ✓ Documents of all patients admitted to the specific ICU following cardiac surgeries, such as coronary artery bypass graft, aortic valve replacement or repair, mitral valve repair or replacement, tricuspid valve repair or replacement, combination of coronary artery bypass graft and valve repair or replacement, closure of atrial or ventricular septal defect repair, from January 2014 to December 2018. ➢ The exclusion criteria were. ✓ Documents of patients with preoperative end-stage kidney disease on dialysis prior to cardiac surgery. Documents of patients that had had kidney transplantation prior to cardiac surgery.
Sampling refers to selecting part of the population to represent the entire population in which a researcher is interested (Polit & Beck 2017:743).	Non-probability consecutive sampling was used for the study. Documents of patients that had undergone cardiac surgery between January 2014 and December 2018 were included.
Data collection refers to the systematic collection of information during the course of the study for statistical exploration of a problem. Data provide the basis for testing hypotheses and provide answers to research questions	A self-developed audit tool was used for data collection.

(Basavanthappa 2011:194 ,195).	
Data analysis refers to the systematic organization and synthesis of research data in order to test hypotheses (Polit & Beck 2017:725).	Descriptive and inferential statistics were used for data analysis. The Pearson chi-square test was performed to test the association between the risk factors and CSA-AKI.
Rigour minimizes bias and ensures control over variables under study (Polit & Beck 2017:160).	Validity and reliability were applied to the data- collection tool to determine rigour. The validity of the audit tool was assessed by means of content validity in which the researcher obtained opinion from a panel of experts. Intra-rater reliability was used to ensure the reliability of the results as the data collection was done by researcher alone.

1.10 DEFINITIONS OF KEY TERMS

For the purposes of the study, the following terms were used as defined below.

1.10.1 Acute kidney injury (AKI)

KDIGO (2012:19) defines AKI as “Increase in serum creatinine by ≥0.3mg/dl (≥26.5µmol/l) within 48hrs or increase in serum creatinine to ≥1.5times the baseline which is known or presumed to have occurred within the prior 7days. Urine volume <0.5ml/kg/hr for 6hrs.”

In this study, acute kidney injury indicated an increase in the patient’s serum creatinine to ≥26.5µmol/L and urine output <0.5ml/kg/hr for more than 6 hours that developed within 7 days after cardiac surgery during their stay in ICU.

1.10.2 Cardiac surgery

Cardiac surgery is any type of surgery performed on the muscles, valves or arteries of the heart through a sternotomy wound (Phillips & Gotter 2018:1). Cardiac surgeries can be elective or emergency. Elective surgeries are pre-scheduled surgery in which a patient

has a stable cardiac function for days and weeks before the surgery. Emergency surgeries are performed within 24hrs to minimize the clinical deterioration (Clark 1994:273).

In this study, cardiac surgery patients referred to patients that underwent coronary artery bypass graft (CABG), aortic valve replacement or repair, mitral valve repair or replacement, tricuspid valve repair or replacement, combination of CABG and valve repair or replacement, or closure of atrial or ventricular septal defect repair.

1.10.3 Cardiac surgery associated acute kidney injury (CSA-AKI)

Cardiac surgery associated acute kidney injury (CSA-AKI) in the study context is explained using the KDIGO criteria as indicated by creatinine ≥26.5μmol/l and urine output <0.5ml/kg/hr for more than 6hrs (KDIGO 2012:19).

In this study, any patients that developed AKI according to the KDIGO criteria after cardiac surgery during their stay in ICU were considered to have CSA-AKI.

1.10.4 Intensive care unit (ICU)

Intensive care units (ICUs) refer to units which provide elaborate medical interventions to critically ill patients, making use of technologically sophisticated equipment and nurses with specialized knowledge in those areas of care (Urden, Stacy & Lough 2014:2).

In this study, the ICU referred to the selected cardiothoracic ICU where patients were admitted after cardiac surgery.

1.10.5 Risk factors

A risk factor is a variable that is present in an individual or population which is associated with the presence of a disease or increases the probability of developing a disease in the future (Skorecki, Chertow, Marsden, Taal & Yu 2016:670).

In the study, risk factors were variables associated with the development of AKI in cardiac surgery patients. Risk factors may be modifiable, partially modifiable and non-modifiable.

1.11 ETHICAL CONSIDERATIONS

Ethics deals with matters of right and wrong. When humans are used as study participants, care must be taken to ensure that their rights are protected (Polit & Beck 2017:139). Ethical considerations are concerned with the degree to which research procedures adhere to professional, legal and social obligations to study participants (Polit & Beck 2017:139). Accordingly, the researcher obtained permission to conduct the study and upheld the principles of beneficence, respect for human dignity and justice.

1.11.1 Permission

The researcher obtained written ethical approval and permission to conduct the study from the University of Pretoria's Research Ethics Committee (see Annexure I) and Ethical Committee of the private hospital health care group (see Annexure A), as well as from the Hospital Manager (see Annexure J) and Nursing Service Manager (see Annexure K) of the hospital where the study was conducted. The researcher also obtained permission to use Cleveland Clinic Score from its developers (see Annexure H).

1.11.2 Beneficence

Beneficence imposes a duty on researchers to maximize benefits and to minimize harm to participants and others (Polit & Beck 2017:141). The principle of beneficence includes the right to freedom from harm and discomfort and to protection from exploitation (Polit & Beck 2017:139). The study was done only with the patients' documents and the researcher ensured that the documents were kept safe and not damaged. The face validity of the audit tool was done at a convenient time and ensured that the experts did not experience any financial loss.

1.11.3 Respect for human dignity

The principle of respect for human dignity includes the right to self-determination and right to full disclosure (Polit & Beck 2017:140). Permission was obtained from the hospital manager before starting data collection. Consent was not obtained from patients as the study involved a retrospective review of patients' documents.

1.11.4 Justice

The principle of justice includes the right to fair treatment and privacy (Polit & Beck 2017:141). Including all the units that met the inclusion criteria ensured equality. All information obtained was kept confidential within the hospital complex. To maintain anonymity, no patient identification details, such as name or hospital visit number, were recorded in the audit tool. Numerical codes were recorded on the audit tool to identify patient documents.

1.12 LAYOUT OF THE CHAPTERS

The study consists of five chapters. Table 1.2 briefly summarises the chapters.

Table 1.2 Layout of the chapters

Chapter	Title	Description
Chapter 1	Orientation to the study	Outlines the problem, purpose, research design and methodology and ethical considerations of the study and defines key terms.
Chapter 2	Literature review	Discusses the literature review conducted on AKI and CSA-AKI.
Chapter 3	Research design and methodology	Describes the research design and methodology used in the study.
Chapter 4	Data analysis and interpretation and findings	Discusses the data analysis and interpretation and findings, with reference to the literature review.
Chapter 5	Findings, limitations and recommendations	Briefly describes the findings and limitations of the study and makes recommendations for practice and further research.

1.13 CONCLUSION

This chapter described the background to the study and problem, the aim and objectives, research design and methodology, and ethical considerations of the study. Chapter 2 discusses the literature review on AKI and CSA-AKI conducted for the study.

CHAPTER 2: LITERATURE REVIEW

2.1 INTRODUCTION

Chapter 1 outlined the problem, purpose, research design and methodology, and ethical considerations of the study. This chapter discusses the literature review conducted for the study. A literature review involves researching, reading and understanding literature relevant to a study (Brink, van der Walt & van Rensburg 2018:55). The purpose of a literature review is to convey what is currently known regarding the topic of interest and to assist researchers to comprehend and extend their knowledge of the phenomenon under study (Polit & Beck 2017:99).

The literature review covered acute kidney injury (AKI) and cardiac surgery-associated acute kidney injury (CSA-AKI), its historical background, definition, epidemiology, causes, phases, signs and symptoms, diagnostic methods, preventive strategies and treatment modalities and complications related to AKI.

2.2 ACUTE KIDNEY INJURY (AKI)

Acute kidney injury (AKI) is a sudden decrease in kidney function with or without kidney damage, occurring over a few hours or days, and a serious, worldwide public health concern. Diabetes, hypertension, and advanced age are primary risk factors for AKI and it is increasingly recognised as an in-hospital complication of sepsis, heart conditions, and surgery. Between 2000 and 2014, a drastic rise was seen in the number of patients admitted with AKI and the need for dialysis in the United States of America (Pavkov, Harding & Burrows 2018:291, 292). At a general hospital in Cameroon, 15 out of 100 patients were diagnosed with AKI between January 2015 and January 2016 with an incidence rate of 22.3% (Halle et al 2018:32). In France, the annual percentage increase in the incidence of AKI requiring dialysis from 2009 to 2014 was +1.7% while the in-hospital mortality among AKI patients remained the same (Garnier, Couchoud, Landais, Moranne & Burdmann 2019:0211541). A systematic review and meta-analysis of long-term outcomes after AKI, including risks of death, chronic kidney disease and

end-stage kidney disease, confirmed the significant event rate of these outcomes and demonstrated that AKI severity and the clinical setting in which AKI occurred were important risk determinants. Each year about 13.2 deaths occur in every 100 people due to AKI. Moreover, a lack of proven interventions and uncertainties over optimal care provision mean that the long-term sequelae of AKI present a major unmet clinical need (Selby & Taal 2019:22). The high morbidity and mortality induced by AKI create a major challenge to the critical care environment (Seller-Pérez, Más-Font, Pérez-Calvo, Villa-Diaz, Celaya-López & Herrera-Gutiérrez 2016:379). The lack of effective treatment other than the use of renal replacement therapy to manage AKI increases the financial burden to the health care system. The best approach relies on early secondary prevention. Early diagnosis facilitation needs a broader definition and a marker with more sensitivity and early detection capacity than serum creatinine (Seller-Pérez et al 2016:380).

This section on AKI discusses its historical background, definition, epidemiology, etiological factors, risk factors, pathophysiology, clinical manifestation, diagnosis, prevention, treatment and complications.

2.2.1 Historical background

Acute kidney injury has affected humanity from ancient times due to the trauma sustained by our ancestors in their survival as hunters and gatherers. Yet, for centuries there was no specific name for the condition. In 1802, William Heberden described it as *ischuria renalis* (Eknoyan 2008:308, 309). In 1909, William Osler used the term "*acute* Bright's disease" to describe the syndrome (Makris & Spanou 2016:86). During the First World War, AKI became known as "war nephritis" (Dunn & McNee 1917:750). In 1951, Homer Smith introduced the term "acute renal failure" and "acute tubular necrosis" due to evidence of patchy renal tubular necrosis. For a long time "acute renal failure" and "acute tubular necrosis" were used interchangeably to describe AKI (Makris & Spanou 2016:86).

Acute renal failure has now been replaced by the term "acute kidney injury" (AKI), which signifies the extent of kidney injury that existed before it could be measured using the routine laboratory test (Bellomo, Kellum & Ronco 2012:756). In 1918, MacNider (1918:521, 536) conducted a study of acute mercuric chloride intoxications in dogs with

special reference to the kidney damage or injury, and coined the term “acute kidney injury” (AKI) (Kellum & Ronco 2011:155).

2.2.2 Definitions

Acute kidney injury (AKI) is characterized by rapid onset of renal impairment resulting in the accumulation of nitrogenous waste products, fluid and electrolyte imbalance and metabolic derangement (Bellomo, Kellum & Ronco 2012:756). Acute kidney injury demands a uniform definition to apply in clinical practice and research. A uniform definition ensures consistency in recognition and treatment in the health care system (Thomas, Blaine, Dawnay, Devonald, Ftouh, Laing et al 2015:62). Even though the term “acute kidney injury” became popular after 1918, a consensus definition was only developed in 2004 by the Acute Dialysis Quality Initiative (ADQI) group (Kellum & Ronco 2011:155; Bellomo, Ronco, Kellum, Mehta & Palevsky 2004:R206).

The Acute Dialysis Quality Initiative (ADQI) developed a multi-level classification based on the creatinine, glomerular filtration rate (GFR) and urine output. In 2004, they classified renal dysfunction using the RIFLE criteria to include the wide range of disease spectrum. The acronym RIFLE indicates **R**isk for renal dysfunction, **I**njury to the kidney, **F**ailure of kidney function, **L**oss of kidney function and **E**nd-stage kidney disease (Bellomo, Ronco, Kellum et al 2004:R206). RIFLE built a new paradigm by advancing the focus from acute renal failure to AKI. The new focus made provision to incorporate patients with functional impairment other than actual damage (Makris & Spanou 2016:87, 88). Table 2.1 summarises the RIFLE criteria.

Table 2.1 RIFLE criteria

Stage	GFR criteria	Urine output criteria
Risk	Increased serum creatinine ×1.5 or GFR decrease > 25%	Urine output < 0.5ml/kg/hr × 6hours
Injury	Increased serum creatinine ×2 or GFR decrease > 50%	Urine output < 0.5ml/kg/hr ×12hours
Failure	Increase serum creatinine ×3, GFR decrease75% or serum creatinine ≥ 4mg/dl	Urine output < 0.3ml/kg/hr × 24hrs. Anuria ×12hours
Loss	Complete loss of kidney function > 4 weeks	

ESKD	End-stage kidney disease for > 3months

Source: Bellomo, Ronco, Kellum, Mehta & Palevsky (2004:R206)

Table 2.1 indicates that RIFLE criteria have five stages depending on the severity of creatinine level, GFR and urine output. The last two stages indicate absolute loss of kidney function and urine production is completely impaired.

In 2007, the Acute Kidney Injury Network (AKIN) modified the RIFLE criteria to enhance the sensitivity for AKI diagnosis criteria and categorized AKI into 3 stages (Mehta, Kellum, Shah, Molitoris, Ronco, Warnock et al 2007:R31). Table 2.2 outlines the Acute Kidney Injury Network classification and staging for AKI. The Acute Kidney Injury Network criteria removed the GFR criterion and outcome classes that were included in RIFLE criteria. Acute kidney injury diagnosis using Acute Kidney Injury Network criteria requires a change in two serum creatinine values within 48 hours whereas in RIFLE it was 7 days (Makris & Spanou 2016:88). The major limitation with RIFLE and Acute Kidney Injury Network criteria is the need for baseline serum creatinine value which is not frequently available. For this reason, an increase in serum creatinine is not recognized and patients are frequently categorized inappropriately (Huber, Schneider, Lahmer, Küchle, Jungwirth, Schmid et al 2018:12465).

Table 2.2 Acute Kidney Injury Network classification and staging for AKI

Stage	Serum creatinine criteria	Urine output criteria
Stage 1	Increase in serum creatinine of ≥0.3mg/dl (≥26.5µmol/L) or ≥1.5 - 2.0 fold increase from baseline.	Urine output <0.5ml/kg/h for 6hours.
Stage 2	Increase in serum creatinine >2.0-3.0 fold from baseline.	Urine output <0.5ml/kg/hr for 12hours.
Stage 3	Increase in serum creatinine >3 fold from baseline or increase of serum creatinine ≥4.0mg/dl (≥354µmol/l) with an acute increase of at least 0.5mg/dl (44µmol/l).	Urine output <0.3ml/kg/h for 24h or anuria for 12hours.

Source: Mehta, Kellum, Shah, Molitoris, Ronco, Warnock et al (2007:R31)

The Acute Kidney Injury Network criteria staged AKI in three stages, based on the baseline creatinine level as well as on the actual increase in creatinine. Urine output is also taken into consideration for staging AKI.

In 2012, considering the shortcomings, Kidney disease improving global outcome (KDIGO) combined the RIFLE and Acute Kidney Injury Network criteria and proposed a definition to apply in clinical practice, public health, and research. KDIGO (2012:19) defines AKI as

- *Increase in serum creatinine by ≥0.3mg/dl (≥26.5µmol/l) within 48hrs or*
- *Increase in serum creatinine to ≥1.5times the baseline which is known or presumed to have occurred within the prior 7days.*
- *Urine volume <0.5ml/kg/hr for 6hrs.*

The new definition by KDIGO simplified and unified the staging criteria by including the 48hr window period and increase in ≥1.5 times from the baseline serum creatinine. Table 2.3 presents the KDIGO criteria for AKI staging. The inclusion of the GFR criteria enhances its applicability in the paediatric population as well (KDIGO 2012:19, 21).

Table 2.3 KDIGO staging of AKI

Stage	Serum creatinine	Urine output
Stage 1	Increase in serum creatinine by 1.5-1.9 from baseline OR ≥0.3mg/dl (26.5µmol/l)	Urine volume <0.5ml/kg/h for 6-12hours
Stage 2	Increase in serum creatinine ≥2.0-2.9 times from baseline.	Urine volume <0.5ml/kg/h for ≥12hours.
Stage 3	Increase in serum creatinine ≥3.0 times from baseline OR Increase in serum creatinine to ≥4.0mg/dl (≥353.6µmol/l) OR Initiation of renal replacement therapy OR In patients <18years, decrease in eGFR to <35ml/min per 1.73 ㎡	Urine volume <0.3ml/kg/h for ≥24hours OR Anuria for ≥12hours.

Source: KDIGO (2012:19)

Table 2.3 shows that there are three main stages of AKI in KDIGO staging. KDIGO staging also focuses on the creatinine level and urine output while special emphasis is given to the GFR criteria for patients <18yrs.

2.2.3 Epidemiology

Epidemiology is the study of distribution and factors associated with health-related issues or events in a defined population. Epidemiology is applied to control the health problems in the given population (Gerstman 2013:4). The incidence rate and relative causes of AKI in developed and developing countries differ widely.

In a study of 309 patients in a tertiary care hospital in India, Vikrant, Gupta and Singh (2018:958) found that AKI occurred in every 6-8 patients per 1,000 hospital admissions over a period of 18 months. Of the patients, 92.2% had community-acquired AKI while 7.8% had hospital-acquired AKI. Of the etiological factors for AKI, 87.4% were medical, 9.4% were surgical and 3.2% were obstetric. The main risks were sepsis, followed by hypovolemia, toxins and cardiac conditions (Vikrant, Gupta & Singh 2018:958).

In a worldwide survey on 354 paediatric AKI patients from 92 centres in 41 countries, Macedo, Cerdá, Hingorani, Hou, Bagga, Burdmann et al (2018:e0196586) reported a significantly higher incidence of community-acquired AKI (80%) in low and lower-middle income countries than higher income countries (20%). In both ICU and non-ICU settings, there were more deaths in lower-middle income countries patients than in upper-middle income countries and higher income countries patients. AKI occurred in different circumstances in higher income countries compared to upper-middle income countries and lower-middle income countries countries. In lower-middle income countries countries, the high rate of community acquired-AKI was likely associated with public health infrastructure-related problems, such as poor sanitation, endemic infections and water-borne gastroenteritis. The overall incidence of paediatric AKI cases was 28.5%, and of these, 21.5% needed renal replacement therapy (RRT). The mortality rate varied from 1.2% among higher income countries to 19.6% among lower-middle income countries (Macedo et al 2018:e0196586).

In 2017, Sawhney, Marks, Fluck, McLernon, Prescott and Black (2017:9) analysed 16,453 patients (2,623 with AKI; 13,830 without AKI) in Scotland, who survived an index hospital admission in 2003, to identify the causes of and predict readmissions. The main outcome was unplanned readmission or death within 90 days of discharge. Of the patients, 2,702 were readmitted and 363 died without readmission. The main reason for readmission was acute pulmonary oedema. The study concluded that AKI is a strong, consistent and independent risk factor for unplanned readmission, especially readmission with acute pulmonary oedema. Moreover, pre-emptive planning at discharge should be considered to minimise readmission in this high risk group (Sawhney et al 2017:9).

In a study to identify any seasonal variation in the occurrence of and outcome following AKI in the UK between October 2015 and September 2016, Phillips, Young, Holmes, Allen, Roberts, Geen et al (2017:e13000) reported that most AKI episodes occurred between January and March and again between October and December. The same trend was seen for community acquired AKI and hospital acquired AKI, and the overall 90-day mortality for all AKI was 27.3%. Community acquired AKI occurred in 49.9% and hospital-acquired AKI occurred in 41% of patients (Phillips et al 2017:e13000).

In Japan, Iwagami, Moriya, Yasunaga, Isshiki, Sato, Mochida et al (2018:1354) examined the seasonality of AKI incidence and mortality among hospitalized patients in 38 community hospitals between 2012 and 2014. The study examined the timing of AKI diagnosis and age, association between month of hospital admission and AKI, seasonal variations in disease severity, and 30-day mortality of patients with AKI. Iwagami et al (2018:1360) found that patients with AKI showed a larger number of failing organs in winter and their 30-day mortality was 16.4% in spring, 15.6% in autumn, and 18.4% in winter.

A multinational study of the epidemiology of AKI in critically ill patients from 97 centres in the first week of ICU admission between June 2013 and December 2015, measured AKI by KDIGO criteria (Hoste, Bagshaw, Bellomo, Cely, Colman, Cruz et al 2015:1411). AKI occurred in 57.3% of the ICU patients; increasing AKI severity was associated with increased mortality, and AKI patients had worse renal function at hospital discharge. Adjusted risks for AKI and mortality were similar across different continents and regions (Hoste et al 2015:1419,1420).

In 2018, Yao, Konan, Tia, Diopoh, Moh and Sanogo (2018:653) examined the outcomes of AKI in the Department of Internal Medicine at the University Hospital of Treichville in Abidjan. Between January 2010 and December 2015, 414 patients were hospitalised for AKI. The mean age of the patients was about 65 years and the majority were males. The factors associated with incomplete or non-recovery of renal function beyond three months were advanced age, hypertension, low haemoglobin level, severe AKI, infection, and drug intake. The study emphasised that prevention was essential (Yao et al 2018:660).

2.2.4 Etiology

Etiology or aetiology refers to the cause, set of causes, or origins of a disease or condition or the reasons for its development. Patients with AKI usually have multiple etiologies which often coexist, complicating the diagnosis and management (Makris & Spanou 2016:85). The etiological factors of AKI are categorized under pre-renal, renal, and post-renal causes which enables the recognition of the pathophysiological relationship between the location of insult and the renal anatomy (Johnson, Feehally & Floege 2019:786; Urden, Stacy & Lough 2014:709). Pre-renal causes refer to AKI induced by inadequate renal perfusion. Intrinsic renal diseases and urinary tract obstruction constitute renal and post-renal causes. Pre-renal causes account for 50-65% of AKI, post-renal causes for 15%, and renal causes for 20-35% of AKI (O'Callaghan 2016:101). Figure 2.1 depicts the etiological factors of AKI.

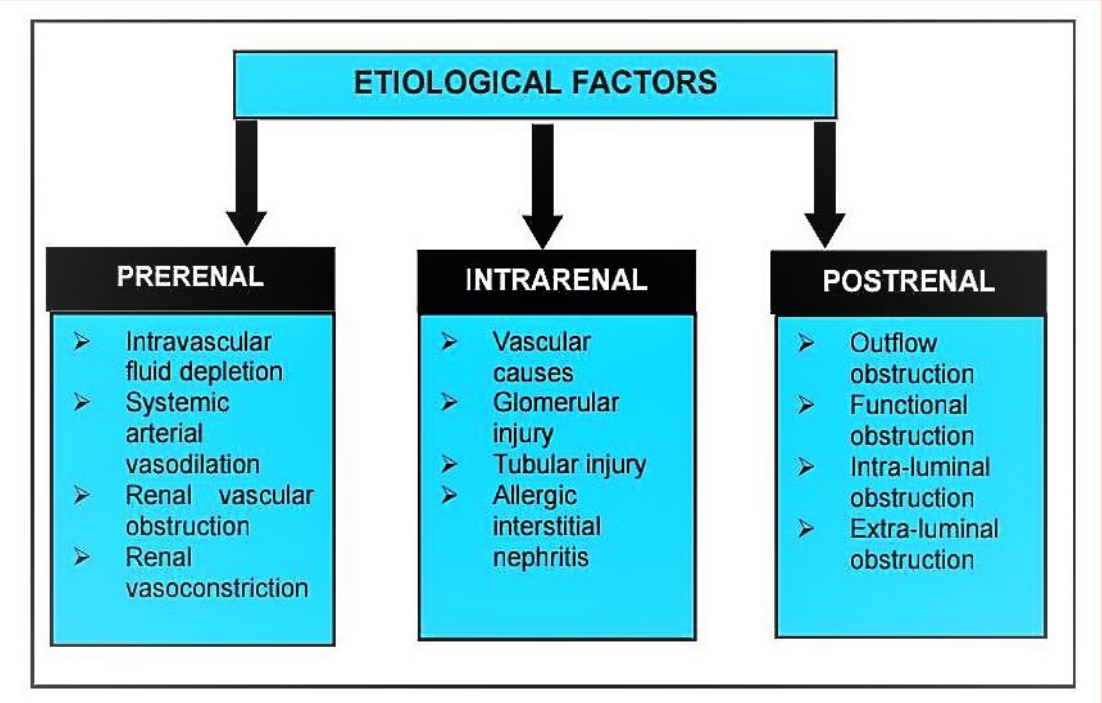

Figure 2.1 Etiological factors of acute kidney injury

The etiological factors of AKI are discussed next.

2.2.4.1 Pre-renal

Pre-renal causes include intravascular fluid depletion, systemic arterial vasodilation, renal vascular obstruction and renal vasoconstriction. Intravascular fluid depletion results from gastrointestinal losses (diarrhoea, vomiting, prolonged naso-gastric drainage), renal losses (diuretics, osmotic diuresis in hyperglycaemia), dermal losses (burns, extensive sweating) or sequestration or third spacing of fluids (acute pancreatitis, muscle trauma). Systemic arterial vasodilation occurs due to sepsis, cirrhosis leads to redistribution of cardiac output into the extra-renal vascular bed thereby diminishing the renal perfusion (Johnson, Feehally & Floege 2019:786).

Renal vascular obstruction induced by renal artery thrombosis or embolism, intraoperative cross clamping, renal artery stenosis, and cholesterol emboli leads to AKI (Molitoris 2016:780). Renal vasoconstriction caused by acute hypercalcemia, norepinephrine, vasopressin, contrast media, and hepato-renal syndrome also contributes to the development of AKI (Parsons, Wiener-Kronish, Stapleton & Berra

2019:303). Drugs such as non-steroidal anti-inflammatory drugs, angiotensin converting enzyme (ACE) inhibitors, angiotensin II receptor blocker (ARB), radio contrast agents, and cocaine also cause renal vasoconstriction leading to AKI (Johnson, Feehally & Floege 2019:793).

2.2.4.2 Intra-renal

Intra-renal causes of AKI are scrutinized under the various anatomic components of the kidney such as vascular supply, glomerular, tubular and interstitial diseases. *Vascular* causes are vasculitis, thrombotic microangiopathy induced by gemcitabine, mitomycin C, clopidogrel, quinine and oral contraceptives, malignant hypertension, eclampsia, postpartum states, disseminated intravascular coagulation (DIC), scleroderma (Johnson, Feehally & Floege 2019:786, 793). *Glomerular injury* is induced by acute or rapidly progressing glomerulonephritis, Goodpasture's syndrome, proliferative glomerulonephritis and drugs like hydralazine, propylthiouracil (O'Callaghan 2016:101; Johnson, Feehally & Floege 2019:793).

Tubular injury is triggered by ischemia or due to the effect of toxic exogenous compounds such as drugs, heavy metal and contrast media. Endogenous compounds, such as haemoglobin or myoglobin, also produce tubular injury resulting in AKI. Muscle damage, exercise and trauma lead to the release of myoglobin. Haemolysis and haemolytic uremic syndrome result in release of haemoglobin. Myoglobin and haemoglobin are toxic to tubular cells. A hypercalcemic state also predisposes the patient to tubular injury by means of vasoconstriction and forming precipitates in the tubules. Tubular injury also results from crystallization due to gout (O'Callaghan 2016:101). Radiocontrast agents are the third leading cause for hospital-acquired AKI. The increased osmolarity of the contrast agent produces tubular toxicity (Gilbert, Weiner, Bomback, Perazella & Tonelli 2017:335). Drugs such as aminoglycosides, amphotericin, foscarnet, tenofovir, cidofovir, adefovir, cisplatin, ifosfamide, acetaminophen, herbal remedies, radiocontrast agents, herbicides and intravenous immunoglobulins induce acute tubular necrosis contributing to AKI (Johnson, Feehally & Floege 2019:793).

Allergic interstitial nephritis from non-steroidal anti-inflammatory drugs (NSAIDs), diuretics, proton pump inhibitors, loop and thiazide diuretics, allopurinol, phenytoin and

cimetidine also promotes AKI (O'Callaghan 2016:101; Johnson, Feehally & Floege 2019:793).

2.2.4.3 Post-renal

Post-renal AKI results from obstruction within the ureter, bladder, prostate or urethra (Parsons et al 2019:303). The obstruction can be outflow obstruction, functional obstruction, intra-luminal obstruction, or extra-luminal obstruction. Outflow obstruction may be caused by prostatic hypertrophy, prostate or cervical cancer and retroperitoneal disorders. Functional obstruction occurs due to the neurogenic bladder. Intra-luminal obstruction results from bilateral renal calculi, papillary necrosis due to non-steroidal anti-inflammatory agents and compound analgesia, blood clots, and bladder cancer. Extra-luminal obstruction is caused by the retroperitoneal fibrosis, colon cancer and lymphomas (Molitoris 2016:779; Johnson, Feehally & Floege 2019:793).

2.2.5 Risk factors

The specific risk factors associated with AKI include age, gender, hyperglycaemia, hypoalbuminemia, hyperuricemia, obesity and other factors are discussed next.

2.2.5.1 Age

Advanced age is a major risk factor for AKI. Elderly patients are at higher risk because of diminished kidney function and reduced body fluid (Gilbert, Weiner, Bomback, Perazella & Tonelli 2017:334; Lerma, Sparks & Topf 2019:47).

In their retrospective analysis of medical records of 117 patients aged 65 and older admitted to the Internal Medicine Department of the Military Hospital of Tunis from 2006 to 2014, Selmi, Ariba and Labidi (2019:679) found that the mean age was 74.2 years; most of the patients were male, and the main causes were hypertension (69.2%) and diabetes (48.7%). Selmi, Ariba and Labidi (2019:682) state that unlike Western populations, the AKI in countries of Africa and India is characterised by its occurrence in younger patients with a mean age of about 40 years due to the low life expectancy in these countries.

In a study of 63 patients admitted with or who developed AKI at a tertiary care government hospital in Andra Pradesh, India, between January and November 2017, Moka (2018:3224) found that 41 were males and 22 were females. Of the males, 25 were 31-60, 9 were 20-30, and 7 were over 60 years old. Of the females, 11 were 31-60, 4 were 20-30, and 7 were over 60 years old. The main factors associated with AKI in this community were advanced age, fever, acute diarrhoea, and sepsis (Moka 2018:3226).

2.2.5.2 Gender

Males are at higher risk for AKI than females (Moka 2018:3224; Selmi, Ariba & Labidi 2019:679; Yao et al 2018:653). Enhanced renal sympathetic nerve activity during an ischemic period and renal venous norepinephrine overflow after reperfusion play important roles in the development of ischemic AKI. In Osaka, Japan, Tanaka, Tsutsui, Kobuchi, Sugiura, Yamagata, Ohkita et al (2012:273, 274) examined the effect of 17β-estradiol on the renal sympathetic nervous system and kidney function in ischemia/reperfusion-induced AKI in anaesthetized rats. Estradiol is an estrogen (or oestrogen) steroid hormone and the major female sex hormone. Intravenous injection of 17β-estradiol before reperfusion suppressed renal sympathetic nerve activity as well as renal venous norepinephrine overflow after reperfusion, and reduced ischemia/reperfusion-induced renal dysfunction with histological damage. The results indicated that 17β-estradiol protects against the development of ischemia/reperfusion-induced AKI (Tanaka et al 2012:274).

In 2013, Tanaka, Tsutsui, Ohkita, Takaoka, Yukimura and Matsumura (2013:402, 403) examined whether sex differences in the pathogenesis of ischemic AKI were derived from the renal sympathetic nervous system. The study found that renal function was impaired after reperfusion in both male and female rats, but the dysfunction and histological damage were more severe in males than females. The males had higher renal venous plasma norepinephrine levels after reperfusion than the females (Tanaka et al 2013:403). There is paucity of data regarding the protective effect of estrogen from human sample.

2.2.5.3 Hyperglycaemia

Hyperglycaemia increases patients' risk for AKI (Nie, Tang, Zhang, Feng & Chen 2017:5605634). Complex factors in critically ill patients contribute to the development of hyperglycaemia. The increased release of counter-regulatory hormones, such as cortisol and epinephrine, high insulin resistance and decreased glucose uptake, glucose toxicity, activation of inflammatory cytokines, and use of glucocorticoids, enteral and parenteral nutrition further predispose patients to develop hyperglycaemia. Hyperglycaemia leads to fluid depletion due to osmotic diuresis resulting in hypo-perfusion and electrolyte loss. At the cellular level, it produces mitochondrial injury, neutrophil and endothelial dysfunction. Moreover, it causes oxidative injury and complement inhibition at the molecular level (Parsons, Wiener-Kronish, Stapleton & Berra et al 2019:9, 10).

2.2.5.4 Hypoalbuminemia

Preoperative hypoalbuminemia is a potentially modifiable risk factors for AKI after thoracic aorta surgery. Kim, Park, Kim, Lim, Shim, Sohn et al (2015:e273) reviewed the electronic records of 739 patients who underwent surgery on the thoracic aorta with cardiopulmonary bypass (CPB) between 2000 and 2010. The study compared 183 patients with AKI and 183 without AKI. Postoperative outcome variables included the need for postoperative RRT, length of hospital stay, and 1-month and 1-year mortality. The study found that patients with AKI were older, had a higher body mass index, smoked more and had poorer baseline renal function. AKI was associated with prolonged hospital stay and higher 1-month and 1-year mortality and modifiable risk factors were preoperative hypoalbuminemia (Kim et al 2015:e273).

Postoperative hypoalbuminemia is an independent risk factor for AKI in patients undergoing total knee arthroplasty (knee replacement) (Kim, Koh, Kim, Park, Song, Ro et al 2016:4489). In a retrospective analysis of 1,309 patients who underwent total knee arthroplasty between 2008 and 2014, Kim et al (2016:4489) found that age, diabetes, uric acid, use of diuretics, and low albumin level (hypoalbuminemia) were risk factors for AKI and lengthened hospital stay.

A retrospective analysis of patients admitted to Seoul National University Bundang Hospital between January and December 2013 found that hypoalbuminemia at admission

was a risk factor for AKI (Yu, Lee, Back, Na, Chae, Chin et al 2017:e0180750). The patients were divided into hypoalbuminemia and normoalbuminemia groups. The hypoalbuminemia group were older, more anaemic, and had more comorbidities, such as diabetes, liver disease, and hypertension. The study found that hypoalbuminemia and AKI resulted in longer hospital stay and lower mortality. In addition, albumin replacement in AKI patients was strongly associated with AKI recovery, but not with the patients' survival (Yu et al 2017:e0180750). Nie, Tang, Zhang, Feng and Chen (2017:5605634) state that the underlying mechanisms between non-traditional risk factors, such as hypoalbuminemia, hyperuricemia and anaemia, and AKI and whether their correction can reduce AKI occurrence need further clarification. Even though the renoprotective threshold value of albumin is still unclear, the beneficial effect of albumin should be considered. Albumin helps to maintain renal perfusion and glomerular filtration. Moreover, it mitigates the effects of nephrotoxic medications and has antioxidant properties (Nie, Tang, Zhang, Feng and Chen 2017:5605634).

2.2.5.5 Hyperuricemia

Hyperuricemia is a risk factor for high morbidity and mortality in several diseases and increases the risks of AKI and all-cause mortality in hospitalised patients (Kang, Chin, Joo, Na, Kim & Han 2019:722). Uric acid is produced in the body as an effect of purine metabolism. Hyperuricemia results in renal vasoconstriction and impaired renal auto-regulation. Consequently the renal blood flow and GFR reduces which results in AKI. Pro-inflammatory and anti-angiogenic effects are also associated with hyperuricemia (Nie et al 2017:5605634). There is a strong link between serum uric acid and AKI across various disease models and exposure to serum uric acid at different times and levels has resulted in AKI (Ejaz, Johnson, Shimada, Mohandas, Alquadan, Beaver et al 2019:276). The elevated serum uric acid forms crystals and can induce tubular obstruction. Moreover, elevated preoperative serum uric acid predicts postoperative AKI in cardiac surgery (Ejaz et al 2019:278).

2.2.5.6 Obesity

Obesity is one of the independent risk factors of AKI (Wang, Yu, Zhai, Liu, Sun & Zhu 2018:2594). A multifactorial and complex pathway is involved in obesity associated with

AKI. Obesity enhances oxidative stress and endothelial dysfunction. Obesity activates the signalling pathways and induces pro-inflammatory molecules and is regarded as a chronic low-grade inflammatory state. Moreover, obesity has adverse effects on the pharmacokinetic factors such as absorption, volume of distribution, protein binding, metabolism and clearance, especially of antibiotics. Drug dosing regimens based on total body weight become confusing as the volume of distribution in the central compartment does not increase proportionately with the increasing body weight in obese patients (Suneja & Kumar 2014:694.e3).

2.2.5.7 Other factors

Other risk factors for AKI include *anaemia*, *pre-existing renal dysfunction*, *central venous pressure* (CVP) and *anaesthetic agents*. Acute kidney injury (AKI) is underreported but a major cause of morbidity and mortality among patients undergoing major surgery in developing countries. In a cohort study of 219 adult patients undergoing major surgery at the University College Hospital in Ibadan, Nigeria, Raji, Ajayi, Ademola, Lawal, Ayandipo, Adigun et al (2018:446, 447) found that preoperative anaemia and pre-existing renal dysfunction increased the risk for AKI by three- and fourfold, respectively.

In 2016, Chen, Cavender, Lee, Feng, Mark, Celi et al (2016:602) conducted a cohort study on critically ill patients admitted to an urban tertiary medical centre between 2001 and 2008 to examine whether the presence of peripheral oedema on admission was associated with an increased risk of AKI within the first 7 days of critical illness. In addition, in those with admission *central venous pressure (CVP)* measurements, the study examined the association of CVP with subsequent AKI. The mean age of the patients was >60 years; 47% were females and 53% were males, and the patients were White, Black, Hispanic, Asian and other nationalities. Peripheral oedema was associated with a higher risk of AKI while pulmonary oedema was not. The study found that venous congestion, whether manifested as peripheral oedema or increased CVP, was directly associated with AKI in critically ill patients (Chen et al 2016:606).

AKI is a primary cause of morbidity and mortality after major abdominal surgery, but little is known about the effect of anaesthetics on the development of AKI after colorectal surgery. Bang, Lee, Oh, Song and Hwang (2016:363) conducted a retrospective study to

compare the effects of anaesthesia with propofol and sevoflurane on postoperative AKI after colorectal surgery. The study reviewed the electronic medical records of 4,320 patients who underwent colorectal surgeries between January 2008 and December 2011. The influence of propofol and sevoflurane on the development of postoperative AKI was analysed by multivariable analysis, and the effect of the anaesthetic agent on the development of postoperative AKI and short-term outcomes was analysed by a Cox proportional hazard model. Multivariate logistical regression and propensity score matching results indicated that when compared with propofol, sevoflurane may be associated with the development of postoperative AKI. The study found no relationship between sevoflurane and overall mortality. The study concluded that compared with anaesthesia with propofol, anaesthesia with sevoflurane may be associated with a moderate increase in the incidence of AKI when RIFLE but not Acute Kidney Injury Network criteria are used. Thus, the clinical mean of these results is uncertain and further work is needed to clarify the relevance of these results (Bang, Lee, Oh, Song & Hwang 2016:369).

2.2.6 Pathophysiology

The pathophysiology of AKI is discussed according to pre-, intra- and post-renal insult to the kidney.

2.2.6.1 Pathophysiology of pre-renal AKI

Pre-renal kidney injury is induced by renal hypo-perfusion, which is caused by a decrease in the total or intravascular fluid volume, or any disease state that diminishes the arterial volume (Molitoris 2016:780). Kidneys require 20% of the cardiac output or 1-1.2L/mnt of blood flow to maintain the renal tissue perfusion (Skorecki, Chertow, Marsden, Taal & Yu 2016:85). When there is a change in the perfusion pressure, renal auto-regulation enables stabilization of the renal blood flow and GFR within the range of systolic pressure between 80-180mmhg (Gilbert, Weiner, Bomback, Perazella & Tonelli 2017:6, 7). Renal auto-regulation is mediated by prostaglandin-induced vasodilation on the afferent arteriole and Angiotensin-induced vasoconstriction of efferent arteriole. However, a significant decline in the renal perfusion overcomes the auto-regulation and drops the GFR (Johnson, Feehally & Floege 2019:786, 789).

During the initial phase of pre-renal AKI, renal parenchyma remains intact and functional. The neuro-hormonal mechanism maintains a normal GFR by causing afferent arteriolar dilation and efferent arteriolar constriction (Molitoris 2016:780). Persistent reduction in the renal blood flow results in tubular cell injury. Attempts should be made to correct the cause for renal hypo-perfusion and restore renal blood flow during the functional pre-renal stage to prevent tubular injury (Johnson, Feehally & Floege 2019:786).

2.2.6.2 Pathophysiology of intra-renal kidney injury

Intra-renal injury occurs along the tubules, interstitium, vasculature or glomerulus. The most common site of injury is the renal tubular epithelial cell, which is commonly called acute tubular necrosis (Molitoris 2016:780). Acute tubular necrosis progresses through four clinical phases: initiation, extension, maintenance, and recovery (diuretic) phase (Lerma, Sparks & Topf 2019:51). Figure 2.2 illustrates the mechanism of pre-renal and intrinsic AKI.

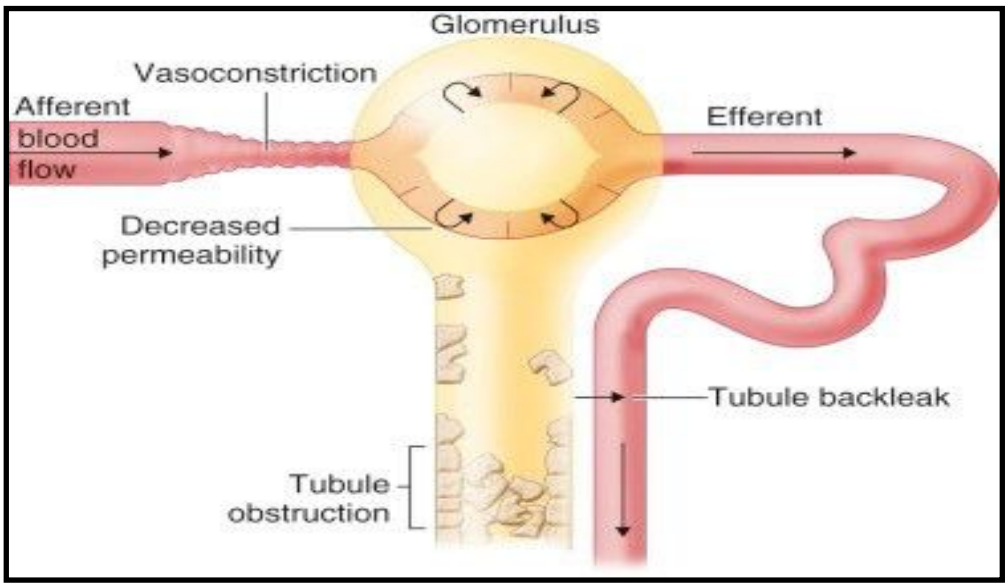

Figure 2.2 Mechanism of pre-renal and intrinsic AKI

Source: Molitoris (2016:779)

During the initiation phase, the patient is exposed to the etiological factors. Clinically, acute tubular necrosis begins not due to exposure to a single factor, but multiple factors

produce a cumulative effect and trigger injury to the kidney. When the initiation phase proceeds to the extension, cellular injury occurs. Even though the triggering has resolved, initial exposure induces microvascular injury and activates the inflammatory mediators (Lerma, Sparks & Topf 2019:51). Proximal tubular cells become vacuolized and lose the brush borders. The surface membrane polarity and integrity of the tight junction also become depleted. As the injury advances, more and more live and necrotic proximal cells get detached and enter the lumen, leading to cast formation in the distal tubule (see figure 2.2). These casts obstruct the tubular urine flow, reduce the GFR and prevent further filtration into that nephron. The glomerular filtrate leaks into the interstitium due to the lack of epithelial cell barrier and the cellular tight junction, which further decreases the GFR (Molitoris 2016:780). The maintenance phase lasts for days to 6 weeks or longer (Lerma, Sparks & Topf 2019:51).

The final phase is the recovery phase, which is also known as the diuretic phase. During the recovery phase, a slight increase in urine output is noticed. The tubular epithelium undergoes regeneration and GFR may return to near normal levels. However, even if the GFR returns to normal, some degree of tubular dysfunction still persists for months to years (Lerma, Sparks & Topf 2019:51).

2.2.6.3 Pathophysiology of post-renal kidney injury

The obstruction within the extra-renal collecting system restricts the luminal flow of glomerular filtrate (Johnson, Feehally & Floege 2019:787; Molitoris 2016:781). The obstruction in the urine flow exerts a back-pressure. Initially, the glomerular afferent arteriole dilates and attempts to preserve the GFR. However, such compensation is temporary. If the obstruction is not relieved within 12 to 24 hours, renal blood flow and the intratubular pressure drop. Consequently the kidney cortex becomes hypoperfused, resulting in a decline in GFR (Molitoris 2016:781).

2.2.7 Clinical manifestations

The clinical manifestations showcased by AKI patients are not disease specific, but manifest the underlying disease process, such as sepsis, heart failure, systemic vasculitis, and thrombotic microangiopathy. Retention of fluid, diminished excretion of electrolyte

and endogenous or exogenous waste products contribute to the symptoms (Patschan & Müller 2015:22). Clinical manifestations of AKI vary depending on the stage at which it is diagnosed. Routinely, AKI in the initial stage is diagnosed by abnormalities in the patient's laboratory studies, not by any specific signs and symptoms (Molitoris 2016:781).

Patients with AKI are usually asymptomatic and if they become symptomatic, the cardinal symptoms that they present with are digestive symptoms (Selmi, Ariba & Labidi 2019:679, 680). The accumulation of uremic toxins is responsible for the presentation of digestive symptoms, neurological symptoms, pruritus and bleeding complications (Patschan & Müller 2015:22). The predominant digestive intestinal symptoms include abdominal pain, nausea, vomiting, diarrhoea, anorexia, and hematemesis. Neurological symptoms like fatigue, uremic encephalopathy and insomnia are also reported among AKI patients (Patschan & Müller 2015:22; Molitoris 2016:781; Moka 2018:3224; Selmi, Ariba & Labidi 2019:679). Oligo-anuria represents the progression of AKI to stage 2 and fluid retention aggravates hypertension and heart failure (Patschan & Müller 2015:22).

Once the AKI progresses, the patient may develop anasarca, dyspnea, jugular vein distention, pulmonary crackles, pulmonary oedema, metabolic acidosis, hyperkalaemia, gastrointestinal bleeding, and haemodynamic instability (Molitoris 2016:781; Moka 2018:3224; Selmi, Ariba & Labidi 2019:679). Cardiac arrhythmia can occur due to electrolyte imbalance and patients will be more prone to infection (Patschan & Müller 2015:22). During the severe stage of AKI, asterixis, myoclonus or pericardial rub can occur (Molitoris 2016:781). Acid-base disturbances occur from AKI that contribute to decreased hepatic blood flow, alter the protein catabolism and lead to haemodynamic instability (Wang & Bellomo 2017:707).

2.2.8 Diagnosis

Acute kidney injury staging and definition has become more scientifically sound since the development of RIFLE, Acute Kidney Injury Network and KDIGO criteria (Bellomo, Ronco, Kellum et al 2004:R206; Mehta, Kellum, Shah et al 2007:R31; KDIGO 2012:19). However, these criteria also have limitations as they are not effective in the early diagnosis of AKI (Ortega-Loubon, Fernández-Molina, Carrascal-Hinojal & Fulquet-Carreras 2016:691). These criteria rely on the changes in the serum creatinine, a by-product of muscle

metabolism, which is secreted by the renal tubules. Regardless that serum creatinine is a poor filtration marker, it is widely used to monitor renal function. Creatinine level is affected by the muscle mass, muscle injury, age, gender, race, physical activity, drugs, consumption of meat or creatinine and decreased renal function (Skorecki, Chertow, Marsden, Taal & Yu 2016:782). Another limitation with creatinine is that a substantial rise in creatinine level is noticed only if the GFR falls around 30L/mnt from 120ml/mnt (O'Callaghan 2016:11).

Due to the shortfalls in monitoring creatinine, serum biomarkers recently gained attention in the early detection of AKI. Tissue inhibitor of metalloproteinase 2 (TIMP-2), Insulin-like growth factor binding protein 7 (IGFBP-7), Hepcidin, Kidney injury molecule 1 (KIM-1), Neutrophil gelatinase associated lipocalin (NGAL), Cystatin C, Interleukin 18 (IL-8) are some of the frequently used biomarkers (Johnson, Feehally & Floege 2019:810). Renal biomarkers are specific and sensitive indicators of AKI which are similar to troponin that is released by injured myocardial cells after ischemia or infarction (Edelstein 2017:246). The AKI incidence can be detected 12-66 hours prior to an actual increase in serum creatinine by means of renal biomarkers (Ronco, Bellomo, Kellum & Ricci 2019:138).

Neutrophil gelatinase-associated lipocalin (NGAL) is a protease-resistant polypeptide present in urine after ischemic and nephrotoxic kidney injury (Edelstein 2017:248). A study of 45 adult patients, of both sexes, who underwent CABG surgery at the Alexandria Main University Hospital in Egypt examined the efficacy of urinary Kidney-injury-molecule-1 (KIM-1) and Neutrophil gelatinase-associated lipocalin separately and in combination in relation to early detection and assessment of severity of AKI after cardiac surgeries (Elmedany, Naga, Elsharkawy, Mahrous & Elnaggar 2017:172). Of the patients, 11 developed AKI, and the patients with AKI had higher Acute Kidney Injury Network stages and Cleveland clinic score. The study found that urinary Neutrophil gelatinase-associated lipocalin is early sensitive but KIM-1, which appears later than Neutrophil gelatinase-associated lipocalin, is a more specific marker to ischemic renal injury. Urinary microscopic examination was found to be highly sensitive and specific injury site informative. The combination of more than one biomarker increases the accuracy and early detection of AKI after cardiac surgery (Elmedany, Naga, Elsharkawy, Mahrous & Elnaggar 2017:177).

Cystatin C is a low molecular weight basic protein produced by the nucleated cells at a constant rate. Normally, very little is excreted through urine as it is reabsorbed by proximal tubular cells and gets metabolised. Cystatin C is not regarded as an ideal biomarker to diagnose AKI, but it is detected in urine at higher levels during glomerular injury with heavy proteinuria. The main disadvantage of cystatin C is that the immunoassay used to measure cystatin C is expensive and is not internationally standardized. Corticosteroids, thyroid dysfunction, obesity, diabetes, smoking, and high c-reactive protein value may affect the cystatin C levels (Skorecki et al 2016:783, 784).

Tissue inhibitor of metalloproteinase 2 (TIMP-2) and Insulin like growth factor binding protein 7 (IGFBP-7) indicate damage to the DNA and other forms of injury and are expressed in the tubular cells. Tissue inhibitor of metalloproteinase 2 (TIMP-2) and Insulin like growth factor binding protein 7 (IGFBP-7) result in G1 cell cycle arrest, preventing cell cycle promotion. These biomarkers are involved in the early phase of cell cycle arrest (Edelstein 2017:254). Urinary tissue inhibitor of metalloproteinase 2 (TIMP-2) and Insulin like growth factor binding protein 7 (IGFBP-7) test are promising biomarkers in detecting patients at risk for AKI within 12 hours of insult (Ronco Bellomo, Kellum & Ricci 2019:138, 139).

Diagnostic tests should be carried out on patients with suspected AKI in order to rule out the cause. Renal imaging techniques, such as ultrasonography, can be implemented to detect any obstruction within the kidney and its related structures (O'Callaghan 2016:11). Nuclear imaging of the kidney provides information regarding the renal blood flow to rule out renal artery embolism, renal vein thrombosis, as well as localized renal function (Patschan & Müller 2015:23; O'Callaghan 2016:11). Urine analysis is also significant as the presence of erythrocyte casts and acanthocytes indicate acute glomerularnephritis. While eosinophiluria and tubular proteinuria imply interstitial nephritis, urine osmolarity specifies whether the impact is pre-renal or intra-renal-pre-renal if the osmolarity >500mosmol/kg and intra-renal if <350mosmol/kg (Patschan & Müller 2015:23; Johnson, Feehally & Floege 2019:815).

Blood analysis for myoglobin and haemoglobin level reflects whether the AKI is due to rhabdomyolysis or haemolysis. Thrombocytopenia, anaemia and increase in lactate

dehydrogenase (LDH) indicate a thrombotic microangiopathic etiology (Patschan & Müller 2015:23).

2.2.9 Prevention

Acute kidney injury (AKI) prevention begins with the risk identification and modification of possible risk factors (Johnson, Feehally & Floege 2019:826). The etiological factors should be promptly identified and corrected to ensure rapid recovery of kidney function. Acute kidney injury (AKI) induced by hypovolemia can be corrected by administration of fluids while carefully monitoring the response to intravenous fluids and avoiding fluid overload. Nephrotoxic medications should be stopped appropriately to alter the kidney dysfunction. The post-renal causes of AKI, such as lower urinary tract obstruction, can be prevented by bladder catheterization. Upper urinary tract obstruction can be relieved by nephrostomy tube or ureteric stents (Gilbert, Weiner, Bomback, Perazella & Tonelli 2017:326). Table 2.4 lists the recommended preventive strategies and supporting literature.

Table 2.4 Recommended preventive measures and supporting literature

Preventive measures	Supporting literature
➢ Optimizing volume and the haemodynamic status ➢ Prevention of contrast-induced AKI ➢ Prevention of drug-induced and nephrotoxin-induced AKI ➢ Management of traumatic and non-traumatic rhabdomyolysis ➢ Blood glucose control ➢ Pharmacological approach	KDIGO 2012:37-40, 61-65; Ronco, Bellomo, Kellum & Ricci 2019:303-306 Joannidis, Druml, Forni, Groeneveld, Honore, Hoste et al 2017:732, 734-738; Fink, Moore, Kochanek, Vincent & Abraham 2017:777, 778; Gilbert, Weiner, Bomback, Perazella & Tonelli 2018:327, 328; Johnson, Feehally & Floege 2019:825-835.

As indicated in Table 2.4, the preventive strategies of AKI should be focused on optimizing volume and the haemodynamic status, prevention of contrast-induced AKI (CI-AKI), prevention of drug-induced and nephrotoxin-induced AKI, management of

traumatic and non-traumatic rhabdomyolysis, blood glucose control and pharmacological approach.

2.2.9.1 Optimizing volume and haemodynamic status

Acute kidney injury can be prevented by maintaining adequate renal perfusion. Optimizing volume status, haemodynamic status and cardiac output guarantees ample renal perfusion. Often a patient's volume status and responsiveness to fluid administration are assessed on the basis of blood pressure, heart rate, oxygen saturation, central venous pressure (CVP) and urine output to monitor. These variables are vague and insensitive. The lack of a simple tool for assessment and proper guideline for optimizing the haemodynamic and volume status to preserve renal function is often challenging (Johnson, Feehally & Floege 2019:825).

In 2014, Hoste, Maitland, Brudney, Mehta, Vincent, Yates et al (2014:742) proposed a fluid therapy model consisting of four phases: ***Rescue, Optimization, Stabilization and De-escalation*** (ROS-D). The rescue phase incorporates rapid fluid boluses to resuscitate patients with life-threatening shock. The fluid boluses include infusion of a minimum of 500ml of isotonic fluid over a maximum period of 15 minutes. The optimization phase is aimed at preventing organ dysfunction by improving cardiac dysfunction and tissue perfusion by means of titrating the fluid type, rate and amount. During this phase fluid challenges are given rather than fluid boluses (Hoste et al 2014:741, 742). A 250ml or 3ml/kg of isotonic fluids is infused over 5-10 minutes while reassessing the stroke volume. A fluid challenge is considered to be effective if there is an increase in stroke volume or cardiac output by 10-15% (Johnson, Feehally & Floege 2019:825).

The stabilization phase begins once the patient's condition is stabilized. An ongoing maintenance fluid is administered in this phase for patients who cannot meet their fluid requirements orally and to meet the fluid losses. Maintenance fluid is infused at a rate of 1-2ml/kg/hour. The de-escalation phase involves minimizing the fluid administration while aiming for a negative fluid balance (Hoste et al 2014:741, 742). During this phase, excess fluid is mobilized by means of oral or intravenous (IV) diuretic use or even with ultra filtration. Moreover, unnecessary IV fluids should be avoided to obtain a negative fluid balance (Johnson, Feehally & Floege 2019:825).

Despite the presence of a conceptual model for fluid therapy, the selection of the amount and type of fluid for resuscitation still remains controversial. Isotonic solutions are recommended over synthetic and non-synthetic colloids in the absence of haemorrhagic shock in patients at risk for AKI (KDIGO 2012:37). Administration of synthetic colloids like Hydroxyethyl starch (HES) enhances its uptake from the renal epithelial cell causing acquired lysosomal storage disease leading to AKI. Non-synthetic colloids like albumin are recommended if larger volumes of crystalloids (2L) are essential to maintain the mean arterial pressure (Johnson, Feehally & Floege 2019:826).

The choice of fluid among the isotonic solutions is also critical. In Halifax, Canada, Kuca, Butler, Erdogan and Green (2017:371) undertook a comparison of balanced and unbalanced crystalloid solutions in surgery patient outcomes. The study wished to evaluate adverse outcomes associated with the choice of IV fluid administered during general anaesthesia. Kuca, Butler, Erdogan and Green (2017:372) conducted a retrospective chart review of 796 vascular surgery patients at a Canadian tertiary care hospital. Of the patients, 425 received balanced crystalloids, 158 received normal saline, and 213 patients received both normal saline and crystalloids. The three groups were similar in age, and varied in gender and general health. The most common adverse event was ventilator required: normal saline (27.9%), balanced crystalloids (7.5%), and both (38.0%). The mortality rates were normal saline (12.0%), balanced crystalloids (5.9%), and both (10.8%). The study found that patients who were administered normal saline or both were more likely to reach the composite endpoint than patients receiving balanced crystalloids alone. The administration of an unbalanced crystalloid solution was associated with poor patient outcomes in the study population (Kuca, Butler, Erdogan & Green 2017:375).

In their 16-month clinical trial at a tertiary care hospital in Nashville, United States of America (USA), Self, Semler, Wanderer, Wang, Byrne, Collins et al (2018:819) compared the clinical effects of balanced crystalloids with saline among non-critically ill adults treated with IV crystalloids in the emergency department and subsequently hospitalised outside an ICU. The primary outcome was hospital-free days (days alive after discharge before day 28). The secondary outcome was adverse kidney events within 30 days – composite of death from any cause, new RRT, or persistent renal dysfunction (an

elevation of creatinine to over 200% of baseline) – all censored at hospital discharge or 30 days, whichever came first. Of the 13,347 patients enrolled, 88.3% exclusively received the assigned crystalloids and 12.7% received normal saline. Both groups had 25 hospital-free days. Of the patients, 4.7% of the crystalloids group and 5.6% of the normal saline group had adverse kidney events within 30 days. Self, Semler, Wanderer, Wang, Byrne, Collins et al (2018:827) found that among non-critically ill adults treated with IV fluids in the emergency department there was no difference in hospital-free days between treatment with crystalloids and treatment with saline.

2.2.9.2 Prevention of contrast-induced acute kidney injury

Contrast-induced AKI risk is influenced by the type, volume and route of administration of contrast agents (Gilbert et al 2017:335). Different types of contrast agents are available. Based on the osmolarity, contrast agents are classified into high osmolar contrast medium (2000mOsm/kg), low osmolar contrast medium (600-800mOsm/kg), and iso-osmolar contrast medium (290mOsm/kg) (Johnson, Feehally & Floege 2019:829). The nephrotoxic risk increases with osmolarity and because of this iso-osmolar and low molecular contrast agents have overtaken high osmolar contrast agents in the market (Gilbert et al 2017:335). The iodinated contrast medium volume should be reduced to a feasible extent and should not be repeated within 48-72 hours (Johnson, Feehally & Floege 2019:829). The maximum recommended volume of radio contrast agent for a patient with serum creatinine 1.5-3.4mg/dL and >3.4mg/dL is 150ml. Intra-arterial administration of radio contrast agents produces more risk for contrast-induced AKI than intravenous administration (Gilbert, Weiner, Bomback, Perazella & Tonelli 2017:335, 336).

Patients at high risk for contrast-induced AKI should receive adequate hydration with isotonic saline before and after the procedure (Johnson, Feehally & Floege 2019:828). Figure 2.4 illustrates the management of contrast-induced AKI based on the GFR level. No preventive strategies are recommended if GFR is >60ml/min/1.73 ㎡. If the GFR is <60ml/min/1.73, nephrotoxic drugs should be stopped 48 hours prior to use of contrast agents and avoid the use of contrast agents within the next 72 hours. Patients should be hydrated with an isotonic solution before and after the contrast exposure.

Contrast-induced AKI results in significant morbidity and mortality and adds to the costs of diagnostic and interventional cardiology procedures. In their study in Tehran, Iran, Firouzi, Maadani, Kiani, Shakerian, Sanati, Zahedmehr et al (2015:521) randomly assigned 122 patients into two groups. The control group (n=64) received routine treatment and the study group (n=62) received routine treatment and IV magnesium sulphate 1g just before the procedure. Serum creatinine was measured before and two days after the procedure. The primary endpoint was the occurrence of contrast-induced AKI within 48 hours. Both the groups were comparable in the overall predicted risk of contrast-induced AKI. Following angioplasty, contrast-induced AKI occurred in 17 (26.6%) patients in the control group and 9 (14.5%) patients in the study group. In addition, there was no mortality or need for haemodialysis in either group. Administration of intravenous magnesium sulphate prior to coronary angioplasty along with fluid therapy significantly reduced the incidence of contrast-induced AKI (Firouzi et al 2015:522, 523). Firouzi et al (2015:524) concluded that in primary percutaneous coronary intervention (PCI) patients, the prophylactic use of intravenous magnesium sulphate can be recommended to be added to traditional hydration for the prevention of contrast-induced AKI.

Contrast-induced nephropathy is considered a possibly severe complication of radiography and remains the main cause of AKI for inpatients. In 2017, Iranirad, Sadeghi, Bagheri, Doostali, Norouzi, Hejazi et al (2017:230) conducted a clinical trial to measure the preventive effectiveness of allopurinol against contrast-induced nephropathy in high-risk patients undergoing coronary angiography in a tertiary hospital in Oom, Iran. In the study, 140 patients with a minimum of two risk factors for contrast-induced nephropathy who were undergoing coronary angiography were randomly allocated to the allopurinol (n=70) or the control (n=70) group. The study group received allopurinol (300 mg) one day before the coronary angiography and IV hydration for 12 hours before and after their procedure while the control group only received IV hydration. Serum creatinine, blood urine nitrogen and uric acid were measured before and 48 hours after the procedure. Contrast-induced nepropathy was defined by a 25% increase in serum creatinine 48 hours after coronary angiography. Contrast-induced nepropathy was observed in 11.4% (n=8) patients in the allopurinol group and 15.7% (n=11) in the control group. The median serum creatinine concentration decreased non-significantly in the allopurinol group 48 hours after the procedure and increased significantly in the control group 48 hours after. Iranirad et al (2017:234, 235) concluded that allopurinol presents no

considerable effectiveness over the hydration protocol for development of contrast-induced nephropathy in high-risk patients. Figure 2.3 illustrates the management of patients receiving iodinated contrast media.

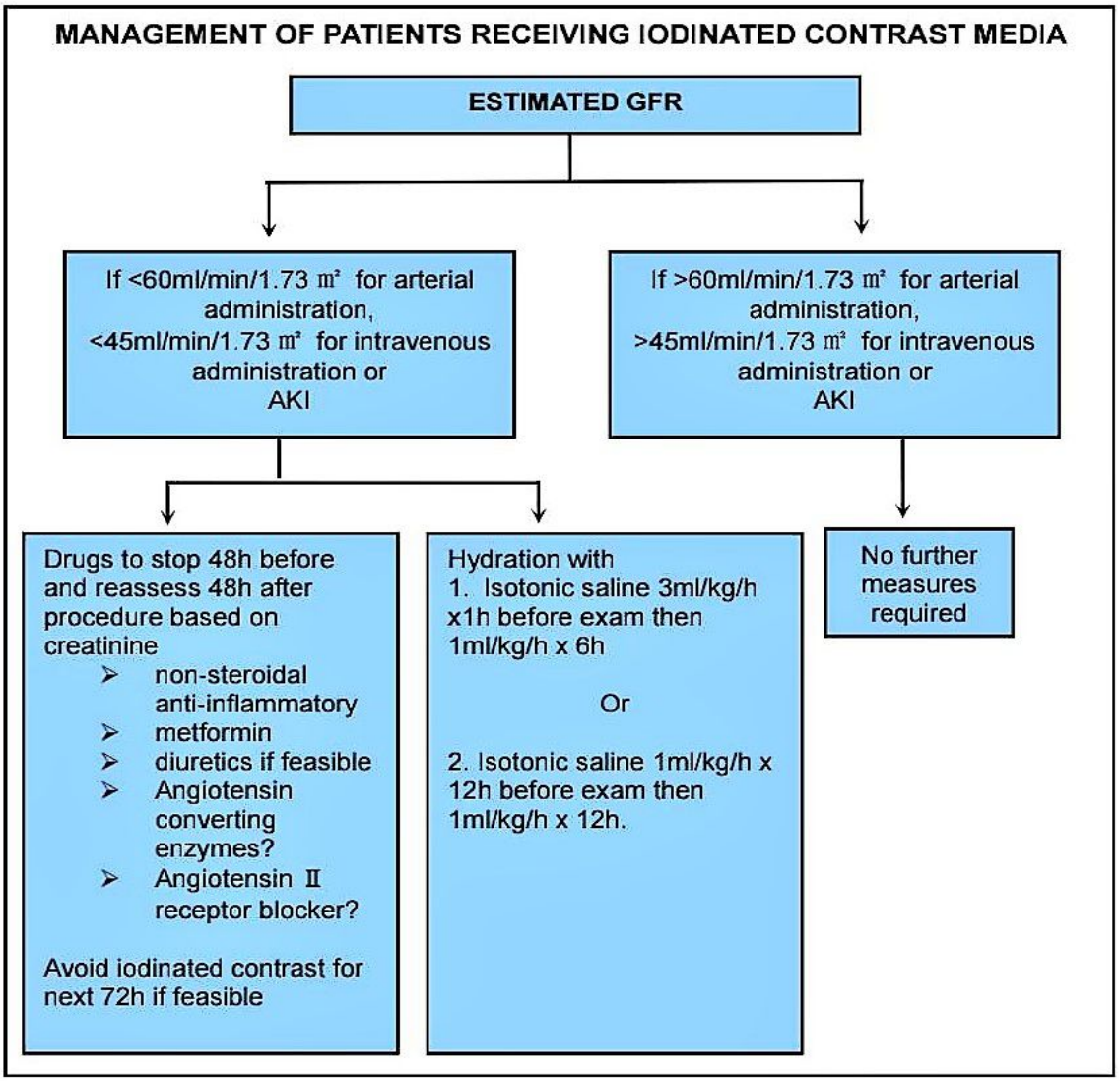

Figure 2.3 Management of patients receiving iodinated contrast media

Source: Johnson, Feehally and Floege (2019:828)

In Seoul, Korea, Cho, Kim, Park, Chung and Kim (2017:1471) conducted a systematic review and meta-analysis of randomised controlled trials to assess the effects of vitamin E for the prevention of contrast-induced AKI. Four trials, including 623 patients, were analysed. All the participants received IV hydration for 12 hours before and after procedures in addition to vitamin E or placebo. The incidence of contrast-induced AKI in

the vitamin E group was lower (5.8%) than that of the control group (15.4%). The use of vitamin E together with hydration reduced the risk ratio of contrast-induced AKI by 62%. Moreover, vitamin E reduced serum creatinine increase post contrast administration. The study found that vitamin E plus hydration significantly reduced the risk of contrast-induced AKI in patients with renal impairment compared with hydration alone (Cho, Kim, Park, Chung & Kim 2017:1473).

Contrast-induced AKI is a leading cause of acquired renal impairment. Rezaei, Khademvatani, Rahimi, Khoshfetrat, Arjmand and Seyyed-Mohammadzad (2016:e002919) conducted a study of vitamin E use to decrease contrast-induced AKI in patients undergoing coronary angiography. In a placebo-controlled randomised trial at two centres in Iran, 300 patients with chronic kidney disease were randomised into two groups to receive saline infusion 12 hours before and after the intervention combined with vitamin E 12 hours before and 2 hours after or to receive placebo. The primary endpoint was the development of contrast-induced AKI defined as an increase in serum creatinine that peaked within 72 hours. Contrast-induced AKI developed in 6.7% (10) of the vitamin E and 14.1% (21) of the placebo patients, and the change in white blood cell count was greater in the vitamin E group compared to the placebo group. Rezaei et al (2016:e002919) concluded that prophylactic short-term high-dose use of vitamin E combined with saline infusion lowered the incidence of contrast-induced AKI in patients undergoing coronary angiography.

2.2.9.3 Prevention of drug-induced acute kidney injury

Acute kidney injury caused by nephrotoxic drugs is often predictable. A thorough knowledge of the mechanism of renal injury and patient-related risk factors is essential for the prevention (Johnson, Feehally & Floege 2019:829). Older age, female gender, unrecognized decreased GFR, hypoalbuminemia, volume depletion, heart failure, liver failure and sepsis enhance patients' risk for nephrotoxicity (Gilbert Weiner, Bomback, Perazella & Tonelli 2017:334). Glomerular filtration rate (GFR) should be estimated before initiation of the therapy (Johnson, Feehally & Kloege 2019:829). Nephrotoxic drugs should be used cautiously or avoided, if possible. Medication dosage needs to be adjusted according to the level of kidney function (Gilbert, Weiner, Bomback, Perazella & Tonelli 2017:326, 327). Nephrotoxic drug combinations ought to be avoided by any

means and other non-nephrotoxic drugs should be considered. Renal function and drug dosage have to be closely monitored while using nephrotoxic drugs (Johnson, Feehally & Kloege 2018:829).

2.2.9.4 Management of traumatic and non-traumatic rhabdomyolysis

Acute kidney injury induced by rhabdomyolysis can be prevented by early initiation of fluid therapy to avoid myoglobin precipitation in the tubular lumen (Johnson, Feehally & Kloege 2019:830). The aim of the treatment modalities is to promote diuresis and dilute the toxic products by means of intravenous rehydration. During the resuscitation phase, normal saline should be given at a rate of 1-1.5L/hr until haemodynamically stable and then 300-500ml/hr. Rehydration therapy is considered to be successful if the urine output is maintained between 200-300ml/hr and serum creatinine kinase level <1000IU/L (Keltz, Khan & Mann 2015:2221). Fluid resuscitation can be stopped if the target urine output and serum creatinine has been achieved with absence of myoglobinuria indicated by negative urine dipstick for blood (Johnson, Feehally & Kloege 2019:830).

Sodium bicarbonate is recommended to reduce the myoglobin precipitation and arteriolar vasoconstriction as well as to keep the urine alkaline. Sodium bicarbonate should be avoided in cases of hypocalcaemia or metabolic acidosis due to the risk of calcium phosphate deposition. Another preventive strategy is mannitol. Mannitol is indicated as a second line of treatment once the patient is rehydrated (Keltz, Khan & Mann 2015:2221). Mannitol prevents the tubular cast deposition, expands extracellular volume, and reduces intra-compartmental pressure, muscle oedema and pain. Mannitol exhibits diuretic, antioxidant and vasodilatory properties. Mannitol is administered only if the urine output is higher than 20ml/hr and the maximum recommended dosage is 1-2g/kg/day. The contraindications such as oliguria, hypervolemia, hypertension and heart failure should be taken into consideration before administration of mannitol (Johnson, Feehally & Kloege 2019:830).

The combination of bicarbonate and mannitol is frequently used to prevent renal failure in patients with rhabdomyolysis. In 2004, Brown, Rhee, Evans, Demetriades and Velmahos (2004:1191) conducted a study to determine whether the combination of bicarbonate and mannitol is effective in the prevention of renal failure in rhabdomyolysis caused by trauma.

A review of all adult trauma ICU admissions between 1997 and 2002 revealed 2,083 trauma ICU admissions and 85% of the patients had abnormal creatinine kinase levels. Renal failure occurred in 10% of trauma ICU patients. The patients received the combination of bicarbonate and mannitol at the surgeon's discretion. Of 384 patients with creatinine kinase greater than 5,000 U/L, 74 (19%) developed renal failure while of 1,701 patients with creatinine kinase less than 5,000 U/L, 143 (8%) developed renal failure. Among the patients with creatinine kinase greater than 5,000 U/L, there was no difference in the rates of renal failure, dialysis, or mortality between those who received the combination of bicarbonate and mannitol and those who did not. Brown, Rhee, Evans, Demetriades and Velmahos (2004:1196) concluded that abnormal creatinine kinase levels are common among critically injured patients and a creatinine kinase level greater than 5,000 U/L is associated with renal failure. The combination of bicarbonate and mannitol does not prevent renal failure, dialysis or mortality in patients with creatinine kinase greater than 5,000 U/L and the standard of administering the combination of bicarbonate and mannitol should be re-evaluated.

2.2.9.5 Glycaemic control

Blood glucose needs to be maintained within the normal range without large fluctuations (Fink, Moore, Kochanek, Vincent & Abraham 2017:1021). A strict blood glucose control should be maintained between 110-149mg/dl (6.1-8.3mmol/l) (KDIGO 2012:43; Johnson, Feehally & Floege 2019:830). Hyperglycaemia and hypoglycaemia are unsafe for the patient. Hypoglycaemic episodes increase not only the length of stay in hospital but also in-patient and post-admission mortality risk (Akirov, Grossman, Shochat & Shimon 2016:418, 421). Moreover, hyperglycaemia increases the patient's risk for 30-day mortality (Mi, Wang, Yang, Pu, Yang & Liu 2018:1756285617731686).

2.2.9.6 Pharmacological prevention

Pharmacological measures used in the prevention of AKI, namely vasoactive agents, diuretics, N-acetylcysteine and statin, are discussed next.

2.2.9.6.1 Vasoactive agents

Since 2005 multiple vasoactive agents, such as dopamine, fenoldopam and atrial natriuretic peptide, have been recommended and clinically studied to enhance the renal blood flow by means of renal vasodilation. A low dose of dopamine is known to improve urine output by increasing the renal blood flow as well as help in creatinine clearance (Gilbert, Weiner, Bomback, Perazella & Tonelli 2017:328). In 2017, a randomized controlled study compared the effectiveness of dopamine against N-acetylcysteine (NAC) among cardiac surgery patients with pre-existing renal insufficiency. The low dose of dopamine (2.5mcg/kg/min) did not show any reno-protective effect (Savluk, Guzelmeric, Yavuz, Cevirme, Gurcu, Ogus et al 2017:12). Due to the adverse effects associated with dopamine, such as arrhythmia and intestinal ischemia, it is currently not proposed for preventing or treating AKI (Gilbert, Weiner, Bomback, Perazella & Tonelli 2017:328).

Fenoldopam, which is a dopamine type I receptor agonist, is also recommended as a reno-protective agent. Fenoldopam produces its reno-protective effect by increasing the renal blood flow and decreasing the systemic vascular resistance (Gilbert, Weiner, Bomback, Perazella & Tonelli 2017:328). Nevertheless, a study in dogs did not find any beneficial effect in the prevention of heat stroke-associated AKI (Segev, Bruchim, Berl, Cohen & Aroch 2018:1112). Due to the lack of finest data support, fenoldopam is not currently recommended for prevention of AKI (Johnson, Feehally & Kloege 2019:831).

A systematic review and meta-analysis examined whether low-dose atrial natriuretic peptide was effective in preventing or treating AKI. Yamada, Doi, Tsukamoto, Kiyomoto, Yamashita, Yanagita et al (2019:41) reviewed 18 randomised controlled trials, namely 16 prevention and 2 treatment trials. The primary outcome was the incidence of new AKI (in the prevention randomised controlled trials) and the secondary outcomes were in-hospital mortality rate, RRT requirement, length of hospital and ICU stay, incidence of hypotension, and peak serum creatinine levels. In the prevention randomised controlled trials, the incidence of new AKI was significantly low in the low-dose atrial natriuretic peptide group compared to the control group. Moreover, the low-dose atrial natriuretic peptide group showed a significantly reduced RRT requirement in both prevention and treatment randomised controlled trials. In some cases, low-dose atrial natriuretic peptide was associated with a reduction in hospital and ICU stay. However, the sample sizes and qualities of the randomised controlled trials were insufficient to conclude the efficacy of

low-dose atrial natriuretic peptide. Yamada et al (2019:41) concluded that low-dose atrial natriuretic peptide might be effective in preventing or treating AKI, but more multicentre, large-sample randomised controlled trials need to be conducted.

In 2017, Joannidis, Druml, Forni, Groeneveld, Honore, Hoste et al (2017:730) systematically examined studies on the prevention of AKI between 1966 and 2017, specifically the role of fluids, diuretics, inotropes, vasopressors/vasodilators, hormonal and nutritional interventions, sedatives, statins, remote ischaemic preconditioning and care bundles. Joannidis et al (2017:733) considered the following clinical conditions: major surgery, critical illness, sepsis, shock, exposure to potentially nephrotoxic drugs and radiocontrast. Clinical endpoints included incidence or grade of AKI, the need for RRT, and mortality. Based on the findings, Joannidis et al (2017:748) recommended controlled fluid resuscitation in volume depletion while avoiding volume overload; correction of hypovolaemia/dehydration using isotonic crystalloids in patients receiving IV contrast media, and regular monitoring of chloride levels and acid-base status in situations where chloride-rich solutions are used. Joannidis et al (2017:748) recommended against the use of starches and suggested not using gelatine or dextrans for fluid resuscitation. Joannidis et al (2017:748, 749) suggested the use of balanced crystalloids for large volume resuscitation; using human serum albumin if a colloid is deemed necessary for the treatment of patients with septic shock; prophylactic volume expansion with crystalloids to prevent AKI by certain drugs, and not delaying urgent contrast-enhanced investigations or interventions for potential preventive measures.

Norepinephrine is currently recommended as the first-line vasopressor in septic shock and early vasopressin has been proposed as an alternative. A randomised control trial was conducted in 18 adult ICUs in the UK between 2013 and 2015 to compare the effect of early vasopressin vs norepinephrine on kidney failure in patients with septic shock (Gordon, Mason, Thirunavukkarasu, Perkins, Cecconi, Cepkova et al 2016:510). The study included 409 patients (median age of 66 years; males 58.2%) who had septic shock requiring vasopressor despite fluid resuscitation within a maximum of six hours after the onset of shock. The patients were randomly assigned to vasopressin and hydrocortisone (101); vasopressin and placebo (104); norepinephrine and hydrocortisone (101), and norepinephrine and placebo (103) groups. The study found less use of RRT in the vasopressin (25.4%) than the norepinephrine (35.3%) group, but no significant difference

in mortality rates. In total, 22 of 205 (10.7%) patients in the vasopressin group and 17 of 204 (8.3%) patients in the norepinephrine group had a serious adverse event (Gordon et al 2016:516). Among adults with septic shock, the early use of vasopressin compared to norepinephrine did not improve the number of kidney failure-free days. Gordon et al (2016:518) state that although the findings do not support the use of vasopressin to replace norepinephrine as initial treatment in patients with septic shock, the confidence level included a potential clinically important benefit for vasopressin and this should be assessed further.

2.2.9.6.2 Diuretics

The fluid management in AKI patients is often a concern. As oliguric AKI has a poorer prognosis than non-oliguric AKI, diuretics are widely used (Johnson, Feehally & Floege 2019:830). Loop diuretics should be avoided to prevent AKI while they can be used to control or avoid fluid overload if the patient is responding to diuretics (KDIGO 2012:47).

2.2.9.6.3 N-acetylcysteine (NAC)

N-acetylcysteine (NAC) is a tripeptide analogous to glutathione which protects the kidney by reducing the generation of oxygen-free radicals and vasoconstriction. The cellular damage in post-ischaemic and nephrotoxic injury is partially induced by oxygen-free radicals (Johnson, Feehally & Floege 2019:830). Administration of an oral dose of 600mg NAC, three times a day was found to be statistically significant in mitigating AKI caused by deoxycholate form of Amphotericin B (Erturk Sengel, Tukenmez Tigen, Toptas, Atagunduz, Tuglular, Ergonul et al 2016:75).

Due to its antioxidant property, NAC has been used in preventing contrast-induced AKI (CI-AKI). In China, Feng, Huang, Li and Chen (2018:530) evaluated the efficacy of N-acetylcysteine (NAC) versus ascorbic acid or NAC plus ascorbic acid in the prevention of contrast-induced nephropathy (CIN) in an analysis of six ramdomised control trial studies with 919 patients. The study found no significant difference in the prevention of contrast-induced nephropathy between NAC and NAC plus ascorbic acid. However, NAC was associated with significantly lower serum creatinine levels compared to ascorbic acid and NAC plus ascorbic acid administration (Feng, Huang, Li & Chen 2018:538).

Intravenous sodium bicarbonate and oral acetylcysteine are widely used to prevent AKI and associated adverse outcomes after angiography. Weisbord, Gallagher, Jneid, Garcia, Cass, Thwin et al (2018:609) evaluated the efficacy of IV sodium bicarbonate and oral acetylcysteine in the prevention of AKI and adverse outcomes after angiography. The study found that among patients at high risk for renal complications undergoing angiography, there was no benefit of intravenous sodium bicarbonate over sodium chloride or of oral acetylcysteine over placebo for the prevention of death, need for dialysis or persistent decline in kidney function at 90 days (Weisbord et al 2018:614).

In Sao Paulo, Brazil, Savluk, Guzelmeric, Yavuz, Cevirme, Gurcu, Ogus et al (2017:8) conducted a placebo-controlled randomised control study to compare the prophylactic efficacy of NAC and dopamine administration in 135 patients with pre-existing moderate renal insufficiency undergoing CABG surgery. The patients' serum creatinine was recorded preoperatively and on the first and second postoperative days. The study found that prophylactic use of intravenous NAC had a protective effect on renal function whereas the application of renal dose dopamine did not have a protective effect in patients with pre-existing moderate renal failure (Savluk et al 2017:12).

In Mashad, Iran, Amini, Robabi, Tashnizi and Vakili (2018:130) investigated the impact of perioperative administration of N-acetylcysteine (NAC), selenium, and vitamin C on the incidence and outcomes of AKI after off-pump CABG. In the study, 291 patients requiring elective off-pump CABG were randomised to receive either NAC, vitamin C, and selenium and nothing twice per day from the day before to two days after surgery. The patients were assessed for the development of AKI using Acute Kidney Injury Network criteria, time of onset, its severity and duration, duration of mechanical ventilation, ICU and hospital length of stay, and in-hospital mortality. Of the patients, 272 completed the study. No significant differences were registered in the incidence, time of occurrence, severity and duration of AKI as well as the duration of mechanical ventilation, ICU and length of hospital stay, and in-hospital mortality between the four groups. Amini, Robabi, Tashnizi and Vakili (2018:132) found that perioperative administration of NAC, vitamin C and selenium were not effective in preventing AKI and associated morbidity and mortality after off-pump CABG.

2.2.9.6.4 Statin

Statins are well-known for their multiple effects. Statins produce down-regulation of angiotensin receptors, decrease the endothelin synthesis and inflammation. Statins inhibit nuclear factor-B thereby improving endothelial function, increase nitric oxide bioavailability, diminish the production of reactive oxygen species and protect against complement mediated injury (Johnson, Feehally & Floege 2019:831).

In Korea, Oh, Song, Cho, Lim, Jeon, Bae et al (2019:25) conducted a retrospective review of patient records to investigate the association between preadmission statin use and AKI incidence among critically ill patients admitted to the ICU for medical care. Patients who continuously took statin for more than one month prior to ICU admission were defined as statin users. The aim was to investigate whether preadmission statin use was associated with AKI incidence within 72 hours after ICU admission and whether the association differed according to preadmission estimated glomerular filtration rate. Out of 21,236 patients, 5,756 (27.1%) were statin users and 15,480 (72.9%) were non-statin users. Total AKI incidence within 72 hours after ICU admission was 31% lower in the preadmission statin users than in the non-statin users. This association was insignificant among patients with estimated GFR less than 30mL. Oh et al (2019:25) state that the results suggest that preadmission statin use is associated with a lower incidence of AKI among critically ill patients, but might not be applicable for patients with estimated GFR <30 mL min^{-1}.

Results of studies on the efficacy of atorvastatin pretreatment on reducing the prevalence of contrast-induced AKI in patients undergoing coronary angiography or percutaneous coronary interventions have been controversial. In China, Liu, Liu, Wu, Sun and Ma (2018:437) undertook a meta-analysis to evaluate the efficacy of atorvastatin on contrast-induced nephropathy after coronary angiogram or percutaneous coronary intervention. The study included ramdomised control trials that compared atorvastatin pretreatment with pretreatment with a low-dose statin or placebo for contrast-induced AKI prevention in patients undergoing coronary angiogram and the main endpoint was contrast-induced nephropathy prevalence. Nine ramdomised control trials were reviewed. High-dose atorvastatin (≥80mg) pretreatment reduced the prevalence of contrast-induced nephropathy significantly and the benefit of the pretreatment was consistent when compared with the control group (Liu, Liu, Wu, Sun & Ma 2018:439). Liu, Liu, Wu, Sun

and Ma (2018:442) concluded that pretreatment with high-dose atorvastatin could be employed to prevent contrast-induced-AKI.

However, in Shenzhen, China, He, Liu, Li, Tian, Chen and Weng (2018:475) examined the effect of perioperative statin on CSA-AKI. The study calculated the relative risk between statin and placebo for preventing CSA-AKI and reviewed eight ramdomised control trials: 5 with atorvastatin, 2 with rosuvastatin, and 1 with simvastatin. In the randomised control trials, 1,603 patients received statin treatment and 1,601 patients had placebo treatment. He, Liu, Li, Tian, Chen and Weng (2018:479) found that perioperative statin therapy did not reduce the incidence of CSA-AKI. Moreover, perioperative rosuvastatin produced a slightly significantly higher risk of AKI than atorvastatin therapy. Statin intervention both pre and post surgery slightly increased the risk of CSA-AKI versus perioperative statin therapy alone. The study concluded that perioperative statin therapy might increase the risk of CSA-AKI after cardiac surgery (He, Liu, Li, Tian, Chen & Weng 2018:482).

AKI frequently occurs in patients with sepsis and acute respiratory distress syndrome (ARDS). An analysis of the outcomes in 511 patients without AKI and 93 patients with stage 1 AKI examined whether statin treatment was protective against AKI in sepsis-associated acute respiratory distress syndrome (Hsu, Truwit, Matthay, Levitt, Thompson & Liu 2018:2054358118789158). Hsu et al (2018:2054358118789158) found that among the patients without AKI rosuvastatin did not change the risk of AKI while among those with stage 1 AKI, rosuvastatin treatment was associated with an increased risk of worsening AKI. When serum creatinine was adjusted for cumulative fluid balance among those with pre-existing AKI, rosuvastatin was no longer associated with worsening AKI. Hsu et al (2018:2054358118789158) concluded that treatment with rosuvastatin in patients with sepsis-associated acute respiratory distress syndrome did not protect against de novo AKI or worsening of pre-existing AKI.

2.2.10 Management

Patients with AKI are managed using the required renal replacement therapy (RRT). RRT is discussed next.

2.2.10.1 Renal replacement therapy (RRT)

Acute kidney injury (AKI) patients are provided supportive management as no effective pharmacological agents are available. Renal replacement therapy is used to support AKI patients with the expectation that kidney function may recover (Lerma, Sparks & Topf 2019:51).

In their study in a tertiary care hospital in India, Vikrant, Gupta and Singh (2018:959, 960) found that most of the AKI patients had community acquired-AKI, sepsis was the most common etiology (53.1%) among medical cases of AKI, 20.1% required vasopressor and 23.3% required dialysis. Dlamini, Heering, Chivese and Rayner (2017:e0177460) reviewed patients admitted between 2012 and 2013 to a tertiary referral hospital in Cape Town, South Africa. Of the patients, 366 had AKI according to KDIGO criteria; the median age was 44; 58.5% were males and 41.5% were females. The majority had community acquired-AKI; the most common comorbidities were hypertension, diabetes mellitus, human immunodeficiency virus (HIV), heart disease, and chronic kidney disease (CKD); 52.2% were in ICU; 39.6% in ICU required dialysis, and the overall 3-month mortality was 38.8%. Of 119 patients with follow-up serum creatinine, 95 (79.8%) had full renal recovery. The incidence of AKI in the population studied was 3.4% of hospital admissions and carried a high mortality risk, most significantly in mechanically ventilated patients. In the study, 36 patients underwent a kidney biopsy and in many of them the results guided patient management. Dlamini, Heering, Chivese and Rayner (2017:e0177460) emphasise that it is imperative that clinicians actively pursue underlying causes of acute renal decline in renal function, including urine analysis and if indicated and safe, a renal biopsy.

In Hong Kong, Shum, Chan, Tam, Yan and Chan (2018:1081) conducted a retrospective analysis of critically ill adult patients with KDIGO stage 3 AKI with or without RRT during ICU stay between 2011 and 2013. Of 661 patients, 50.5% received RRT; the 90-day mortality rate was 42.5% in patients that received RRT and 54.1% in patients that did not. Among 322 propensity-matched pairs, RRT was associated with lower ICU and hospital stay and 90-day mortality, and a higher 90-day renal recovery rate compared with no RRT (Shum, Chan, Tam, Yan & Chan 2018:1084).

Non-obstructive oliguria, severe acidemia, azotemia, hyperkalaemia, uremia, severe dysnatremia, clinically significant organ oedema, drug overdose with dialyzable toxins and coagulopathy requiring large amounts of blood products in patients at risk for acute respiratory distress syndrome (ARDS) are the major indications for performing RRT in AKI patients. Table 2.5 lists the indications for RRT with supporting literature.

Table 2.5 Indications for renal replacement therapy

Indication	Supporting literature
➢ Non-obstructive oliguria (urine output <200ml/12hrs) or anuria) ➢ Severe acidemia ➢ Azotemia (blood urea nitrogen >80mg/dl) ➢ Hyperkalemia ➢ Uremia (encephalitis, pericarditis, neuropathy, myopathy) ➢ Severe dysnatremia (Na+ >160 or <115mmol/l) ➢ significant organ oedema (pulmonary oedema) ➢ Drug overdose with dialyzable toxins ➢ Coagulopathy requiring large amount of blood products in a patient at risk for acute respiratory distress syndrome	Bellomo, Kellum & Ronco 2012:762; Doi, Nishida, Shigematsu, Sadahiro, Itami et al 2018:996; Lerma, Sparks & Topf 2019:53.

RRT should be initiated if any of these indications exist, and is desirable in the presence of two of these indications (Fink, Moore, Kochanek, Vincent & Abraham 2017:779). There is still uncertainty regarding the appropriate time to initiate RRT. The serum creatinine and blood urea nitrogen (BUN) should not be the only component to consider while initiating dialysis; the decision to dialyse should be based on the critical analysis of the fluid balance, nutritional requirement, underlying diseases, and acid base and electrolyte balance (Lerma, Sparks & Topf 2019:53). There are several recommendations for the appropriate time to start RRT (KDIGO 2012:12; National Institute for Health and Care Excellence [NICE] 2013:22, 23; Doi, Nishida, Shigematsu, Sadahiro, Itami et al 2018:985-1045).

KIDIGO (2012:89) recommends:

- Initiate RRT when life-threatening changes in fluid, electrolyte, and acid-base balance exist. (Not Graded)
- Consider the broader clinical context, the presence of conditions that can be modified with RRT, and trends of laboratory tests rather than single BUN and creatinine thresholds alone, when making the decision to start RRT. (Not Graded).

The National Institute for Health and Care Excellence (NICE 2013:22, 23) recommends the following:

- Discuss any potential indications for RRT with a nephrologist, paediatric nephrologist and/or critical care specialist immediately to ensure that the therapy is started as soon as needed.
- Refer adults, children and young people immediately for RRT if any of the following are not responding to medical management: hyperkalemia, metabolic acidosis, symptoms or complications of uremia (for example, pericarditis or encephalopathy), fluid overload and pulmonary edema.
- Base the decision to start RRT on the condition of the adult, child or young person as a whole and not on an isolated urea, creatinine or potassium values.

The Japanese clinical practice guideline for AKI, 2016 recommends that timing of initiation of RRT should be decided on the basis of clinical symptoms and disease conditions (Doi, Nishida, Shigematsu, Sadahiro, Itami et al 2018:1011).

However, the best time to initiate RRT in ICU patients with AKI patients is not clear. In 2017, a study in Denmark examined the impact of early RRT on long-term mortality, risk of chronic kidney disease (CKD) and end-stage renal disease (ESRD). Christiansen, Christensen, Pedersen, Gammelager, Layton, Brookhart et al (2017:326) conducted a cohort study of all adult patients treated with continuous RRT in the ICU at Aarhus University Hospital in Denmark between 2005 and 2015. The study defined early treatment as RRT initiated at AKI stage 2 or below, and late treatment as RRT initiated at AKI stage 3. The mortality, chronic kidney disease and end stage renal disease analyses

included 1213, 313 and 617 patients, respectively. The 90-day mortality in the early RRT group was 53.6% compared with 46.0% in the late RRT group. In patients that survived to day 90, early initiation was not associated with a major impact on long-term mortality or risk of chronic kidney disease and end stage renal disease. Christiansen, Christensen, Pedersen et al (2017:326) concluded that the findings did not support that early RRT initiation is superior to late initiation.

In a retrospective study of data from 28 hospitals in Beijing, China, Jia, Jiang, Wen, Wang, Xi and Du (2018:405-410) examined the effect of timing of RRT on the outcomes of 281 critically ill patients who received RRT between March and August 2012. In patients with oliguria/anuria, the 28-day mortality rate was higher than those without. Late initiation of RRT was an independent risk factor for 28-day mortality. Early initiation of RRT (within 24 hours of ICU admission) showed a significant increase in the patient survival rate compared to late initiation (≥24hrs after ICU admission) (Jia, Jiang, Wen, Wang, Xi & Du 2018:408).

Different modalities of RRT are available to treat patients with AKI (Lerma, Sparks & Topf 2019:54) including

- Intermittent haemodialysis (IHD)
- Various types of continuous renal replacement therapy (CRRT) - continuous venovenous haemofiltration (CVVH), continuous venovenous haemodialysis (CVVHD), continuous venovenous hemodiafiltration (CVVHDF)
- Prolonged intermittent RRT (PIRRT) in which IHD and CRRT are combined. Slow low-efficiency dialysis (SLED), slow continuous ultrafiltration (SCUF) or extended daily diafiltration
- Peritoneal dialysis (PD).

Intermittent haemodialysis is the most traditional form of RRT which achieves a fastest removal of small solutes while limiting the exposure to the extracorporeal circuit. Intermittent haemodialysis is commonly used among patients with severe hyperkalaemia, poisoning and tumour lysis syndrome. Continuous renal replacement therapy is usually available in ICUs and is delivered continuously, using lower blood flow rates. The continuous nature of the therapy ensures total clearance over 24hrs and the slower rate of solute clearance avoids large fluid shifts between the intracellular and extracellular fluid

compartments. Due to these features it is recommended for patients with haemodynamic instability and brain injury patients who are at risk for cerebral oedema. Prolonged intermittent RRT is a recently developed variant of intermittent haemodialysis. The prolonged therapy is also known as hybrid therapy, which incorporates the intermittent haemodialysis equipment while achieving the therapeutic aim of continuous renal replacement therapy. This hybrid therapy improves the haemodynamic tolerability, using a lower blood flow rate, and provides gradual solute and fluid removal (Gilbert, Weiner, Bomback, Perazella & Tonelli 2017:329, 330).

Intermittent haemodialysis lasts for 3-5 hours while hybrid therapy is performed over 8-12 hours. The decision on the specific modality of RRT depends on the availability of resources, the patient's need and staff expertise, but continuous RRT is preferred for haemodynamically unstable patients (Lerma, Sparks & Topf 2019:54). Table 2.6 summarises the advantages and disadvantages of intermittent haemodialysis

Table 2.6 Advantages and disadvantages of intermittent haemodialysis

Advantages	Disadvantages
➢ Shorter duration of therapy ➢ Rapid correction of electrolyte and acid-base disturbances ➢ Rapid fluid removal ➢ Availability of the machines ➢ Availability of trained nurses	➢ Limited control over fluid regulation ➢ Limited control over acid-base and electrolyte balance ➢ Not suitable for haemodynamically unstable patients

Source: Lerma, Sparks & Topf (2019:54)

Due to the shorter duration of therapy, it provides rapid correction of electrolyte and acid-base disturbances and rapid fluid removal. There is adequate availability of trained staff and machines. The disadvantages are that it has limited control over fluid, acid-base and electrolyte balance and it is unsuitable for haemodynamically unstable patients (Lerma, Sparks & Topf 2019:54). Table 2.7 lists the advantages and disadvantages of continuous RRT.

Table 2.7 Advantages and disadvantages of continuous renal replacement therapy

Advantages	Disadvantages
➢ Slower fluid removal, which promotes ➢ haemodynamic stability ➢ Better solute clearance ➢ Better correction of acid-base and electrolyte abnormalities ➢ Better metabolic control	➢ Needs continuous anticoagulants ➢ Unable to mobilise the patient ➢ Requires human resources and ICU monitoring

Source: Lerma, Sparks & Topf (2019:54)

The main advantages of continuous RRT are that it promotes haemodynamic stability by means of slow fluid removal, ensures better solute clearance, metabolic control and better correction of acid-base and electrolyte abnormalities. The disadvantages are that it needs continuous anticoagulants; patients cannot be mobilised, need close monitoring in ICU and it requires experienced staff (Lerma, Sparks & Topf 2019:54).

Critically ill adults with AKI experience considerable morbidity and mortality. To date, there is no consensus on which RRT modality is safer for AKI patients. A prospective study in Finland that assessed the one- and three-year outcomes of AKI patients treated with intermittent haemodialysis found increased mortality and RRT dependency (Eskola, Vaara, Korhonen, Sauranen, Koivuviita, Honkanen et al 2018:1456).

In Ottawa, Canada, Kovacs, Sullivan, Hiremath and Patel (2017:343) compared the effect of slow low-efficiency dialysis versus continuous RRT on renal recovery after AKI in the ICU. Their meta-analysis of 1,564 patients from 18 studies indicated no significant difference in the overall proportion of renal recovery or the time to renal recovery. Statistically, slow low-efficiency dialysis was marginally favored over continuous RRT for the secondary outcome of mortality. There appeared to be no clear advantage for continuous RRT in haemodynamically unstable patients (Kovacs, Sullivan, Hiremath & Patel 2017:350). Kovacs, Sullivan, Hiremath and Patel (2017:353) concluded that currently, both modalities were safe and effective means of treating AKI in critically ill adults.

2.2.11 Consequences of AKI

The major consequences associated with AKI are fluid overload, metabolic acidosis, hyperkalaemia, sodium disorders, calcium phosphate and magnesium disorders, respiratory complications, systemic inflammatory response syndrome (SIRS), and nutritional imbalance. These consequences are discussed next.

2.2.11.1 Fluid overload

Fluid overload is a common complication among AKI patients which contributes to interstitial oedema, impaired oxygen and metabolite diffusion. Moreover it leads to increased intra-abdominal pressure (Wang & Bellomo 2017:707). Acute kidney injury (AKI) patients develop fluid overload due to diverse factors such as

- Inadequate urine output
- Hypoalbuminemia, which decreases the intravascular oncotic pressure causing more fluid to leak into the interstitial space resulting in peripheral oedema
- Inflammation due to AKI or other coexisting non-renal disease, which increases the vascular permeability. As a result, fluid escapes from the intravascular to the interstitial space (Urden, Stacy & Lough 2014:715).

The initial management of fluid overload includes minimizing the fluid intake. If the patient becomes symptomatic due to the excess fluid, diuretic therapy can be initiated. Diuretics can be administered intravenously either as bolus doses or continuous infusion in patients with heart failure or hepatic syndrome (Johnson, Feehally & Floege 2019:834).

2.2.11.2 Metabolic acidosis

Metabolic acidosis results from accumulation of unexcreted acidic waste products such as anions, hyperphosphatemia, elevated sulphate, urate and lactic acid. Hypoalbuminemia also aggravates acidosis as albumin has a mild alkalinizing effect (Urden, Stacy & Lough 2014:709). The decreased renal production of bicarbonate and impaired excretion of ammonium ions also contribute to metabolic acidosis (Johnson, Feehally & Floege 2019:835). Severe acidosis contributes to decreased myocardial

contractility and response to vasopressors and results in arrhythmia (Faubel & Shah 2016:179).

The management of acidosis varies depending on the underlying cause. Even though the use of sodium bicarbonate is still controversial, it is recommended for severe metabolic acidosis (pH <7.10 - 7.15) or if the bicarbonate level is less than 15-18mmol/L. The adverse effects of sodium bicarbonate administration should be considered, such as volume overload and carbon dioxide generation, which further aggravate the intracellular acidosis (Johnson, Feehally & Floege 2019:835).

2.2.11.3 Hyperkalaemia

Hyperkalaemia is a life-threatening complication of AKI due to decreased renal potassium excretion. Hyperkalaemia affects the cardiac conduction and repolarization, which is manifested by tall T waves (tending), prolonged PR interval, widened QRS complex and even progress to ventricular fibrillation. Diaphragmatic muscle weakness can develop due to hyperkalaemia, ultimately resulting in respiratory failure (Johnson, Feehally & Floege 2019:118).

The initial step in the management of hyperkalaemia is removing the potassium-raising medications, such as β adrenergic antagonists, potassium-sparing diuretics, Angiotensin converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs). Secondly, intravenous dextrose insulin infusion is given to shift potassium to intracellular space. If metabolic acidosis co-exists with hyperkalaemia, sodium bicarbonate is recommended as it also promotes the shift of potassium. The next step is to promote potassium excretion by administration of saline, loop diuretics and cation exchange resins. Sodium polystyrene sulfonate or calcium resins can be used which is administered orally or rectally as retention enema. Finally, if the conservative management fails, haemodialysis can be initiated (Gilbert, Weiner, Bomback, Perazella & Tonelli 2018:327; Johnson, Feehally & Floege 2019:835).

2.2.11.4 Sodium disorders

Hyponatremia and hypernatremia can occur as a complication of AKI. Hyponatremia occurs due to fluid overload and strict fluid restriction is indicated (Gilbert, Weiner, Bomback, Perazella & Tonelli 2018:327; Johnson, Feehally & Kloege 2019:835). Hypernatremia results from free water intake, loss of hypotonic fluid and administration of large volume of IV saline infusion during resuscitation (Gilbert, Weiner, Bomback, Perazella & Tonelli 2018:327). Fluids should be administered orally or intravenously. Optimal correction of sodium disorder may even require dialysis (Johnson, Feehally & Floege 2019:835).

2.2.11.4 Calcium phosphate and magnesium disorders

AKI patients commonly present with hyperphosphatemia, hypocalcemia and mild hypermagnesemia. Hyperphosphatemia occurs as a result of decreased renal excretion of phosphate. Hypocalcemia results from elevated phosphate, skeletal resistance to parathyroid hormone and decreased production of calcitriol. Intravenous administration of sodium bicarbonate also results in hypocalcemia. Hypocalcemia causes haemodynamic instability and can be treated by administration of calcium gluconate (Johnson, Feehally & Floege 2019:835). If AKI patients present with hyperphosphatemia, it is essential to control the serum phosphate level which is mostly achieved by decreasing the absorption of dietary phosphate. Phosphate binders are used to minimize the adsorption of the dietary phosphate and the commonly used ones are calcium acetate (1334mg), lanthanum carbonate (500mg), sevelamer (300-1000mg) or aluminium hydroxide (300-600mg). Phosphate binders are added with each meal (Molitoris 2016:782).

2.2.11.5 Respiratory complications

The major respiratory complication associated with AKI is pulmonary oedema resulting in respiratory failure often requiring mechanical ventilation (Faubel & Shah 2016:181; Ronco, Bellomo, Kellum & Ricci 2019:930). Pulmonary oedema-associated AKI can be of two types, namely cardiogenic pulmonary oedema or non-cardiogenic pulmonary oedema. Cardiogenic pulmonary oedema, also termed hydrostatic pulmonary oedema, is due to the increased hydrostatic pressure in the pulmonary capillaries leading to leakage of fluid from the capillaries into the interstitium and alveoli. Non-cardiogenic pulmonary

oedema is mediated by pro-inflammatory cytokines that cause direct injury to the lung capillary endothelium resulting in the seeping of fluid from capillaries (Faubel & Shah 2016:181).

Morphine and nitrates are used to treat respiratory symptoms of pulmonary oedema. 2-4mg of morphine is given over 3 minutes as an initial dose and repeated at 5-15 minute intervals if the need arises. Nitrates are used to decrease left ventricular filling pressure by means of venodilation. Nitrates are administered intravenously with an initial dose of 5mcg per minute. If the medical management fails, invasive or non-invasive positive pressure mechanical ventilation and dialysis can be used (Johnson, Feehally & Floege 2019:834).

2.2.11.6 Systemic inflammatory response syndrome (SIRS)

Acute kidney injury (AKI) is the manifestation of localized damage which has the potential to trigger systemic inflammatory response (Ratliff, Rabadi, Vasko, Yasuda & Goligorsky 2013:534; Johnson, Feehally & Floege 2019:791). An increase in plasma proinflammatory cytokine levels predicts mortality in patients with AKI. Akcay, Nguyen and Edelstein (2009:8) found that in AKI, both renal endothelial cells and proximal tubular epithelial cells produce cytokines and chemokines that result in infiltration of inflammatory cells into the interstitium of the kidney. Inflammatory cells in the kidney produce pro- and anti-inflammatory cytokines that may further increase or decrease inflammation in the kidney. These cytokines and chemokines have the potential to induce infiltration of inflammatory cells. Systemic inflammatory response syndrome in AKI is mediated by inflammatory cytokines (Faubel & Shah 2016:180). The cytokines are normally degraded within the renal tubular system (Druml 2014:616). During AKI, production of cytokines increases and renal clearance will be reduced, thus elevating the plasma concentration of cytokines and triggering systemic inflammatory response syndrome (Druml 2014:616; Faubel & Shah 2016:180).

2.2.11.7 Nutritional imbalance

AKI patients have poor nutritional intake and a high catabolic rate which predispose them to protein-energy malnutrition. Patients at any stage of AKI require 20-30kcal/kg/d and no

protein restriction should be imposed (KDIGO 2012:45). A non-catabolic AKI patient needs a basic protein intake of 0.8-1g/kg/d whereas patients on RRT need 1-1.5g/kg/d (KDIGO 2012:45; Fink, Moore, Kochanek, Vincent & Abraham 2017:778). The protein requirement for hypercatabolic patients and patients on continuous renal replacement therapy is 1.7g/kg/d utmost (KDIGO 2012:45).

2.2.11.8 Long-term consequences

Acute kidney injury imposes long-term consequences among patients. In their review and meta-analysis of 25 studies, Odutayo, Wong, Farkouh, Altman, Hopewell, Emdin et al (2017:382) found that AKI was associated with 86% increased risk of cardiovascular mortality; 58% increased risk of congestive heart failure (CHF); 40% increased relative risk of myocardial infarction, 38% increased risk of major cardiovascular events, and 15% increased risk of stroke. Corredor, Thomson and Al-Subaie (2016:72) examined the effect of AKI associated with cardiac surgery on long-term mortality. The occurrence of postoperative AKI is associated with a significantly increased risk of long-term mortality. Recovery of renal function before hospital discharge is associated with a lower long-term mortality risk compared with patients who experienced persistent abnormal renal function on hospital discharge (Corredor, Thomson & Al-Subaie 2016:75).

In Taiwan, Wu, Wu, Huang, Wang, Lai, Shiao et al (2014:596) investigated hospitalised patients who recovered from *de novo* dialysis-requiring AKI between 1999 and 2008. The results revealed that AKI with recovery was associated with higher long-term risks of coronary events and death in this cohort which suggested that AKI might identify patients with high risk of future coronary events. Wu et al (2014:601) concluded that enhanced post-discharge follow-up of renal function of patients who had recovered from temporary dialysis might be warranted.

Chronic kidney disease (CKD) is recognized as one of the major consequences of AKI. Patients with AKI have a threefold higher risk for chronic kidney disease (See, Jayasinghe, Glassford, Bailey, Johnson, Polkinghorne et al 2019:164). Another identified long-term risk among AKI patients is stroke. Patients who recovered from AKI that required dialysis have increased risk for ischemic stroke (Wu, Wu, Wu, Huang, Chang, Tsai et al 2014:7). Wang, Chao, Huang, Wang, Chang, Huang et al (2014:679) found that

even after recovering from dialysis-requiring AKI patients have a high long-term risk for bone fracture.

2.3 CARDIAC SURGERY-ASSOCIATED AKI (CSA-AKI)

Acute kidney injury has been identified as one of the major complications which occur in cardiac surgery patients. The incidence of AKI increases the length of hospital stay as well as health care costs (Alshaikh et al 2018:471). Acute kidney injury (AKI) onset increases patients' risk for long-term complications, such as heart failure, by threefold with AKI onset (Ninni, Seunes, Ortmans, Mouton, Modine, Koussa et al 2018:55). The mortality rate is also higher among patients that experience AKI after cardiac surgery (Petäjä, Vaara, Liuhanen, Suojaranta-Ylinen, Mildh, Nisula et al 2017:831). CSA-AKI is discussed in detail in terms of pathophysiology, risk factors, available risk prediction tools, preventive strategies, treatments and consequences in this section.

2.3.1 Pathophysiology

Acute kidney injury in cardiac surgery patients results from multiple factors. The pathophysiological mechanism is complex and not fully understood (Ortega-Loubon, Fernández-Molina, Carrascal-Hinojal & Fulquet-Carreras 2016:689). Multiple factors, such as exposure to endogenous and exogenous toxins, ischemia-reperfusion injury, embolization, changes in the haemodynamic status, inflammation, neurohormonal activation, metabolic factors and oxidative stress, predispose cardiac surgery patients to renal injury (see figure 2.4) (Thiele, Isbell & Rosner 2015:501; Wang & Bellomo 2017:699).

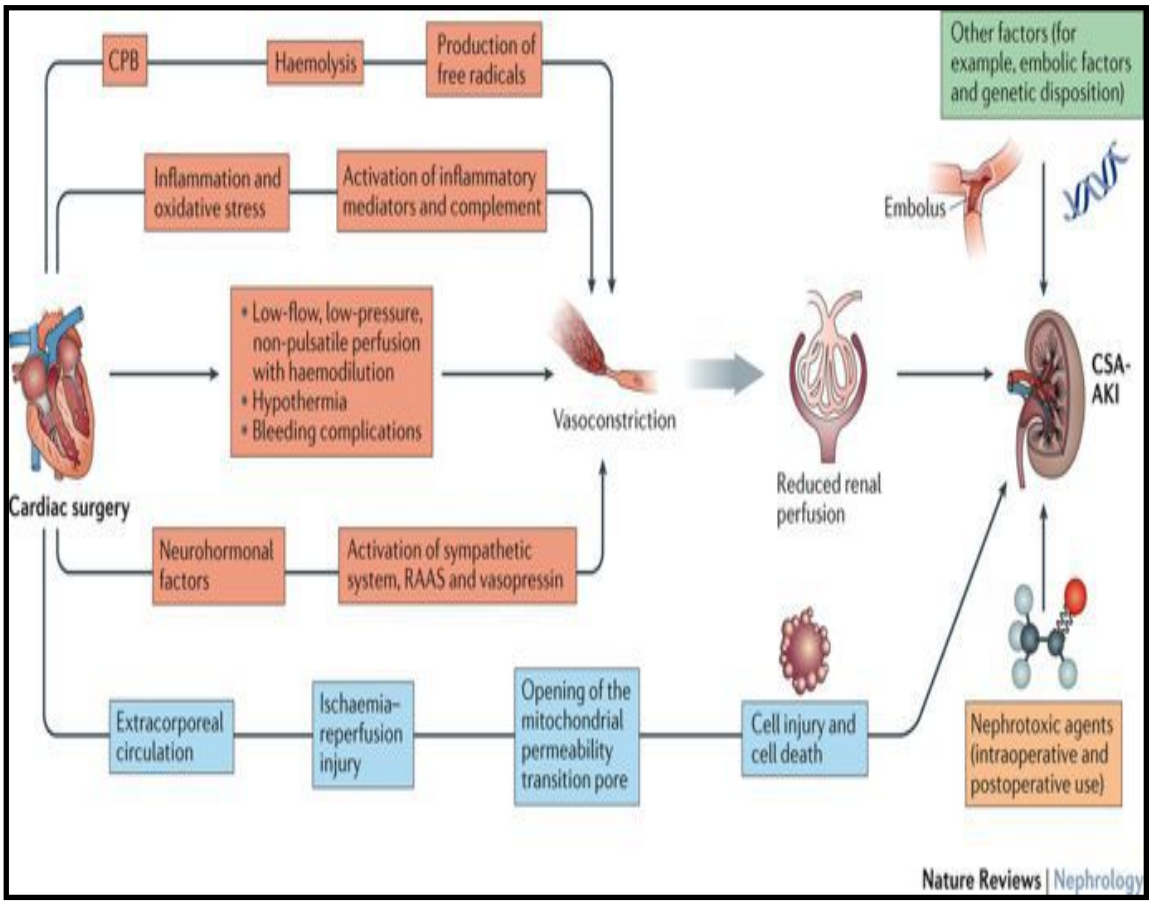

Figure 2.4. ***Pathophysiology of cardiac surgery associated acute kidney injury***
Source: Wang & Bellomo (2017:699) refferenced -no permission obtained

Cardiac surgery patients are exposed to nephrotoxic agents in the pre-, intra- and post-operative phase (Wang & Bellomo 2017:700). Nephrotoxic agents induce kidney injury by means of direct tubular injury, altering the renal haemodynamics, causing interstitial nephritis and tubular obstruction (Johnson, Feehally & Floege 2019:792).

Cardiopulmonary bypass (CPB) contributes significant damage to the kidneys. Cardiopulmonary bypass-induced renal hypoperfusion occurs as a result of low-flow, low-pressure, non-pulsatile perfusion with haemodilution and rapid changes in the temperature. Inflammatory response also contributes to hypoperfusion. Prolonged periods of hypoperfusion cause decline in GFR and renal ischemia. If the renal ischemia persists, it damages the tubular epithelial cells and tubular dysfunction occurs (Wang & Bellomo 2017:699).

Cardiopulmonary bypass (CPB) also initiates systemic inflammatory response when the blood is exposed to the cardiopulmonary bypass pump and circuit. Surgical injury also precipitates the inflammatory response (Wang & Bellomo 2017:699). Haemolysis also occurs when the blood is exposed to non-endothelialized circuits or due to the mechanical shear (Mamikonian, Mamo, Smith, Koo, Lodge & Turi 2014:e111, e112, e114). Haemolysis results in the release of haemoglobin and iron into the circulation which has proxidant and redox activity (Zakkar, Guida, Suleiman & Angelini 2015:189863). The non-endothelialized cardiopulmonary bypass circuit triggers the activation of polymorphonuclear leukocytes which could contribute to the production of reactive oxygen species. Haemolysis, ischaemia, and perfusion injury and neutrophils activation during CPB play a pivotal role in reactive oxygen species and oxidative stress and activation of pro-inflammatory and pro-apoptotic pathways (Zakker, Guida, Suleiman & Angelini et al 2015:189865).

Emboli also cause ischaemic injury to the kidneys. The atheromatous plaques formed within the walls of the arterial beds consist of smooth muscles, mononuclear cells, calcium deposits, fibrous caps, lipids and cholesterol crystals. The cholesterol crystals get deposited within the small vessels of multiple organs including the kidney when the plaques get disrupted. The obstruction to the renal blood vessels decreases the blood supply to the kidney causing ischemic injury as well as initiating immune response. The thrombolytic agents, anticoagulants and percutaneous coronary interventions cause spontaneous atheroemboli. Meanwhile procedures, such as angioplasty for renal artery stenosis, vascular surgery and cardiac surgery, result in mechanical trauma. The vessel cannulation, incision or clamping during these procedures leads to mechanical injury and disrupts the plaque, paving the way for AKI (Gilbert, Weiner, Bomback, Perazella & Tonelli 2018:313).

2.3.2 Risk factors

Risk for AKI increases with ***age, body mass index (BMI),*** history of ***chronic hypertension*** and ***chronic kidney disease*** (Ninni et al 2018:55). Amini, Najafi, Karrari, Mashhadi, Mirzaei, Tashnizi et al (2019:72, 73) found a strong association between advanced age (>65 years), diabetes, on-pump surgery, transfusion of more than one unit of red blood cells and prolonged mechanical ventilation and the development of AKI.

Patients older than 65 years and with preoperative eGFR ≤60ml/min have a higher risk for CSA-AKI (Nah, Ti, Liu, Ng, Shen & Chew 2016:759).

Preoperative ***anaemia*** and ***hypoalbuminemia*** are independent risk factors for CSA-AKI (Kim et al 2015:e273; Ng, Chew, Liu, Shen & Ti 2014:1358). Preoperative ***bicarbonate*** levels play an important role in enhancing the patient's postoperative risk for AKI. A retrospective analysis revealed that elevated levels of bicarbonate (>24mEq/L) predicted a lower incidence of AKI. However, normal levels (23-24mEq/L) and below normal levels (<23mEq/L) have higher risk for AKI after cardiac surgery (Jung, Park, Kwon, Kim, Ryu, Lee et al 2016:3216). Preoperative high-dose atorvastatin was found to increase the serum creatinine level within the first 48hrs rather than reduce the incidence or severity of AKI (Billings, Hendricks, Schildcrout, Shi, Petracek, Byrne, et al 2016:883). ***Contrast exposure*** within three days before cardiac surgery, CVP on ICU admission, and erythrocyte transfusion on first day of surgery contributed to the development of AKI (Jiang, Shen, Wang, Xu, Luo, Ding et al 2019.35).

Intra-operative factors such as ***longer operation time*** (>7hrs) also aggravate the risk for developing AKI (Kim et al 2015:e273; Ninni et al 2018:55). In their retrospective study of AKI after cardiac surgery, Xie, Wan, Ji, Chen, Liu, Chen et al (2017:278) found that prolonged ***mechanical ventilation***, CPB duration of more than 110 minutes, erythrocytes, and postoperative temperature higher than 38^{o}C were risk factors for CSA-AKI.

Elevated ***central venous pressure (CVP)*** also has a profound impact on the development of AKI. Jiang et al (2019:33) examined potentially modifiable predictors for RRT in patients with CSA-AKI and found that CVP >10cmH2O on ICU admission is an independent risk factor for AKI requiring RRT. Central venous pressure indicates the systemic venous pressure. Renal afterload increases with increases in CVP, delays the cardiac function recovery and diminishes renal perfusion. The possibility for CSA-AKI increases by 1.6 per mmH2O increase (Jiang et al 2019:35, 38). ***Hyperthermia*** is another risk factor for AKI among cardiac surgery patients. Hyperthermic episodes induce acute tubular necrosis by increasing the renal tubular metabolic rate thereby increasing the consumption of adenosine triphosphate (ATP) (Johnson, Feehally & Floege 2019:787).

Oxygen deficiency, defined as ***hypoxia***, elicits adaptive responses in cells and tissues. Lower oxygen concentration can alter renal function and cause cellular damage induced by ***hypoxia*** due to tissue necrosis (Samanta, Patra, Mandal, Roy, Das, Kar, et al 2018:886).

Transfusion of ***red blood cells (RBC) or erythrocytes*** is another risk factor for CSA-AKI. The decreased deformability of the transfused erythrocytes causes small capillary occlusion, decreases the oxygen carrying capacity and reduces the lifespan of erythrocytes. As a result, erythrocytes undergo haemolysis and produce more free iron resulting in AKI (Amini et al 2019:73). Kindzelski, Corcoran, Siegenthaler and Horvath (2018:62) explored the association between intraoperative usage of red blood cell (RBC), fresh frozen plasma, cryoprecipitate or platelet transfusions and AKI. The study found that intraoperative ***blood product transfusions*** were independently associated increased odds of developing AKI following cardiac surgery (Kindzelski, Corcoran, Siegenthaler & Horvath 2018:65). In a study of 1,444 patients, Karkouti, Grocott, Hall, Jessen, Kruger, Lerner et al (2015:378) examined the interrelationship of ***preoperative anaemia***, ***intraoperative anaemia*** and ***RBC transfusion*** on the day of surgery with AKI in cardiac surgery. The study found that patients with these three risk factors had a 2.6-fold increased risk for AKI (Karkouti et al 2015:380). Despite the fact that postoperative red blood cell transfusion poses more risk than preoperative anemia in the development of CSA- AKI, preoperative anemia tends to enhance the need for postoperative red blood cell transfusion by 4fold (LaPar, Hawkins, McMurry, Isbell, Rich, Speir, *et al*. 2018:69, 70).

In Finland, Petäjä et al (2017:827-836) evaluated the incidence of AKI after cardiac surgery and the independent association of KDIGO criteria, especially the urine output criterion, and 2.5-year mortality. Out of 638 cardiac surgery patients between September 2011 and June 2012, 183 developed AKI. Hourly urine output, daily plasma creatinine, risk factors for AKI, and variables for EuroSCORE II were recorded. AKI diagnosed using only the urine output criterion without fulfilling the creatinine criterion and all stages of AKI were associated with long-term mortality (Petäjä et al 2017:834). KDIGO clinical practice guidelines discourage the use of diuretics in prevention of AKI (KDIGO 2012:47). Postoperative fluid overload has also been found to have poor prognosis among cardiac surgery patients (Xu, Shen, Fang, Liu, Zou, Liu et al 2015:e1360).

Circulatory and respiratory support use can also have a negative impact on kidney function. One of the complications associated with extra corporeal membrane oxygenation ***(ECMO***) is renal failure (Lerma, Sparks & Topf 2019:133). Extra corporeal membrane oxygenator use was associated with the development of AKI in 73.2% patients and veno-arterial (VA) configuration significantly increases the risk (Chang, Guo, Xu & Li 2017:16666, 16667). The prolonged use of intra-aortic balloon pump can aggravate renal ischaemia due to the risk of thrombus formation (Yi et al 2016:248).

Electrolyte imbalance can contribute to the development of AKI. A retrospective study of 250 adult patients admitted to a multidisciplinary ICU in KwaZulu-Natal, South Africa evaluated serum chloride within 48 hours of admission, changes in serum chloride, and other biochemical and clinical parameters as predictors of AKI and mortality. ***Hyperchloraemia*** occurred in 57.2% of the patients within 48hrs of ICU admission and was significantly associated with AKI (De Vasconcellos & Skinner 2018:47). An increase in serum chloride was also associated with a significantly increased risk of AKI and mortality. Hyperchloraemia on admission was, however, not associated with AKI or death (De Vasconcellos & Skinner 2018:48).

Hyponatremia and AKI are common and harmful in hospitalised patients. A large retrospective cohort study in Seoul, Korea examined the combined effects of ***hyponatremia*** and AKI on patient mortality. Of the patients, 8.2% had pre-existing hyponatremia. Pre-existing hyponatremia and subsequent development of AKI increased in-hospital mortality by 85 times compared to patients with normonatremia and no AKI (Lee, Baek, Ahn, Na, Chae, Chin, et al 2016:e0162990).

2.3.3 Diagnosis

The Acute Dialysis Quality Initiative (ADQI) (Nadim, Forni, Bihorac, Hobson, Koyner, Shaw et al 2018:e008834) make the following recommendations for the diagnosis and definition of CSA-AKI:

- KDIGO criteria should be used to define AKI while including both the serum creatinine and urine output criteria.

- Monitor serum creatinine and GFR immediately before surgery to assess renal function and to monitor AKI postoperatively.
- Reassess the patient's risk for AKI within the first 12hrs of surgery using the intraoperative and postoperative risk factors.
- Include biomarkers such as TIMP2.IGFBP7 or NGAL in high risk patients.

2.3.4 Risk assessment

Risk assessment is a dynamic process in which patients with fixed preoperative risk derived from underlying comorbidities are evaluated on the basis of additional and potentially modifiable risk from their clinical status before surgery. Although many cases of AKI are reversible within days or weeks of occurrence, many large studies indicate a strong association between AKI and subsequent chronic kidney disease and end stage renal disease (Nadim, Forni, Bihorac, Hobson,Koyner, Shaw et al 2018:e008834). Nadim, et al (2018:e008834) recommend routine implementation of validated risk-prediction models in the preoperative assessment of all patients undergoing cardiovascular surgery, using eGFR, cystatis C, and/or albuminuria to improve risk stratification of those at intermediate and high risk of AKI postoperatively (not graded). Preoperative risk assessment is useful for communicating the associated risks to patients and implementing preventive strategies in the intra and postoperative periods. Identifying the associated risk and implement preventive strategies while peri- and postoperative helps in early identification and initiate proactive treatment strategies (Nadim et al 2018:e008834). Postoperative risk assessment is aimed at early identification of AKI that might allow earlier implementation of preventive strategies. The purpose of peri- and postoperative assessment is early identification of AKI that may allow proactive treatment (Nadim, et al 2018:e008834).

AKI complicates recovery from cardiac surgery, injures and impairs the functioning of the brain, lungs and gut, and places patients at a fivefold increased risk of death during hospitalisation (O'Neal, Shaw & Billings 2016:187). There are limited preventive strategies, but current evidence supports maintenance of renal perfusion and intravascular volume while avoiding venous congestion, administration of balanced salt as opposed to high-chloride IV fluids, and the avoidance or limitation of cardiopulmonary bypass exposure (O'Neal, Shaw & Billings 2016:187). For now, efforts to reduce AKI

following cardiac surgery and its influence on patient morbidity are confined to haemodynamic manipulations, close attention to intravenous resuscitation strategies including goal-directed therapy and balanced-salt fluid administration, reduced exposure to CPB, and the identification and mitigation of modifiable risk factors (O'Neal, Shaw & Billings 2016:187).

In 2005, Thakar, Arrigain, Worley, Yared and Paganini (2005:162-168) developed the Cleveland Clinic score to predict postoperative acute renal failure (ARF) or AKI because accurate prediction thereof provides an opportunity to develop strategies for early diagnosis and treatment. The clinical score was developed by incorporating the effect of all its major risk factors. A study in Canada evaluated the Cleveland Clinic scoring tool (CCS) in predicting both AKI requiring dialysis (AKI-D) and less severe stages of AKI in patients after cardiac surgery in a Canadian tertiary care centre (Wong, Onge, Korkola & Prasad 2015:37). The Cleveland Clinic score was valid in predicting severe AKI (Stage 3), but less successful in predicting patients with AKI Stage 1 and 2. Wong, Onge, Korkola and Prasad (2015:37) state that the short- and long-term outcomes associated with less severe forms of AKI indicate that prevention and treatment measures are desperately needed. In Karnataka, India, Rao, Shenoy and Gopalakrishnan (2018:535) found that the modified CCS was valid in risk identification of patients with severe stage AKI but did not have strong discrimination for early AKI stages.

In 2016, Jiang et al (2016:e003754) developed dynamic predictive risk scores for CSA-AKI in the Zhongshan Hospital, Shanghai. The study was carried out prospectively and developed dynamic predictive scores for CSA-AKI in cardiac surgical patients with the KDIGO definition for AKI, and included not only preoperative risk factors, but also enrolled the intra-operative and post-operative factors in the multivariate analysis for better predictive ability. This may improve the early recognition and intervention against CSA-AKI, fix those modifiable factors, reduce the incidence of CSA-AKI, and improve the renal and overall prognosis. Embedding these scores into the electronic medical record system may improve their clinical practical utility (Jiang et al 2016:e003754).

2.3.5 Preventive strategies

Antioxidants have been recommended for the prevention of oxidative stress from cardiopulmonary bypass (CPB) surgery. Antioxidants neutralize the free radicals by accepting or donating electrons and avoiding the unpaired condition of the radicals. Free radicals become less potent once they are neutralized. The use of additive oxidants such as propofol, L-arginine, and NAC during CPB as IV infusion or mixed with cardioplegia could be an appropriate strategy to counteract the impact of reactive oxygen species (Zakkar, Guida, Suleiman & Angelini 2015:189863). Zakkar, Guida, Suleiman and Angelini (2015:189863) state that the administration of agents with antioxidant properties during surgery either intravenously or in the cardioplegia solution may reduce reactive oxygen species burst and oxidative stress during CPB, but more in-depth research and ramdomised control trial with strict CPB protocols are required.

To date, several pharmacological agents have been recommended for the prevention of CSA-AKI. In Nanchang, China, Chen, Huang, Cao and Xu (2018:49) compared the efficacy of ten pharmacological strategies used in the prevention of CSA-AKI. Their meta-analysis revealed that the odds ratio (OR) for AKI was 0.24 with natriuretic peptide; 0.33 with fenoldopam; 0.54 with dexmedetomidine; .85 with NAC; .96 with sodium bicarbonate, and 1.05 with statins. Chen, Huang, Cao and Xu (2018:52,) concluded that natriuretic peptide is probably the preferred pharmacologic strategy to prevent AKI in adult patients undergoing cardiac surgery, especially those at high risk of AKI. Meanwhile, the researchers were uncertain if the dose and type of the natriuretic peptide can have an impact on the efficacy. Table 2.8 lists the recommended preventive strategies for CSA-AKI with supporting literature.

Table 2.8 Recommended preventive strategies of CSA-AKI and supporting literature

Preventive strategies	Supporting literature
Pre-operative measures ➢ Withhold metformin on the day of surgery as it can cause lactic acidosis. ➢ Avoid nephrotoxic agents. ➢ Hydrate. ➢ Maintain adequate renal perfusion. ➢ Haemodynamic optimization ➢ Monitor serum creatinine in high risk patients and postpone surgery, if possible, until the serum creatinine returns to baseline. Intraoperative measures ➢ Perform off-pump surgery, if possible. ➢ To minimize bleeding, use antifibrinolytics. ➢ Avoid hyperglycaemia. On-pump consideration: Maintain perfusion pressure (>75-70mmHg), reduce CPB time, use leukocyte-reducing filter, use haemofiltration to remove excess fluids.	KDIGO 2012:43,62,64,66; Ortega-Loubon, et al 2016:693; Wang & Bellomo 2017:702; Meersch, Schmidt, Hoffmeier, Van Aken, Wempe, Gerss et al 2017:1555.

2.3.6 Management

Patients with CSA-AKI should be managed with the aim of limiting the progression of AKI, promoting renal recovery, and managing acute and chronic complications of AKI. Avoid the use of natriuretic peptide, fenoldopam, diuretics, dopamine and mannitol for managing patients with CSA-AKI (Doi et al 2018:1007, 1008, 1009; Nadim et al 2018:e008834). Patients' renal function or the stage of AKI should not be the basis for initiating renal replacement therapy. The patient's clinical status should guide the clinician to decide when to start RRT (Doi, et al 2018:1011; Nadim et al 2018:e008834). RRT is discussed in detail in section 2.2.10.1. Continuous or intermittent RRT can be used in haemodynamically stable patients. Continuous RRT should be considered when the patient is haemodynamically unstable or if the fluid shift is poorly tolerated (Doi, et al 2018:1015; Nadim et al 2018:e008834).

2.4 CONCLUSION

This chapter discussed the literature review conducted on AKI and CSA-AKI with specific focus on the historical background, epidemiology, etiological factors and clinical manufestations. The pathophysiology reviewed under AKI and CSA-AKI clarifes the mechanism of kidney injury in cardiac surgery and non-cardiac surgery patients. This chapter addressed the various diagnostic measures and recommended preventative strategies as well as available treatment strategies. Chapter 3 describes the research design and methodology.

CHAPTER 3: RESEARCH DESIGN AND METHODOLOGY

3.1 INTRODUCTION

Chapter 2 discussed the literature review undertaken for the study. This chapter describes the research design and methodology of the study.

3.2 AIM AND OBJECTIVES OF THE STUDY

The aim of the study was to identify the risk factors associated with acute kidney injury (AKI) in patients who undergo cardiac surgery. The objectives of the study were to

- Assess the frequency of acute kidney injury among cardiac surgery patients in the study context.
- Identify the risk factors associated with acute kidney injury in patients who undergo cardiac surgery.
- Determine the association between the identified risk factors and acute kidney injury in patients who undergo cardiac surgery.
- Categorize the identified risk factors into modifiable, partially modifiable and non-modifiable categories.

Two hypotheses were tested in the study:

i. **Null hypothesis (Ho):** The development of AKI in cardiac surgery patients is not associated with modifiable, partially modifiable and non-modifiable risk factors.
ii. **Alternate hypothesis (Ha)**: The development of AKI in cardiac surgery patients is associated with modifiable, partially modifiable and non-modifiable risk factors.

3.3 RESEARCH QUESTION

In order to achieve the aim, the study wished to answer the following question:

> What are the risk factors associated with acute kidney injury in patients who undergo cardiac surgery?

3.4 RESEARCH DESIGN

A research design is the overall plan for addressing a research question, including the specifications for enhancing the integrity of the study (Polit & Beck 2017:41; Brink, van der Walt & van Rensburg 2018:81). The nature of research questions guides researchers to choose appropriate research designs to collect data to answer the research questions (Ellis 2016:15; Polit & Beck 2017:41). In this study, the researcher chose a quantitative correlational retrospective design to answer the research question. Quantitative studies collect numerical data by means of formal measurements which need statistical analysis (Polit & Beck 2017:41). Quantitative research deals with numbers and statistics that are collected by a structured instrument, analysed and structured into an organised report to examine relationships between phenomena (Creswell 2014:4). The researcher considered a quantitative correlational design best suited to examine the relationship between the variables (risk factors and AKI) in patients that undergo cardiac surgery. Moreover, the design was adaptable to the available resources in terms of time, funding and sources of information (Brink, van der Walt & van Rensburg 2018:81). Accordingly, the researcher conducted a retrospective chart review to assess the risk factors associated with AKI in patients that had undergone cardiac surgery. A retrospective chart review involves collecting information that is available from data sources. The data sources include case notes, inpatient case files, attendance registers, nursing records, pharmacy records, disease registries, and laboratory records (Sarkar & Seshadri 2014:JG01). The quantitative correlational retrospective chart review enabled the researcher to identify risk factors and statistically assess the association between risk factors and AKI in patients who had undergone cardiac surgery (Sarkar & Seshadri 2014:JG01; Polit & Beck 2017:51,61).

3.4.1 Quantitative Research

Quantitative research is the investigation of phenomena that lend themselves to precise measurement and quantification, often involving a rigorous and controlled design. Quantitative researchers collect numerical data by means of formal instruments for statistical analysis (Polit & Beck 2017:11, 741). The focus of quantitative research is to assess the link between attributes by means of quantifying, collecting and analyzing numerical data related to social phenomena (Antwi & Hamza 2015:223). A well-structured theoretical framework and hypothesis form the foundation for a quantitative study (Queirós, Faria & Almeida 2017:371).

Quantitative research uses deductive reasoning to generate predictions and proceed in a systematic manner through a series of steps according to an established plan (Polit & Beck 2017:11). The aim of quantitative research is to identify cause-and-effect relationships to make predictions and generalizations. Quantitative researchers make use of a “narrow angle lens” - as only one or a few causal factors are examined at a time (Antwi & Hamza 2015:221). In the study, the researcher wished to identify the association between risk factors and AKI in patients who underwent cardiac surgery.

Quantitative researchers value objectivity and attempt to avoid human bias by remaining neutral or value free and attempt to view phenomena from a distance (Antwi & Hamza 2015:221). Empirical data are collected in quantitative research with the help of structured procedures and formal instruments (Polit & Beck 2017:11; Queirós, Faria & Almeida 2017:370). Data is collected based on reality rather than influenced by researchers’ personal beliefs (Polit & Beck 2017:11). The objectively and systematically collected data are analyzed by means of statistical procedures (Queirós, Faria & Almeida 2017:370). The researcher used a self-developed audit tool to collect data and a statistician analyzed the data, using statistical software SAS 9.4.

The main limitations in quantitative research are that moral or ethical questions cannot be answered and researchers cannot capture the full range of human experiences (Polit & Beck 2017:11,12). A quantitative design is suitable for a study if the variables can be quantified and inferences can be made from the sample population (Queirós, Faria & Almeida 2017:370).

3.4.2 Correlational Study

Correlational studies explore relationships between variables without implementing any intervention (Polit & Beck 2017:203,724). Correlational research is also known as “ex post facto” or “after the fact” research. The fundamental aim of correlational study is to determine the relationship between independent and dependent variables (Brink, van der Walt & van Rensburg 2018:97). The relationship between two or more variables is determined without manipulating the variables. The strength and direction of the relationship are significant features of correlational studies (Queirós, Faria & Almeida 2017:381).

Even though a correlation between variables can be confirmed, a correlational design fails to indicate the causal relationship (Brink, van der Walt & van Rensburg 2018:98). Table 3.1 lists the advantages and disadvantages of correlational designs.

Table 3.1 Advantages and disadvantages of a correlational design

Advantages	Disadvantages
➢ No manipulation of the variables is required. ➢ Degree of association between variables can be calculated. ➢ It is inexpensive. ➢ Is useful if the research problem cannot be studied by experimentation. ➢ Can be performed in a shorter span of time. ➢ Informs about the function of variables in relation to one another. ➢ A larger sample can be studied from a given population. ➢ Provides vast information from different domains.	➢ Does not indicate the direct cause-and-effect relationship between variables. ➢ Lacks internal and external validity. ➢ Does not provide a conclusive reason for the existence of correlation between the variables. ➢ Does not have control over the independent variable.

Adapted from: Polit & Beck (2017:203); Queirós, Faria & Almeida (2017:383); Brink, van der Walt & van Rensburg (2018:98)

In this study, the researcher assessed the association between the risk factors and AKI in cardiac surgery patients. The researcher conducted a retrospective chart review as there is no control over the independent variable in correlational studies. The validity and

reliablity of the audit tool was assessed to mitigate the disadvantage of correlational study. The independent variables were the risk factors and the dependent variable was CSA-AKI. The correlational design enabled the researcher to determine the correlation between the associated risk factors and development of AKI in patients that had undergone cardiac surgery.

3.4.3 Retrospective Record Review

Polit and Beck (2017:743) define a retrospective design as “a study that begins with the manifestation of the dependent variable in the present, followed by a search for a presumed cause occurring in the past”. By applying a retrospective design, a researcher attempts to link the phenomena (risk factors) that occurred in the past with one that occurs in the present (CSA-AKI). The main characteristic of a retrospective design is that it correlates the dependent variable, namely the effect, with one or more previous independent variables, namely the causes (Polit & Beck 2017:204). A retrospective study is useful for the analysis of data recorded in case notes or a structured database (Sarkar & Seshadri 2014:JG01). In this study, the researcher conducted a retrospective record review to assess the risk factors associated with AKI in patients that had undergone cardiac surgery.

Retrospective record review is also known as clinical record review, retrospective data analysis, clinical chart review, and chart review. It involves collecting and summarizing data from a previously recorded database, and statistically analyzing and making inferences from the result (Sarkar & Seshadri 2014:JG01). Retrospective record review contributes to an economic source of information which permits investigating trends over time and does not need the participants’ co-operation (Brink, van der Walt & van Rensburg 2018:146).

Retrospective record review involves collecting information that is available from data sources. The data sources are selected on the basis of convenience and the requirements of the clinical query. The data sources include case notes, inpatient case files, attendance registers, nursing records, pharmacy records, disease registries, and laboratory records. The extent and the type of information that can be gathered vary on the basis of the data sources (Sarkar & Seshadri 2014:JG01). In this study, patients’

admission assessment documents, doctors' notes, ward prescription charts, ICU charts, and laboratory results were used to collect data.

The advantages of a retrospective record review are that it is inexpensive and effortless; reduces interference with patients' time for assessment and minimizes recall bias for events that occurred. Moreover, it enables researchers to collect data from larger samples at limited cost and is helpful in finding associations rather than causal relationships (Sarkar & Seshadri 2014:JG01).

A retrospective record review also has limitations, such as records cannot be utilized for data collection if particular information is unreliably recorded. Any discrepancy in collecting and recording in the chart hinders the extraction and interpretation of variables. Moreover, incomplete, irretrievable and lost records restrict the utilization of data (Sarkar & Seshadri 2014:JG01).

Researchers frequently make mistakes while conducting retrospective record reviews, such as failing to create clear research questions, define variables and indicate definite inclusion and exclusion criteria (Vassar & Holzmann 2013:12; Sarkar & Seshadri 2014:JG02). The researcher paid careful attention to avoiding these errors while designing the study. Table 3.2 presents the possible errors and the researcher's steps to avoid them.

Table 3.2 Possible errors and measures to avoid errors

Common errors	Measures to avoid errors
Failure to create well-defined, clearly articulated research questions.	The researcher developed the following research question for the study: *What are the risk factors associated with acute kidney injury in patients who undergo cardiac surgery?*
Failure to consider sampling issues a priori.	The researcher considered the sample size and sampling strategies. The sample size was decided on the basis of the statistician's advice. The researcher used a consecutive sampling technique to meet the sample size as the data collection was done only in one selected hospital.

Common errors	Measures to avoid errors
Failure to operationalise the variables in the study.	The main study variables such as AKI, cardiac surgery, CSA-AKI, intensive care unit and risk factors were defined in chapter 1.
Failure to train and monitor abstractors.	Only the researcher abstracted or collected data and no external help was obtained to collect data.
Failure to use a standardized abstraction form.	The researcher used a self-developed audit tool for data collection. A paper format was used for economic reasons as it was a small- scale study.
Failure to create a procedure manual for data abstraction.	The researcher did not develop a specific procedure manual but the detailed plan for data collection is described in section 3.5.4.2.
Failure to explicitly develop inclusion and exclusion criteria.	The researcher developed the inclusion and exclusion criteria based on the literature review and her knowledge of the data sources.
Failure to specify the data sources.	The data sources used in data collection are described in section 3.5.2.
Failure to specify what elements of data were extracted.	The categorical variables collected from the data sources are stipulated in section 3.5.4.1.
Failure to specify who collected the data.	The researcher specified that she collected the data.
Failure to address inter-rater or intra-rater reliability.	Reliability was assessed by implementing intra-rater reliability as data collection was done by the researcher alone. The statistician's assistance was obtained to assess the proportion of agreement by comparing the two data sets and calculating the percentage of match and mismatch (see section 3.5.6).
Failure to perform a pilot study.	The researcher conducted a pilot study as soon ethical clearance was obtained (see section 3.5.4.3).
Failure to address confidentiality and ethical considerations.	The ethical considerations pertaining to ethical clearance, maintaining confidentiality during data collection and data storage are discussed in section 3.6.

Adapted from: Vassar & Holzmann 2013:12; Sarkar & Seshadri 2014:JG02

The quantitative correlational retrospective record review enabled the researcher to identify the risk factors and statistically assess the association between the risk factors and AKI in the patients that underwent cardiac surgery. (Sarkar & Seshadri 2014:JG01; Polit & Beck 2017:51, 61).

3.5 RESEARCH METHODOLOGY

Research methodology is the plan for conducting a study and research methods are the techniques used to structure a study and to gather and analyse information relevant to the research questions systematically (Polit & Beck 2017:54). The methodology includes the setting, population, sample and sampling, data collection and analysis and ethical considerations.

3.5.1 Setting

The setting refers to the location and conditions in which data collection occurs in a study (Polit & Beck 2017:744). The study was conducted in a 323-bed private hospital located in Gauteng Province, South Africa. Bed occupancy for the year prior to the study exceeded 86%. Two cardiothoracic surgeons and five cardiologists worked permanently in the hospital. Generally, a cardiologist and cardiothoracic surgeon were involved in the care of cardiac surgery patients. Additional specialist consultation was done only on referral by a cardiothoracic surgeon. Nephrology services were provided by three resident nephrologists and nephrology nurse specialists. The major cardiac surgeries performed in the hospital were coronary artery bypass graft (CABG), valvular surgeries, and aortic aneurysm repair. Occasionally cardiac septal repair and other cardiac surgeries were also performed in the hospital. Approximately 80 to100 cardiac surgeries per year were performed in the hospital. The hospital had four ICUs, two High care units and ten wards. One of the four ICUs was a cardiothoracic ICU where cardiac surgery patients were admitted post-operatively.

The cardiothoracic ICU had eleven beds and each bed was enclosed within a separate cubicle. An admission book was maintained in the unit where the patient's hospital sticker, date and time of admission, doctors involved, and surgical procedure performed on the patient were documented. Patients' details were also available on an electronic billing

system named ‘impilo’ which was kept in the stock room as well as in the nurse’s station. Postoperative patient observations, doctors’ notes, nursing care notes, multidisciplinary team care notes, medications and laboratory results were documented on a 24-hour ICU chart. Nursing care for cardiac surgery patients was provided by critical care specialized nurses or by professional nurses with a minimum of two years’ cardiothoracic ICU experience. The permanent staff of the cardiothoracic ICU included ten critical care specialized Registered nurses, sixteen Professional nurses and four Enrolled nurses. The nursing staff in the ICU worked in two shifts: day (7H00-19H00) and night (19H00-7hH00) shifts. Post-operatively cardiac surgery patients spent almost 5-7 days in ICU after which they were transferred to the cardiac ward.

3.5.2 Unit of analysis

The unit of analysis refers to the entire case on which the researcher focuses in the study (Polit & Beck 2017:249). The entire accessible population may not always be available, which demands the researcher to limit the unit of analysis by including characteristics that define the population (Brink, van der Walt & van Rensburg 2018:116). In this study, the unit of analysis referred to patients’ documents, including admission assessment documents, doctors’ notes, ward prescription charts, ICU charts and laboratory results.

A retrospective review of the patients’ documents was done to assess the preoperative CSA-AKI risk score and frequency of CSA-AKI, and to identify the risk factors associated with CSA-AKI. Polit and Beck (2017:250) state that the researcher must define the unit of analysis and delineate eligibility criteria. The researcher’s decision on whether an individual could or could not be included in the unit of analysis should be based on these criteria. Eligibility criteria or inclusion criteria specify the population characteristics while exclusion criteria indicate the characteristics that the population must not possess (Polit & Beck 2017:250). The researcher identified the following inclusion and exclusion criteria for the study.

3.5.2.1 Inclusion criteria

The researcher included only the following documents in the study:

- All patients aged 18 years and older.

- All patients admitted to the specific ICU following cardiac surgeries such as coronary artery bypass graft (CABG), aortic valve replacement or repair, mitral valve repair or replacement, tricuspid valve repair or replacement, combination of coronary artery bypass graft (CABG) and valve repair or replacement, closure of atrial or ventricular septal defect repair from January 2014 to December 2018.

3.5.2.2 Exclusion criteria

The researcher excluded the following documents

- Patients with pre-operative end-stage kidney disease (ESRD) on dialysis prior to cardiac surgery.
- Patients that had kidney transplantation prior to cardiac surgery.

3.5.3 Sampling

Sampling refers to selecting part of the population to represent the entire population in which a researcher is interested (Polit & Beck 2017:743). Sampling enables a researcher to select cases which represent the entire population in order to obtain information about a phenomenon (Polit & Beck 2017:250; Brink, van der Walt & van Rensburg 2018:115). A sample is a subset or elements of the population about which the information is gathered (Basavanthappa 2011:141). Representativeness and size are the key aspects that should be taken into consideration in assessing a sample in quantitative research (Polit & Beck 2017:250). A sample is considered representative of the population if it is homogeneous to the entire population. There is less chance for sampling error if the sample is larger in size and homogeneous to the population (Brink, van der Walt & van Rensburg 2018:117, 118).

The researcher used non-probability consecutive sampling which makes use of non-random sampling methods. The selection of a sampling technique is based on a researcher's judgment and available samples are selected with the assumption that the sample will be able to provide data for the study (Stratton 2019:228). The records of all the eligible candidates from the available population were enrolled over a specific time period or to achieve the specific sample size. Consecutive sampling is preferred as it is

useful to avoid potential bias due to seasonal and other time-related fluctuations in the sample, especially if the sampling period is sufficiently long (Polit and Beck 2017:254). Even though non-probability sampling cannot be used to infer study findings to the target population, it allows researchers to make inferences and identify themes and patterns to understand complex social, behavioural or cultural phenomena (Stratton 2019:228).

The researcher considered non-probability consecutive sampling appropriate for the study to meet the sample size as data was collected only in one selected hospital. As reflected in the conceptual framework, all patients that undergo cardiac surgery are exposed to risk factors during the pre-, intra- or post-operative phase. A consecutive sample may not be a true representative of a study population as each element does not have an equal chance of being included in the study. The representativeness can be enhanced by using a larger sample (Polit & Beck 2017:124, 254). The sample was selected from a period of five years (January 2014 to December 2018). The researcher was able to access 133 files from 412 files, of which 4 did not meet the inclusion criteria and 1 patient died intraoperatively.

The researcher used the ICU and cardiac theatre admission registers as the sampling frame. Sampling began by obtaining the patients' details from the cardiothoracic ICU admission book after obtaining ethical approval from the University Ethics Committee and the ethics committee of the private hospital. The researcher then wrote a formal letter to the hospital manager and nursing service manager to obtain permission to access the patients' documents (see Annexure J & K). Patients' documents were stored safely outside the hospital premises, with the use of private record and information management methods such as *Metrofiles* and *Scanco*.

After receiving permission from the hospital manager and nursing service manager, the researcher contacted the case managers to obtain the patients' documents The researcher followed the hospital policy with regard to accessing the patients' documents. Hard copies of the patient's documents were stored via *Metrofiles* until December 2015 and from the beginning of 2016 all the patients' documents were available as electronic scanned documents through *Scanco*. The hard copies of the patient's documents were send back from Metrofiles on request by the case managers. The case managers released ten to fifteen patients' documents at a time. Data analysis was done in a comfort

room next to the cardiothoracic ICU. The patients' documents were not taken outside the hospital complex as they were legal documents and belonged to the specific health care group.

3.5.4 Data collection

Data collection refers to the systematic collection of information during the course of a study for statistical exploration of a problem. Data provide the basis for testing hypotheses and provide answers to research questions (Basavanthappa 2011:194, 195). The success of retrospective data collection from recorded data depends on the collection of precise and detailed data (Gregory & Radovinsky 2012:111). In this study, data collection was only done by the researcher because she was familiar with cardiac surgery patients' documents. Documents of all the patients that had undergone cardiac surgery from January 2014 to December 2018 were assessed and only those that met the inclusion criteria were considered for further analysis. The documents that met the inclusion criteria were critically analyzed against the variables in the audit tool and recorded in the audit tool (see Annexure G). Data collection took place in the comfort room next to the cardiothoracic ICU over a period of approximately five months.

3.5.4.1 Audit tool

The researcher adapted the input-process-output model (Dulebohn & Hoch 2017:571) as the conceptual framework for the study (see figure 1.1). The researcher adapted the model by including a feedback component. The input-process-output-feedback model provided a general structure for the phenomenon under study and guided the direction of the study. The model helped the researcher to relate the impact of AKI on cardiac surgery patients' outcomes. The conceptual framework indicates the linear association between the input-process-output factors. The researcher identified risk factors and risk prediction scores applied in other populations from the literature review. The researcher then developed an audit tool for data collection based on the literature review, and inputs from the supervisors, cardiologist, cardiothoracic surgeon and nephrologist (see Annexure G). Data collection was done with the help of that specific audit tool. The audit tool consisted of five sections.

- **Section A** consisted of the patients' demographic data. This section included the file code allocated to each patient's document and covered age, gender, ethnicity, body mass index (BMI), comorbidities such as diabetes mellitus, hypertension, high cholesterol, smoking, peripheral vascular disease, chronic obstructive pulmonary disease and cerebrovascular disease.

- **Section B** consisted of a CSA-AKI risk prediction tool. For the purpose of the study, the researcher adapted the Cleveland Clinic Score (Thakar, Arrigain, Worley, Yared & Paganini 2005:165). Permission to use the Cleveland Clinic Score was obtained from the developer (see Annexure H). Patients' risk for CSA-AKI was assessed based on variables such as female gender, congestive cardiac failure, left ventricular ejection fraction <35%, preoperative use of intra-aortic balloon pump (IABP), chronic obstructive pulmonary disease, insulin dependent diabetes, previous history of cardiac surgery, valve surgery, coronary artery bypass graft and valve surgery, other cardiac surgery and preoperative creatinine level. Specific scores were allocated and risk category determined according to the presence of these variables in the patients' preoperative documents.

- **Section C** consisted of the identified pre-, intra- and post-operative risk factors. Pre-operative risk factors were anemia, hypoalbuminemia, low bicarbonate level, hyperglycemia, angiogram within 72hrs of surgery, contrast use within 72hrs of surgery, hyperuricemia and hyponatremia. Intra-operative risk factors were cardiopulmonary bypass use and duration, cross clamp time, total duration of surgery more than 7hrs and mean arterial pressure <65mmhg. Post-operative risk factors were use of extracorporeal membranous oxygenator (ECMO) and its type, mechanical ventilator use for >72hrs, administration of voluven or volulyte, hyperchloremia within 72hrs of surgery, transfusion of fresh frozen plasma (>500ml) on the day of surgery, transfusion of more than 1000ml of packed cells on the day of surgery, fluid overload within 48hrs of surgery, hyperthermia within 72hrs of surgery, hypoxia (<80mmhg) within 48hrs of surgery and central venous pressure >12mmhg within 24hrs of surgery.

- **Section D** consisted of medication administered to the cardiac surgery patients during the pre-, intra- and post-operative phases. Pre-operative use of N-acetylcysteine, diuretics, inotropes, vasopressors and antibiotics. Intra-operative administration of diuretics. Post-operative use of inotropes, vasopressors, nephrotoxic antibiotics and diuretics.

- **Section E** consisted of the cardiac surgery patients' outcome which was measured in terms of normal renal function, development of AKI, deceased, discharged, and total days of stay in ICU and hospital.

3.5.4.2 Pilot study or pre-test

A pilot study or pre-test is a trial run to determine whether an instrument is clearly worded and free from major biases and whether it solicits the desired information (Brink, van der Walt & van Rensburg 2018:94; Polit & Beck 2017:632). The researcher conducted a pilot study to test the audit tool for content, clarity and coverage. The pilot study gave the researcher an insight into the institutional chart retrieval procedures and the feasibility of data abstraction, and helped her to estimate the time required to complete the audit tool, examine the missing data and assess comprehension (Polit & Beck 2017:632). It also allowed the researcher to test the inclusion and exclusion criteria, assess the frequency that the operationalised variables were missing from the patient records, and evaluate the data sampling and reliability (Vassar & Holzmann 2013:12).

Five critical care specialized nurses with more than two years' working experience in the specific ICU pre-tested the audit tool. Each critical care specialized nurse was asked to use the audit tool on one cardiac surgery patient's documents. Any doubts related to the audit tool were clarified by the researcher and a specific column was provided at the end of the audit tool to record their feedback. The nurses took approximately one and a half to two hours to collect the data. Two of the nurses recommended having the laboratory values beyond what is considered increased or decreased as slight variation was noticed depending on the pathologist used. Another issue was that no uric acid test was done on any of the five cardiac surgery patients. Readmission into the ICU created confusion in

terms of the patients' outcome and whether the readmission days in ICU needed to be counted with the total days spent in ICU.

3.5.4.3 Data-collection process

Data collection started with sampling (see section 3.5.3). The researcher then made a list of all the patients that had undergone cardiac surgery from January 2014 to December 2018. A specific numerical code was allocated to each patient depending on the sequence in which the patient's documents were obtained. The numerical code was recorded on the audit tool for patient document identification. Patients' documents that met the inclusion criteria were analyzed and the demographic data was recorded. The patients' risk for CSA-AKI was assessed using the Cleveland Clinic Score and risk category was recorded. Patients' documents were assessed for the pre-, intra- and post-operative risk factors indicated in the audit tool as well as the patients' outcome after the cardiac surgery was recorded in the audit tool.

3.5.5 Data analysis

Data analysis entails categorising, ordering, manipulating, summarising and describing the data in meaningful terms (Brink, van der Walt & van Rensburg 2018:124). The purpose of data analysis is to organise, provide structure to and bring about meaning from data collected (Polit & Beck 2017:530).

Numerical information is systematically arranged, clarified and translated into conveyable form by means of statistical analysis (Polit & Beck 2017:356). A statistician captured and analysed the data using the statistical software SAS 9.4 program. The statistician analysed the data using descriptive statistics (frequencies tables for categorical variables and means, medians and standard deviations for continuous variables) and inferential statistics. The Pearson chi-square test was performed to test association between the risk factors (modifiable, partially modifiable and non-modifiable) and the patient outcome. Where the number of counts within the categories was less than 5, the Fisher exact test was performed to test for association. The odds ratio and the relative risk of developing CSA-AKI were computed (see Annexure E for letter of statistical support).

3.5.6 Rigour

Rigour minimizes bias and ensures control over variables under study (Polit & Beck 2017:310). Validity and reliability were applied to the data collection tool to determine rigour. The quality of a research instrument is determined by its validity and reliability.

3.5.6.1 Validity

Validity refers to the degree to which an instrument accurately measures what it is intended to measure (Polit & Beck 2017:312). The audit tool was designed to achieve validity by accurately measuring the risk factors that contributed to AKI in cardiac surgery patients. The validity of the audit tool ensured that the results obtained by the instrument accurately measured the context in which it was applied (Brink, van der Walt & van Rensburg 2018:151).

The researcher applied content validity to determine the validity of the audit tool. Content validity ensured that the variables included in the audit tool covered and reflected the risk factors (Heale & Twycross 2015:66). Since the audit tool was developed by the researcher, the content validity was assessed to ensure that all the components of the variables to be measured were well presented (Brink, van der Walt & van Rensburg 2018:152). Due to a lack of objective methods to ensure adequate content coverage, the researcher depended on a panel of experts to determine the content validity of the audit tool (Taherdoost 2016:30; Polit & Beck 2017:311). The researcher used the following steps to ensure content validity.

1. A literature review was conducted to ensure that all relevant items were extracted.
2. The audit tool was sent to a panel of experts in the field of research.
3. The content validity index was calculated.
4. The least significant items were eliminated.

The researcher developed the audit tool on the basis of the literature review which revealed the essential variables to be included in the content (Brink, van der Walt & van Rensburg 2018:152). The audit tool was given to a panel of experts to ensure the relevance of the variables included (Polit & Beck 2017:310). The panel consisted of a cardiothoracic surgeon, a nephrologist, a physician, two intensivists and two critical care

specialized nurses to evaluate the content of the audit tool. The experts were asked to rate each item on the audit tool using a four-point scale: 1=not relevant, 2=somewhat relevant, 3=quite relevant and 4=highly relevant. The item content validity index (I-CVI) was calculated. The items with I-CVI >0.8 were included in the audit tool (Polit, Beck & Owen 2007:466; Polit & Beck 2017:311).

Six of the seven experts responded. The I-CVI score was calculated for all the variables in the audit tool. The variables that were rated as “not relevant” and “somewhat relevant” by four out of six experts were excluded from the audit tool. The variables that were rated as “quite relevant” and “highly relevant” by five out of six experts had I-CVI score >0.83. The final audit tool only contained those variables with I-CVI >0.8.

3.5.6.2 Reliability

Reliability refers to the degree of consistency or dependability with which the instrument measures the attributes it is designed to measure (Polit & Beck 2017:303). Reliability indicates the consistency in the results on repeated measurements on different occasions or by different people (Polit & Beck 2017:303, 305). Reliability of data collection enhances the overall confidence in a study’s accuracy. If the study variables are recorded accurately by the researcher, it strengthens the research data (McHugh 2012:277). Reliability safeguards the scores from measurement errors (Polit & Beck 2017:303).

Intra-rater reliability was used to evaluate the reliability of the results as the data collection was done by the researcher alone. Intra-rater reliability refers to the application of the tool on two or more occasions to the same sample to assess a researcher’s self-consistency. It is an index of self-consistency which concerns the consistency of the person making the measurements (Polit & Beck 2017:305, 306). As ten to fifteen patients’ documents were released by the hospital at a time which needed to be returned before they issued the next set, the researcher reassessed every fifteenth patient’s documents two days after collecting the data from each specific set. The statistician assessed the proportion of agreement by comparing the two data sets and calculated the percentage of match and mismatches.

3.6 CONCLUSION

This chapter described the research design and methodology including the setting, unit of analysis, data-collection tool, data collection process and analysis. This chapter also emphasised quality control measures implemented to ensure the validity and reliability of the audit tool. Chapter 4 discusses the data analysis and interpretation and findings.

CHAPTER 4: DATA ANALYSIS, INTERPRETATION AND RESULTS

4.1 INTRODUCTION

Chapter 3 described the research design and methodology. This chapter discusses the data analysis and interpretation, and findings of the information gathered from the patient's documents using the audit tool. The variables in the audit tool were systematically analysed and significant variables that contributed to the development of CSA-AKI were supported with relevant literature to add value to the findings.

4.2 DATA MANAGEMENT AND ANALYSIS

Data was collected between December 2019 and April 2020 from the files of patients who had undergone cardiac surgery between January 2014 and December 2018. The researcher developed and used an audit tool based on the literature review for the retrospective data collection. Only the researcher collected data, spending 60-90 minutes auditing each patient's documents. Although the researcher requested 412 patients' records from the case manager, only 133 were issued within the five-month period. Out of 133 patients' records, 4 did not meet the inclusion criteria, and 1 patient died intraoperatively. A total of 128 patients' records were audited.

The statistician analyzed the data using descriptive statistics (frequencies, tables for categorical variables and means, medians and standard deviations for continuous variables) to describe the results. For inferential statistics, the Pearson chi-square test was performed to test association between the risk factors (modifiable, partially modifiable and non-modifiable) and the patient outcome. Where the number of counts within the categories was less than 5, the Fisher exact test was performed to test for association. The odds ratio and the relative risk of developing CSA-AKI were computed (see Annexure E).

The results are presented according to the five sections of the audit tool:

- Section A: Demographic data

- Section B: Cleveland clinic score
- Section C: Risk factors
- Section D: Medications
- Section E: Patient outcome

4.2.1 Demographic profile

The patients' demographic data included age, gender, ethnicity, body mass index (BMI), comorbidities such as diabetes mellitus, hypertension, high cholesterol, smoking, peripheral vascular disease, chronic obstructive pulmonary disease (COPD) and cerebrovascular accident (CVA). Table 4.1 presents the patients' demographic profile.

Table 4.1 Patients' demographic profile

Variable	N statistics	Minimum statistics	Maximum statistics	Mean statistics	Standard error
Age	128	20	84	61.49	1.074
Variable	**Variable subdivision**	**Frequency**	**Percentage**	**Valid percent**	**Cumulative percent**
Gender	Male	55	43	43	43
	Female	73	57	57	100
Ethnicity	African	14	10.9	11.2	11.2
	Caucasian	93	72.7	74.4	85.6
	Asian	17	13.3	13.6	99.2
	Mixed	1	0.8	0.8	100
	Missing	3	2.3		
Body mass index(BMI)	BMI>30	45	35.2	35.2	35.2
	BMI<30	83	64.8	64.8	100
Diabetes mellitus	Yes	39	30.5	30.5	30.5
	No	89	69.5	69.5	100
Hypertension	Yes	88	68.8	68.8	68.8
	No	40	31.3	31.3	100
High cholesterol	Yes	25	19.5	19.7	19.7
	No	102	79.7	80.3	100
Smoking	Yes	36	28.1	28.1	28.1
	No	92	71.9	71.9	100
Peripheral vascular disease	Yes	14	10.9	10.9	10.9
	No	114	89.1	89.1	100
COPD	Yes	11	8.6	8.6	8.6
	No	117	91.4	91.4	100
Cerebrovascular accident	Yes	4	3.1	3.1	3.1
	No	124	96.9	96.9	100

4.2.1.1 Age

The patients' age ranged between 20 and 84 years with a mean age of 61.49 years. Advanced age has been found to have a greater impact on developing CSA-AKI (Amini et al 2019:72; Wang, Yu, Zhai, Liu, Sun & Zhu 2018:2594). Age is a major risk factor for AKI. Elderly patients are at higher risk because of diminished kidney function and reduced body fluid (Gilbert, Weiner, Bomback, Perazella & Tonelli 2017:334; Lerma, Sparks & Topf 2019:47). This study found no relationship between the patients' age and development of AKI.

4.2.1.2 Gender

Of the patients, 57% (n=73) were females and 43% (n=55) were males. A higher incidence of AKI has been reported among female cardiac surgery patients by some researchers (Saydy, Mazine, Stevens, Jeamart, Demers, Pagé et al 2018:259). Meanwhile others claimed that male patients are at higher risk as compared to females (Jiang et al 2016:e003754; Xie et al 2017:278). Of the patients, 25.5% (n=14) males and 20.5% (n=15) females developed AKI, but no significant relationship was found between gender and development of CSA-AKI as the Pearson chi-square p-value was >0.05.

4.2.1.3 Ethnicity

Cardiac surgery patient's race is recognised as a risk factor for the development of AKI mostly in African-Americans (Kertai, Zhou, Karhausen, Cooter, Jooste, Li et al 2016:344; Mitchell, Vinnakota, Deo, Markowitz, Sareyyupoglu, Elgudin et al 2018:318, 319). The researcher assessed the patients' ethnic background. Of the patients, 72.7% (n=93) were Caucasian; 13.3% (n=17) were Asian; 10.9% (n=14) were African, and 0.8% (n=1) were mixed race or Coloured (see Figure 4.1). Three of the records did not record the patient's ethnic background. The study found no relationship between the patients' ethnicity and development of CSA-AKI.

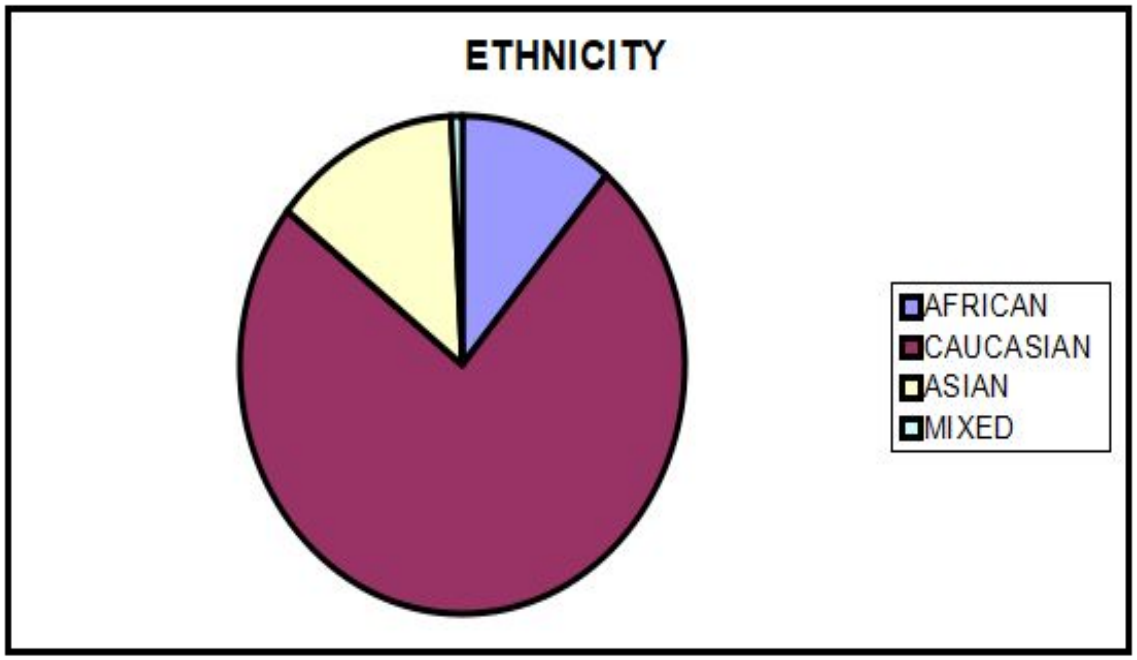

Figure 4.1 Patients' ethnic background

4.2.1.4 Body mass index (BMI)

Of the patients, 64.8% (n=83) were in the lower BMI (<30) category and 35.2% (n=45) had BMI >30. Increased body mass index (BMI) is an independent risk factor for AKI in cardiac surgery patients (Wang, Yu, Zhai, Liu, Sun & Zhu 2018:2594; Kim et al 2015:e273). This study found no significant relationship between BMI and development of CSA-AKI.

4.2.1.5 Diabetes mellitus

Of the patients, 30.5% (n=39) had diabetes mellitus and 69.5% (n=89) were non-diabetics. Diabetes mellitus is a known risk factor for the development of CSA-AKI (Amini et al 2019:72; Jiang, Shen, Wang, Xu, Luo, Ding et al 2019:35; Saydy et al 2018:259). The Cleveland Clinic score included insulin dependent diabetes mellitus as one of the variables (Thakar et al 2005:165). This study did not find a direct link between diabetes mellitus and CSA-AKI.

4.2.1.6 Hypertension

Hypertension was the major comorbidity among the patients. Of the patients, 68.8% (n=88) had hypertension and 31.3% (n=40) did not. Preoperative history of hypertension tends to enhance the patients risk for developing postoperative AKI (Kim et al 2015:e273; Ng, Chew, Liu, Shen & Ti 2014:1358). In this study, hypertension did not shown any impact on development of CSA-AKI.

4.2.1.7 High cholesterol

High cholesterol has been identified as a risk factor for the development of AKI in cardiac surgery patients (Ji, Li, Young, Yeranossian & Liu 2013:e77446; O'Neal, Shaw & Billings 2016:187). Of the patients, 79.7% (n=102) did not have high cholesterol and 19.5% (n=25) had high cholesterol. The study found no direct association between high cholesterol and CSA-AKI.

4.2.1.8 Smoking

Of the patients, 71.9% (n=92) were non-smokers and 28.1% (n=36) were smokers. Smoking contributes to increased serum creatinine levels, especially in older patients, and is an enhanced risk for CSA-AKI (Kim et al 2015:e273; Saydy et al 2018:261). This study found no association between smoking and AKI in the patients.

4.2.1.9 Peripheral vascular disease

Peripheral vascular disease is one of the least identified risk factors for CSA-AKI but has the potential to cause an increase in postoperative serum creatinine level in both young and older cohorts (Harky, Joshi, Gupta, Teoh, Gatta & Snosi 2020:213; Saydy et al 2018:261). Of the patients, 89.1% (n=114) had no history of peripheral vascular disease while 10.9% (n=14) had peripheral vascular disease. The study found that peripheral vascular disease showed no remarkable effect in the development of CSA-AKI.

4.2.1.10 Chronic obstructive pulmonary disease (COPD)

Chronic obstructive pulmonary disease is a risk factor for CSA-AKI (Harky, Joshi, Gupta, Teoh, Gatta & Snosi 2020:213; Thakar et al 2005:165). Of the patients, 91.4% (n=117)

did not have COPD, and 8.6% (n=11) had COPD. The study found no association between COPD and the development of CSA-AKI.

4.2.1.11 Cerebrovascular accident (CVA)

Cerebrovascular accident or stroke was the least seen co-morbidity. Of the patients, 3.1% (n=4) had cerebrovascular accident prior to cardiac surgery. The statistical analysis failed to indicate any relation with the development of postoperative AKI which is similar to that of Borde, Asegaonkar, Apsingekar, Khade, Khodve, Joshi et al (2019:478) and Thanavaro, Taylor, Vitt, & Guignon (2019:34) findings.

4.2.2 Cleveland Clinic Score

In Section B, the researcher included the Cleveland Clinic score to assess the pre-operative risk for developing AKI in patients that underwent cardiac surgery. The risk factors such as gender, congestive cardiac failure, left ventricular ejection fraction <35%, pre-operative use of intra-aortic balloon pump (IABP), COPD, insulin dependent diabetes, previous cardiac surgery, valve surgery, coronary artery bypass graft (CABG) along with valve surgery, other cardiac surgery, preoperative creatinine (106.08 - 185.6µmol/l) and preoperative creatinine (185.6µmol/l) were assessed. Depending on the presence or absence of these risk factors, a predetermined score was allocated and the risk category identified. Table 4.2 shows the patients' risk category.

Table 4.2 Patients' risk category

RISK CATEGORY	FREQUENCY	PERCENT	VALID PERCENT	CUMULATIVE PERCENT
0	1	0.8	0.8	0.8
0 - 2	92	71.9	71.9	72.7
3 - 5	27	21.1	21.1	93.8
6 - 8	7	5.5	5.5	99.2
9 - 13	1	0.8	0.8	100

The Cleveland Clinic score lists four risk categories: low risk (score 0-2), moderate risk (score 3-5), intermediate risk (score 6-8) and severe risk (9-13) (Thakar et al 2005:165). Table 4.2 indicates that of the patients, 71.9% (n=92) had low preoperative risk for developing CSA-AKI; 21.1% (n=27) had moderate risk; 5.5% (n=7) had intermediate risk, and 0.8% (n=1) had severe risk. In this study, cross-tabulation showed no correlation between the risk category and risk for developing CSA-AKI due to the small sample size (Rao, Shenoy & Gopalakrishnan 2018:535; Wong, Onge, Korkola & Prasad 2015:37).

4.2.3 Risk Factor

In Section C the researcher included the risk factors and categorized them into preoperative, intraoperative and postoperative variables. The preoperative risk factors included in the audit tool were anaemia, hypoalbuminemia, bicarbonate level <22mmol/l, hyperglycaemia, angiogram within 72hrs of surgery, contrast use within 72hrs of surgery, hyperuricemia and hyponatremia. The cardiopulmonary bypass time, cross clamp time, total duration of surgery >7hrs and mean arterial pressure <65mmhg were the intraoperative risk factors included.

The postoperative risk factors focused on use of extra corporeal membrane oxygenation ECMO, mechanical ventilator use for more than 72hrs, administration of voluven/volulyte, presence of hyperchloremia within 72hrs, transfusion of fresh frozen plasma (FFP) >500ml on the day of the surgery, transfusion of red cell concentrate >1000ml on the day of surgery, hypercalcemia within 48hrs of surgery, fluid overload within 48hrs of surgery, hyperthermia within 72hrs of surgery, hypothermia within 24hrs of surgery, hypoxemia <80mmhg within 48hrs of surgery and central venous pressure (CVP) >12mmhg within 24hrs of surgery.

4.2.3.1 Preoperative risk factors

Table 4.3 presents the patients' preoperative risk factors.

Table 4.3 Patients' preoperative risk factors

VARIABLES		FREQUENCY	PERCENT	VALID PERCENT
Anaemia (<12g/dl)	Yes	23	18.0	18.0
	No	105	82.0	82.0
Hypoalbuminemia (<34g/l)	Yes	28	21.9	21.9
	No	100	78.1	78.1
Bicarbonate level (<22mmol/l)	Yes	20	15.6	15.6
	No	108	84.4	84.4
Hyperglycaemia (8mmol/l)	Yes	45	35.2	35.4
	No	82	64.1	64.6
Angiogram within 72hrs of surgery	Yes	52	40.6	40.9
	No	75	58.6	59.1
Contrast use within 72hrs of surgery	Yes	51	39.8	39.8
	No	77	60.2	60.2
Hyperuricemia	Yes	0		
	No	0		
	Missing	128		
Hyponatremia (135mmol/l)	Yes	16	12.5	12.5
	No	112	87.5	87.5

4.2.3.1.1 Anaemia

Anaemia is a preoperative modifiable risk factor for CSA-AKI (Kim et al 2015:e273). In this study, anaemia was defined as haemoglobin level <12g/dl. Of the patients, 82% (n=105) did not have anaemia, and 18% (n=23) presented with preoperative anaemia. The Pearson chi-square p-value calculated for anaemia and CSA-AKI is 0.000 which is <0.05 showed a positive association between anaemia and CSA-AKI. The odds ratio was 5.647 and relative risk was 3.2, which indicated that the patients with preoperative anaemia had 3 times more risk for developing CSA-AKI. Preoperative anaemia has an incremental effect in the development of CSA-AKI (Ng Chew, Liu, Shen & Ti 2014:1358; Oprea, Del Rio, Cooter, Green, Karhausen, Nailer, *et al*. 2018:54; Saydy et al 2018:261).

4.2.3.1.2 Hypoalbuminemia

In this study, serum albumin level <34g/l was considered hypoalbuminemia. The patients' albumin level was obtained from the laboratory result done closest to the surgery. Of the patients, 78.1% (n=100) did not have hypoalbuminemia and 21.9% (n=28) had

hypoalbuminemia. The risk estimate showed a p-value 0.001 and an odds ratio of 4.550. The presence of hypoalbuminemia increases the risk for developing CSA-AKI by 2.9 times compared to normal albumin level. Hypoalbuminemia is one of the modifiable risk factors for CSA-AKI (Kim et al 2015:e273; Nie, Tang, Zhang, Feng & Chen 2017:5605634). An increase in preoperative serum albumin decreases the postoperative incidence of AKI (Lee, Jung, Park, Song, Kim, Lim et al 2018:1376).

4.2.3.1.3 Bicarbonate level

In this study, the normal bicarbonate level was defined as serum bicarbonate level >22mmol/L. Of the patients, 84.4% (n=108) did not have a low preoperative bicarbonate level while 15.6% (n=20) had a low preoperative bicarbonate level <22mmol/L. The study found a positive association between low bicarbonate level and CSA-AKI. The results from previous studies showed that the patients presented with bicarbonate level <24mmol/L on admission had the potential to develop AKI (Kendrick, Chonchol, You, & Jovanovich (2020:[5]). Jung et al (2016:3216) found that preoperative low serum bicarbonate levels predicted AKI after cardiac surgery.

4.2.3.1.4 Hyperglycaemia

In this study, hyperglycaemia was defined as serum glucose level >8mmol/L. Of the patients, 35.4% (n=45) had preoperative hyperglycaemia while 64.6% (n=82) did not. Of the patients with preoperative hyperglycaemia, 51.7% (n=15) developed CSA-AKI. Hyperglycaemia in the pre-operative phase increases the postoperative risk for AKI (Nie, Tang, Zhang, Feng & Chen 2017:5605634; Oezkur, Wagner, Weismann, Krannich, Schimmer, Riegler, et al. 2015:41). The bivariate analysis showed a p-value of 0.037 and the odds ratio was 2.429. The risk for CSA-AKI is 1.95 times higher if the patient has preoperative hyperglycaemia. Joannidis, Druml, Forni et al (2017:737) recommend keeping the glucose level <10mmol/L in ICU patients to prevent kidney injury.

4.2.3.1.5 Angiogram within 72hrs of surgery

The duration between a coronary angiogram and cardiac surgery influences the patient's postoperative renal function. A shorter duration of <7days has a detrimental effect on the incidence of CSA-AKI whereas a longer duration of >7days has been found to be a renal

protective strategy (Jiang, Yu, Xu, Shen, Wang, Luo et al. 2018:191; Kim, Joung, Ji, Kim, Lee, Chung et al 2016:256). Of the patients, 40.6% (n=52) had cardiac surgery within 3 days (72hrs) of coronary angiogram and 59.1% (n=75) did not. The cross-tabulation failed to indicate any association between the duration of angiogram and AKI. Borde et al (2019:479) had a similar finding that the duration between coronary angiogram had no direct effect on the development of CSA-AKI.

4.2.3.1.6 Contrast use within 72hrs of surgery

Contrast-induced AKI risk is influenced by the type, volume and route of administration of contrast agents (Gilbert, Weiner, Bomback, Perazella & Tonelli 2017:335). In this study, contrast use within 72hrs of surgery included patients that had contrast for any diagnostic procedures. Of the patients, 39.8% (n=51) had contrast exposure within 72hrs of surgery and 60.2% (n=77) did not. The study found no association between contrast use and the occurrence of CSA-AKI. Jiang, Shen, Wang, Xu, Luo, Ding et al (2019:35) found that contrast exposure within three days before surgery had an effect on development of CSA-AKI.

4.2.3.1.7 Hyperuricemia

Hyperuricemia is an independent risk factor for the development of AKI in cardiac surgery patients (Kaufeld, Foerster, Schilling, Kielstein, Kaufeld, Shrestha et al 2018:161; Nie, Tang, Zhang, Feng & Chen 2017:5605634). In this study, uric acid level was not available in any of the patients' records and is not tested on a routine basis with other preoperative blood tests.

4.2.3.1.8 Hyponatremia

In this study, hyponatremia was defined as serum sodium level <135mmol/l. Of the patients, 12.5% (n=16) had hyponatremia while 87.5% (n=112) did not. Hyponatremia on admission in patients admitted to ICU has been found to enhance the risk for AKI (Lee, Baek, Ahn, Na, Chae, Chin et al 2016:e0162990). The study found no association between preoperative hyponatremia and risk for developing CSA-AKI as the Fisher's exact value was >0.05.

4.2.3.2. Intraoperative risk factors

Table 4.4 shows the patients' intraoperative risk factors.

Table 4.4 Patients' intraoperative risk factors

VARIABLES		FREQUENCY	PERCENT	VALID PERCENT
Cardiopulmonary bypass	Yes	123	96.1	97.6
	No	3	2.3	2.4
	Missing	2	1.6	
Cardiopulmonary bypass time	<60mnts	3	2.3	2.4
	60-89mnts	21	16.4	16.8
	90-119mnts	42	32.8	33.6
	120-149mnts	23	18.0	18.4
	>150mnts	36	28.1	28.8
Cross clamp time in minutes	N statistics	Minimum statistics	Maximum statistics	Mean statistics
Valid	123	0	227	93.65
Missing	5			
Total duration of surgery >7hrs	Yes	34	26.6	27.2
	No	91	71.1	72.8
Mean arterial pressure <65mmhg	Yes	29	22.7	23.4
	No	95	74.2	76.6

4.2.3.2.1 Cardiopulmonary bypass

Cardiopulmonary bypass (CPB) contributes significant damage to the kidneys. The researcher assessed whether the patients had to be on cardiopulmonary bypass during the surgery and the duration was calculated. The cardiopulmonary bypass time was subdivided into five categories: a) <60mins, b) 60-89mins, c) 90-119mins, d) 120-149mins and e) >150mins. Of the patients, 2.4% (n=3) had cardiopulmonary bypass time <60mins; 16.8% (n=21) had 60-89mins; 33.6% (n=42) had 90-119mins; 18.4% (n=23) had 120-149mins, and 28.8% (n=36) had >150mins. The duration of cardiopulmonary bypass time has been associated with the occurrence of AKI in cardiac surgery patients (Jiang et al 2019:35; Ng, Chew, Liu, Shen & Ti 2014:1357; Thanavaro, Taylor, Vitt & Guignon 2019:37). This study found no association between

cardiopulmonary bypass duration and development of CSA-AKI as the Pearson chi-square value and Fisher's exact test results were >0.05.

4.2.3.2.2 Cross clamp time

Longer aortic cross clamp time is a potential risk factor for the development of CSA-AKI (Karim, Yunus, Saikia, Kalita, & Mandal 2017:23; Ng, Chew, Liu, Shen & Ti 2014:1357; Xie et al 2017:276). In this study, the mean cross clamp time was 93.65mins and inferential analysis results were significantly >0.05 which did not indicate a linear association with AKI.

4.2.3.2.3 Total duration of surgery >7hrs

The duration of cardiac surgery plays a crucial role in the development of CSA-AKI (Che, Wang, Liu, Xie, Xue, Yan et al 2019:295). This study assessed whether the duration of surgery >7hrs contributed to AKI. Of the patients, 27.2% (n=34) had cardiac surgery for >7hrs, while 72.8% (n=91) had surgery for <7hrs. The calculated p-value was 0.002 with an odds ratio of 3.85. Risk estimates found that the duration of surgery of >7hrs enhanced the risk for CSA-AKI by 2.676 times. Kim et al (2015:e273) found that surgery time longer than 7hrs had a twofold greater risk for CSA-AKI.

4.2.3.2.4 Mean arterial pressure <65mmhg

AKI preventive strategies recommend maintaining arterial pressure >65mmhg during the intraoperative phase to prevent the incidence of CSA-AKI (KDIGO 2012:41). Of the patients, 76.6**%** (n=95) had mean arterial pressure >65mmhg, and 23.4% (n=29) had mean arterial pressure <65mmhg. Statistical analysis failed to denote a direct effect of low mean arterial pressure on the development of CSA-AKI.

4.2.3.3. Postoperative risk factors

Table 4.5 illustrates the patients' postoperative risk factors.

Table 4.5 Patients' postoperative risk factors

VARIABLE		FREQUENCY	PERCENT	VALID PERCENT
Use of extra corporeal membrane oxygenation (ECMO)	Yes	7	5.5	5.5
	No	121	94.5	94.5
Veno-arterial extra corporeal membrane oxygenation (ECMO)	Yes	4	3.1	100
	No	124	96.9	
Veno-venous extra corporeal membrane oxygenation (ECMO)	Yes	0		
	No	128	100	
Mechanically ventilated for >72hrs	Yes	23	18.0	18.1
	No	104	81.3	81.9
Administration of voluven/ volulyte	Yes	103	80.5	81.7
	No	23	18.0	18.3
Hyperchloremia within 72hrs of surgery	Yes	105	82.0	82.0
	No	23	18.0	18.0
Transfusion of fresh frozen plasma >500ml on the day of the surgery	Yes	46	35.9	35.9
	No	82	64.1	64.1
Transfusion of red cell concentrate >1000ml on the day of the surgery	Yes	20	15.6	15.6
	No	108	84.4	84.4
Hypercalcemia within 48hrs of surgery	Yes	7	5.5	5.6
	No	119	93.0	94.4
Fluid overload within 48hrs after surgery	Yes	34	26.6	26.8
	No	93	72.7	73.2
Fluid overload >2000-3000ml		19	14.8	57.6
Fluid overload >3000ml		14	10.9	42.4
Hyperthermia within 72hrs of surgery	Yes	86	67.2	68.3
	No	40	31.3	31.7
Hypothermia within 24hrs of surgery	Yes	21	16.4	16.4
	No	107	83.6	83.6
Hypoxemia <80mmhg within 48hrs of surgery	Yes	43	33.6	33.6
	No	85	66.4	66.4
Central venous pressure >12mmhg within 24hrs of surgery	Yes	93	72.7	72.7
	No	35	27.3	27.3

4.2.3.3.1 Extra corporeal membrane oxygenation (ECMO)

Circulatory and respiratory support using extra corporeal membrane oxygenation can have a negative impact on kidney function. One of the complications associated with extra corporeal membrane oxygenation (ECMO) is renal failure (Lerma, Sparks & Topf 2019:133). Chang, Guo, Xu and Li (2017:16666, 16667) found extra corporeal membrane oxygenator use associated with the development of AKI in 73.2% patients and veno-arterial (VA) configuration significantly increased the risk. In this study, 5.5% (n=7) of the patients had postoperative use of extra corporeal membrane oxygenation, and of

these, 3.1% (n=4) had veno-arterial extra corporeal membrane oxygenation. The records of the other three patients did not specify the type of extra corporeal membrane oxygenation and the veno-venous type was not found in any of the records. The sample size was too small to provide evidence of its contribution to the promotion of postoperative AKI.

4.2.3.3.2 Mechanically ventilated for >72hrs

Of the patients, 81.9% (n=104) were extubated within 24hrs of cardiac surgery while 18.1% (n=23) were mechanically ventilated for more than 72hrs after surgery. The study found a significant association between the prolonged use of mechanical ventilator and risk for development of CSA-AKI. Moreover, the risk analysis supported it as the odds ratio was 16 and the risk for developing CSA-AKI increased 5.56 times with mechanical ventilator use for more than 72hrs. Amini et al (2019:72) and Xie et al (2017:277) found an association between prolonged mechanical ventilation and the development of AKI.

4.2.3.3.3 Administration of voluven/volulyte (hydroxyethyl starch)

Administration of hydroxyethyl starch in cardiac surgery patients increases the risk for CSA-AKI (Lagny, Roediger, Koch, Dubois, Senard, Donneau et al 2016:873). Of the patients, 81.7% (n=103) received postoperative administration of hydroxyethyl starch, such as voluven or volulyte, while 18.3% (n=23) did not. The cross-tabulation could not determine an association between postoperative use of hydroxyethy starch and its contribution to CSA-AKI.

4.2.3.3.4 Hyperchloremia within 72hrs of surgery

Hyperchloremia is associated with acute kidney injury and mortality in the critically ill. In this study, hyperchloremia was defined as chloride level >106mEq/L. Hyperchloremia in critically ill patients has exhibited an independent association with the development of AKI (De Vasconcellos & Skinner 2018:47). The researcher assessed whether postoperative hyperchloremia within 72hrs of surgery contributed to the development of CSA-AKI. Of the patients, 82% (n=105) had hyperchloremia while 18% (n=23) did not. The study failed to indicate any significant association between postoperative hyperchloremia and

CSA-AKI which is similar to findings from previous study done in surgical patients (Oh, Song, Kim, Lim, Do, Hwang et al 2018:277).

4.2.3.3.5 Fresh frozen plasma transfusion >500ml on the day of the surgery

Transfusion of fresh frozen plasma during the postoperative period is associated with development of AKI in cardiac surgery patients (De Loor, Herck, Francois, Van Wesemael, Nuytinck, Meyer et al 2017:24). In this study, most of the patients were given fresh frozen plasma transfusions. Of the patients, 35.9% (n=46) received more than 500ml on the day of surgery while 64.1% (n=82) did not. The cross tabulation found a p-value of 0.014 with an odds ratio of 2.83. In this study, transfusion of >500ml of fresh frozen plasma enhanced the patients' risk for CSA-AKI by 2.19 times which agreed with Kim et al's (2015:e273) finding.

4.2.3.3.6 Red cell concentration transfusion >1000ml on the day of the surgery

Red cell concentrate or erythrocyte transfusion is a potentially modifiable risk factor CSA-AKI (Kim et al 2015:e273). Jiang et al (2016:e003754) found that erythrocyte transfusion was a risk factor and the risk increased with each unit. Of the patients, 15.6% (n=20) received more than 1000ml of red cell concentrate on the day of the surgery while 84.4**%** (n=108) did not. The study found a p-value of 0.001 and Fisher's exact score of 0.003. The risk estimate revealed that the patients who received red cell concentrate >1000ml had 2.8 times greater risk for CSA-AKI and had an odds ratio of 4.684.

4.2.3.3.7 Hypercalcemia within 48hrs of surgery

In this study, hypercalcemia was defined as serum calcium level >2.5mmol/L. A recently published case study reported the development of AKI due to hypercalcemia in surgical patients (von Bormann, Suksompong & von Bormann 2019:1117). The researcher examined electrolyte imbalance like hypercalcemia to assess whether it contributed to the development of CSA-AKI. Of the patients, 5.6% (n=7) patients had hypercalcemia within 48hrs of surgery and 94.4% (n=119) did not. The study found no significant correlation between postoperative hypercalcemia and CSA-AKI.

4.2.3.3.8 Fluid overload within 48hrs after surgery

Positive fluid balance tends to enhance AKI risk by means of tissue edema (Moore, Tobin, Reid, Santamaria, Paul & Bellomo 2015:1233; De Loor et al 2017:24). The researcher examined the patients' records for a positive fluid balance >2000ml within 24hrs of surgery. Of the patients, 26.8% (n=34) had fluid overload and 73.2% (n=93) did not. Of the patients with fluid overload, 14.8% (n=19) had a fluid balance between 2000-3000ml and 10.9% (n=14) had a fluid balance >3000ml. The cross-tabulation revealed a linear association between the incidence of AKI and the patients with fluid balance >2000ml within 48hrs of cardiac surgery (p-value=0.000). However, the study failed to determine whether the patients with fluid balance between 2000-3000ml or >3000ml had a higher risk. A recent study which assessed the association between postoperative fluid management and AKI in cardiac surgery patients revealed that fluid intake ≤40 or >40ml/kg/h escalates the risk for AKI (Shen, Zhang, Cheng, & Ying 2018:274). In this study, the odds ratio was 6.750 and risk for CSA-AKI increased by 3.87 times if the patient has a positive fluid balance of >2000ml within 48hrs of cardiac surgery.

4.2.3.3.9 Hyperthermia within 72hrs of surgery (>37.2°c)

A spike in the body temperature within 3 days of cardiac surgery is a potential risk factor for AKI, as it creates an alteration in the metabolism (Xie et al 2017:278, 280). Hyperthermic episodes induce acute tubular necrosis by increasing the renal tubular metabolic rate thereby increasing the consumption of adenosine triphosphate (ATP) (Johnson, Feehally & Floege 2019:787). Of the patients, 68.3% (n=86) experienced hyperthermia within 72hrs of surgery and 31.7% (n=40) did not. Pearson's chi-square (p-value) failed to indicate any direct association between occurrence of CSA-AKI and hyperthermia within 72hrs of cardiac surgery as the p value was significantly >0.05.

4.2.3.3.10 Hypothermia within 24hrs of surgery (<35.5°c)

Of the patients, 16.4% (n=21) experienced hypothermia within 24hrs of cardiac surgery and 83.6% (n=107) did not. The inferential statistics revealed a p-value of 3.417 which was non-significant and failed to indicate any effect on the occurrence of postoperative CSA-AKI.

4.2.3.3.11 Hypoxemia within 48hrs of surgery (PO2 <80mmhg)

Diminished oxygen supply to the kidney induce hypoxic injury to the renal tissues which later progress to AKI (Shu, Wang, Zheng, Liu, Cai, Tang et al 2019:207). Of the patients, 33.6% (n=43) had hypoxemia within 48hrs of cardiac surgery while 66.4**%** (n=85) did not. The study failed to identify any direct association between hypoxemia within 48hrs of surgery and incidence of postoperative AKI. The p-value was significantly >0.05.

4.2.3.3.12 Central venous pressure >12mmhg within 24hrs of surgery

An increase in central venous pressure (CVP) enhances the risk for AKI as it results in renal congestion and reduces the venous blood flow. Each 1cm H2O rise in CVP increases the risk for AKI by 10-11% (Chen, Cavender, Lee, Feng, Mark, Celi et al 2016:606; Chen, Wang, Honore, Spapen, & Liu 2018:91; McCoy, Montez-Rath, Chertow, & Chang 2020:70). Central venous pressure should be adequate enough to maintain the cardiac output and to preserve organ perfusion (Chen, Wang, Honore, Spapen, & Liu 2018:91). Of the patients, 72.7% (n=93) had central venous pressure >12mmhg within 24hrs of surgery and 27.3% (n=35) did not. The study found a p-value of 1.926, which did not indicate any direct association between higher CVP and incidence of CSA-AKI.

4.2.4 Medications

Section D examined the specific medications administered to the cardiac surgery patients in the pre-, intra- and postoperative phases. The information on preoperative medications was obtained from the ward prescription chart as well as from the ICU chart if the patient was admitted in the ICU pre-operatively. The medications included in the preoperative phase were N-acetylcysteine (NAC), diuretics, inotropes, vasopressors and antibiotics. The intraoperative medication record could be obtained from the perioperative document and the researcher only examined diuretic use. The details of medications used in the postoperative phase were procured from the ICU chart and focused on the use of inotropes, vasopressors, nephrotoxic antibiotics and diuretics. Table 4.6 presents the patients' medications.

Table 4.6 Patients' medications

VARIABLES		FREQUENCY	PERCENT	VALID PERCENT
Preoperative				
N-acetyl- cysteine	Yes	11	8.6	8.6
	No	117	91.4	91.4
Diuretics	Yes	27	21.1	21.3
	No	100	78.1	78.7
	Bolus	16	12.5	100
	Infusion	10	7.8	83.3
Inotropes (dobutamine)	Yes	7	5.5	5.6
	No	118	92.2	94.4
Vasopressors	Yes	5	3.9	4.0
	No	121	94.5	96.0
	Noradrenalin	4	3.1	100
	Adrenalin	1	0.8	100
	Vasopressin	0		
	Phenylephrine	0		
Antibiotics	Yes	13	10.2	10.2
	No	115	89.8	89.8
	Vancomycin	1	0.8	100
	Gentamicin	1	0.8	100
	Amphotericin	1	0.8	50
	Aminoglycoside	3	2.3	75
Intraoperative				
Diuretics	Yes	20	15.6	15.7
	No	107	83.6	84.3
Postoperative				
Inotropes (dobutamine)	Yes	106	82.8	82.8
	No	22	17.2	17.2
Vasopressors	Yes	124	96.9	96.9

	No	4	3.1	3.1
	Noradrenalin	120	93.8	100
	Vasopressin	33	25.8	100
	Adrenalin	17	13.3	100
	Phenylephrine	1	0.8	33.3
Nephrotoxic antibiotics	Yes	15	11.7	11.7
	No	113	88.3	91.1
	Vancomycin	3	2.3	100
	Gentamycin	3	2.3	100
	Amphotericin	2	1.6	100
	Aminoglycoside	7	5.5	100
Diuretics	Yes	125	97.7	97.7
	No	3	2.3	2.3
	Bolus	106	82.8	100
	Infusion	22	17.2	100

4.2.3.1 Preoperative use of N-acetylcysteine

N-acetylcysteine (NAC) has been found to have a renoprotective effect on renal function in patients with pre-existing moderate renal failure by causing a rise in eGFR while decreasing the creatinine (Savluk, Guzelmeric, Yavuz, Cevirme et al 2017:12). Of the patients, 8.6% (n=11) received NAC in intravenous or oral form and 91.4% (n=117) did not. The bivariate analysis found a direct association between preoperative use of NAC and development of CSA-AKI. Pearson's chi-square value was 0.001 and the Fisher exact value was 0.003. The risk estimate showed an odds ratio of 7.557 and patients who received NAC had 3.38 times greater risk for CSA-AKI in comparison to those who did not.

4.2.3.2 Preoperative use of diuretics

Preoperative use of diuretics has shown to increase the patients risk for CSA-AKI (De Loor et al 2017:24; Rasmussen, Kandler, Nielsen, Cornelius, Knudsen, Ranucci et al 2019:1292). KDIGO clinical practice guidelines discourage the use of diuretics in

prevention of AKI (KDIGO 2012:47). Of the patients, 21.1% (n=27) received diuretics during the preoperative phase while 78.7% (n=100) did not. The researcher examined whether the diuretics were administered as bolus doses or as infusion. Of the patients who received diuretics, 12.5% (n=16) received bolus doses while 7.8% (n=10) received continuous infusion. Cross-tabulation indicated a P-value of 0.008 for diuretic use but did not indicate whether the bolus dose or infusion mainly contributed to CSA-AKI. The study revealed that preoperative diuretic use has an odds ratio of 3.35 and increases the risk for AKI in cardiac surgery patients by 2.4fold.

4.2.3.3 Preoperative use of inotropes

Of the patients, 5.6% (n=7) were given inotropes while 94.4**%** (n=118) were not. Dobutamine was the only inotrope used among the patients. The prolonged use of dobutamine was associated with AKI in intensive care patients (Hashemian, Jamaati, Farzanegan Bidgoli, Farrokhi, Malekmohammad, Roozdar et al 2016:91). In this study, inferential analysis found no sequential relationship between the preoperative use of inotropes and postoperative occurrence of AKI in the patients as the Fisher's exact test value was 0.05.

4.2.3.4 Preoperative use of vasopressors

The researcher examined the preoperative use of vasopressors, namely noradrenaline, adrenaline, vasopressin and phenylephrine. Hashemian et al (2016:91) study indicated that the development of AKI in critically ill patients has shown an association with longer duration of vasopressor use. Of the patients, 4% (n=5) were given vasopressors and 96% (n=121) were not. The vasopressor used was noradrenaline while vasopressin and phenylephrine were not used. Fisher's exact value was 0.072 which was non-significant to indicate a possible relation in the development of CSA-AKI.

4.2.3.5 Preoperative use of antibiotics

Of the patients, 10.2% (n=13) received antibiotics while 89.8% (n=115) did not. Of the patients who received antibiotics, 4.7% (n=6) received nephrotoxic antibiotics, such as vancomycin, gentamicin, amphotericin and aminoglycoside (see Table 4.6). Pearson's chi-square (p-value) for preoperative use of antibiotics was 0.000 and the Fisher exact

test value was 0.002 which indicated a positive association with the occurrence of CSA-AKI. The risk estimate showed an odds ratio of 7.162 and the risk for CSA-AKI is 3.37 times more in patients who received antibiotics preoperatively. In Qingdao, China, Guan, Li, Xu, Zhen, Zhang, Zhao et al (2019:939) found that preoperative use of antibiotics contributed to the development of AKI.

4.2.3.6 Intraoperative use of diuretics

Of the patients, 15.7% (n=20) were given diuretics and 84.3% (n=107) were not. The inferential statistics did not indicate a positive relationship with the intraoperative use of diuretics and postoperative occurrence of CSA-AKI. The Pearson chi-square value (0.406) and Fisher's exact value (0.397) were significantly >0.05. The result of this study is identical to Xie et al (2017:277) study where they assessed the impact of intraoperative use of mannitol in cardiac surgery patients and was insignificant.

4.2.3.7 Postoperative use of inotropes

Of the patients, 82.8% (n=106) received dobutamine, which was the only inotrope used, and 17.2**%** (n=22) did not. Postoperative use of dobutamine was found to affect the development of AKI (O'Neal, Shaw & Billings 2016:187; Ramos & Dias 2018:459). The study found that inotropic support during the postoperative phase did not contribute to AKI as the p-value and Fisher exact value were greater than the expected range.

4.2.3.8 Postoperative use of vasopressors

Noradrenaline, vasopressin, adrenaline and phenylephrine were the vasopressors used among the patients. Of the patients, 93.8% (n=120) received Noradrenaline; 25.8% (n=33) received vasopressin; 13.3% (n=17) received adrenalin, and 0.8% (n=1) received phenylephrine. Noradrenaline use during the post cardiac surgery phase is recognized as a risk factor for AKI (De Loor et al 2017:24; Ramos & Dias 2018:459). The study found no relationship between the postoperative use of vasopressors and the development of CSA-AKI as the p-value and Fisher's exact test value were significantly >0.05.

4.2.3.9 Postoperative use of nephrotoxic antibiotics

Of the patients, 11.7% (n=15) were given nephrotoxic antibiotics and 91.1% (n=113) were not. Of the patients, 5.5% (n=7) received aminoglycoside; 1.6% (n=2) received amphotericin; 2.3% (n=3) received vancomycin, and 2.3% (n=3) received gentamicin. The previous risk assessment studies among cardiac surgery patients has identified that postoperative use of antibiotics in sepsis and suspected sepsis enhances the patients risk for AKI and vancomycin found to be the most common risk factor (Fuhrman, Nguyen, Sanchez-de-Toledo, Priyanka & Kellum 2019:1418; Kwiatkowski, Price, Axelrod, Romfh, Han, Sutherland et al 2017:1071). The inferential analysis in this study found no direct relationship between CSA-AKI and post-operative use of nephrotoxic antibiotics as the p-value was 0.046 and Fisher exact test value was 0.06, which were non-significant.

4.2.3.10 Postoperative use of diuretics

Diuretic use during the postoperative period is recognised as a risk factor for CSA-AKI (O'Neal, Shaw & Billings 2016:187). Of the patients, 97.7% (n=125) received diuretics and 2.3% (n=3) did not. Of the patients who received diuretics, 82.8% (n=106) received bolus doses while 17.2 % (n=22) received infusion. The study found no relationship between the postoperative use of diuretics and the development of CSA-AKI, as the p-value and Fisher exact test value were non-significant (>0.05) which agreed with Shen, Zhang, Cheng, & Ying (2018:274) findings.

4.2.5 Patient outcome

In this study, patient outcome was assessed in terms of whether the patients had normal renal function, developed kidney injury, were discharged, were deceased, total days spent in ICU, and total days of hospitalisation.

4.2.5.1 Normal renal function

Of the patients, 81.3% (n=104) had normal renal function after the cardiac surgery and 18.8% (n=24) did not. Borde et al (2019:478) also reported normal renal function in about 76% of their study population

4.2.5.2 Developed acute kidney injury

Of the patients, 22.7% (n=29) developed CSA-AKI and 77.3% (n=99) did not. The incidence of CSA-AKI was higher in the unit of analysis as compared to the previous studies (Amini et al 2019:71; Che et al 2019:295).

4.2.5.3 Discharged

Of the patients, 89.1% (n=114) were discharged from the hospital after cardiac surgery and 10.9% (n=14) were not. Of the patients who were discharged, 14% (n=16) had developed AKI.

4.2.5.4 Deceased

The incidence of AKI during the postoperative period increases the risk for mortality in cardiac surgery patients (Amini et al 2019:72; Thanavaro, Taylor, Vitt & Guignon 2019:37). In this study, the total mortality rate was 10.9% (n=14). Of the patients who died, 10.1% (n=13) had CSA-AKI.

4.2.5.5 Total days in ICU and hospitalisation

The incidence of AKI increases the length of ICU and hospital stay as well as health care costs (Alshaikh, Katz, Gani, Nagarajan, Canner, Kacker et al 2018:471; De Loor et al. 2017:24; Thanavaro, Taylor, Vitt & Guignon 2019:37). In the unit of analysis, cardiac surgery patients spend minimum of 4days and maximum of 95 days in ICU after the surgery. The patients' total days of hospitalisation varied from 5 to 102 days. The Pearson's correlation coefficient assessed the association between occurrence of AKI with length of stay in ICU and hospital and indicated 0.299 and 0.268, respectively which indicates a weak association between the variables. The study failed to indicate if the development of CSA-AKI increased the length of stay in ICU and hospital.

4.3 RISK FACTORS

Table 4.7 lists the bivariate analysis of the patients' risk factors of CSA-AKI.

Table 4.7 Analysis of patients' risk factors for CSA-AKI

VARIABLES	AKI (n-29)	NO AKI (n-99)	P-VALUE (<0.05)	ODDS RATIO
Cleveland clinic score Low risk (0-2)	14	79	0.006	
Moderate risk (3-5)	12	15		
Intermediate risk (6-8)	3	4		
Severe risk (9-13)	0	1		
Preoperative anaemia	12	11	0.000	5.647
Preoperative hypoalbuminemia	13	15	0.001	4.550
Preoperative bicarbonate <22mmol/L	11	9	0.000	6.111
Preoperative hyperglycaemia	15	30	0.037	2.429
Total duration of surgery >7h	14	20	0.002	3.850
Postoperative use of mechanical ventilation for >72h	16	7	0.000	16.00
Postoperative fresh frozen plasma transfusion >500ml on the day of surgery	16	30	0.014	2.831
Postoperative red blood cell transfusion>1000ml on the day of surgery	10	10	0.001	4.684
Fluid overload within 48h after surgery	17	17	0.000	6.750
Preoperative use of N-acetyl- cysteine	7	4	0.001	7.557
Preoperative use of diuretics	11	16	0.008	3.357
Preoperative use of antibiotics	8	5	0.000	7.162

Table 4.5 indicates that the patients had the following risk factors for the development of CSA-AKI: anaemia, hypoalbuminemia, bicarbonate level <22mmol/L, hyperglycaemia, longer duration of surgery, prolonged mechanical ventilation, fresh frozen plasma use >500ml on the day of surgery, red blood cell transfusion >1L on the day of the surgery, fluid overload within 48h of surgery, preoperative use of N-acetylcysteine, diuretics and antibiotics.

4.4 INTRARATER RELIABILITY FINDINGS

The researcher assessed the reliability of the study by means of intra-rater reliability. Every 15th patient's record was reassessed two days apart and the statistician's assistance was obtained to match and mismatch the two sets of data. The statistical analysis found 93.1% agreement between the data sets which indicated that the data were reliable. A reliability coefficient of ≥0.8 ensured the reliability of the two sets of data (Ploit & Beck 2017:306).

4.5 CONCLUSION

This chapter discussed the data analysis and interpretation, and the findings. This chapter unveiled the pre-, intra- and postoperative risk factors that contributed to the development of AKI in patients who underwent cardiac surgery in the study population. Chapter 5 discusses the conclusions drawn from these findings and limitations of the study, and makes recommendations for practice and further research.

CHAPTER 5: CONCLUSIONS, LIMITATIONS AND RECOMMENDATIONS

5.1 INTRODUCTION

Chapter 4 discussed the data analysis and findings. This chapter briefly summarises the findings according to the objectives of the study, presents the limitations, and makes recommendations for practice and further research. A personal reflection on the study and final conclusion indicating possible areas of future research.

5.2 AIM AND OBJECTIVES

The aim of the study was to identify the risk factors associated with acute kidney injury (AKI) in patients who undergo cardiac surgery. The objectives of the study were to

- Assess the frequency of acute kidney injury among cardiac surgery patients in the study context.
- Identify the risk factors associated with acute kidney injury in patients who undergo cardiac surgery.
- Determine the association between the identified risk factors and acute kidney injury in patients who undergo cardiac surgery.
- Categorize the identified risk factors into modifiable, partially modifiable and non-modifiable categories.

In order to achieve the aim, the study wished to answer the following question:

What are the risk factors associated with acute kidney injury in patients who undergo cardiac surgery?

5.3 FINDINGS

The findings are discussed according to the objectives.

5.3.1 Assess the frequency of acute kidney injury among cardiac surgery patients in the study context

The study found a 22.7% frequency of AKI in cardiac surgery patients in the study context.

5.3.2 Identify the risk factors associated with acute kidney injury in patients who underwent cardiac surgery

The following risk factors were associated with the development of CSA-AKI. The preoperative risk factors were anaemia, hypoalbuminemia, bicarbonate level <22mmol/L, hyperglycaemia, use of N-acetylcysteine, diuretics and antibiotics. The longer duration of surgery was the intraoperative risk factor. The postoperative risk factors were prolonged use of mechanical ventilator, fresh frozen plasma use >500ml on the day of surgery, red blood cell transfusion >1L on the day of surgery, and fluid overload within 48h of surgery.

5.3.3 Determine the association between the identified risk factors and acute kidney injury in patients who underwent cardiac surgery

Table 5.1 indicates the association between the risk factors and AKI in the cardiac surgery patients.

Table 5.1 Association between the risk factors and AKI in cardiac surgery patients

Variables	AKI (n-29)	No AKI (n-99)	P-value (<0.05)	Odd ratio
Preoperative anaemia	12	11	0.000	5.647
Preoperative hypoalbuminemia	13	15	0.001	4.550
Preoperative bicarbonate <22mmol/L	11	9	0.000	6.111
Preoperative hyperglycaemia	15	30	0.037	2.429
Total duration of surgery >7h	14	20	0.002	3.850
Mechanically ventilated for >72h	16	7	0.000	16.00
Fresh frozen plasma transfusion >500ml on the day of surgery	16	30	0.014	2.831
Red blood cell transfusion>1000ml on the day of surgery	10	10	0.001	4.684
Fluid overload within 48h after surgery	17	17	0.000	6.750
Preoperative use of N-acetyl cysteine	7	4	0.001	7.557
Preoperative use of diuretics	11	16	0.008	3.357
Preoperative use of antibiotics	8	5	0.000	7.162

5.3.4 Categorize the identified risk factors into modifiable, partially modifiable and non-modifiable categories

The researcher categorized the identified risk factors into modifiable and partially modifiable risks (see Table 5.2). No non-modifiable risk factors were identified in the study context.

Table 5.2 Risk factors contributing to acute kidney injury in cardiac surgery patients

Modifiable	Partially modifiable	Non-modifiable
➢ Anaemia ➢ Hypoalbuminemia ➢ Hyperglycaemia ➢ Use of N-acetylcysteine ➢ Fluid overload within 48h of surgery	➢ Pre-operative Bicarbonate level <22mmol/L ➢ Pre-operative use of diuretics ➢ Pre-operative use of antibiotics ➢ Longer duration of surgery ➢ Fresh frozen plasma use >500ml on the day of surgery ➢ Red blood cell transfusion >1L on the day of the surgery. ➢ Prolonged use of mechanical ventilator	No non-modifiable risk factors

Table 5.1 indicates that anaemia, hypoalbuminemia, hyperglycaemia, use of N-acetylcysteine, and fluid overload within 48h of cardiac surgery were modifiable risk factors in this study. Preoperative bicarbonate level <22mmol/L, preoperative use of diuretics and antibiotics, longer duration of surgery, use of fresh frozen plasma transfusion >500ml on the day of the surgery, use of red blood cell transfusion >1L on the day of the surgery and prolonged use of mechanical ventilator were partially modifiable risk factors.

5.4 LIMITATIONS

The study was limited to one private hospital in one province. Although it was a retrospective study intended to include all the patients that underwent cardiac surgery from January 2014 to December 2018, the Covid-19 outbreak prevented the researcher from accessing more than 128 patient records. AKI diagnosis with KDIGO criteria only

focused on the creatinine level as the urine output was influenced by the diuretic use. The researcher was unable to correlate pre-operative uric acid level with CSA-AKI as it was not available in any of the patient records. Finally, the small sample size did not allow for comparison with other studies or for validation of the Cleveland clinic score.

5.5 RECOMMENDATIONS

Based on the findings, the researcher makes the following recommendations for practice and further research.

5.5.1 Modifiable risk factors

- The patients undergoing cardiac surgery should be assessed for preoperative risk factors such as anaemia, hypoalbuminemia, bicarbonate level <22mmol/L ,and hyperglycaemia.
- Treatment strategies should be implemented to correct preoperative anaemia as postoperative red blood cell transfusion is also associated with development of CSA-AKI.
- Hypoalbuminemia can be treated with the help of intravenous albumin infusion.
- Hyperglycaemia is a modifiable risk factor and proper monitoring and management of serum blood sugar by means of insulin infusion may reduce the risk for developing AKI.
- N-acetylcysteine use should be avoided in cardiac surgery patients as it has shown no beneficial effect in reducing the incidence of AKI.
- Avoid fluid overload during the postoperative phase, as a positive balance of >2000ml is associated with CSA-AKI. Diuretics may be used to prevent a positive fluid balance and postoperative use of diuretics was not shown to increase the risk for CSA-AKI in this study.

5.5.2 Partially modifiable risk factors

- Sodium bicarbonate infusion may be used pre-operatively to treat low bicarbonate level in cardiac surgery patients.

- Preoperative use of diuretics and antibiotics should be avoided whenever possible to reduce the patient's postoperative risk for AKI.
- Longer duration of surgery is a potential risk factor for CSA-AKI and focus on shortening the surgical duration may lessen the risk.
- Intraoperative blood loss should be minimized as much as possible to avoid the postoperative need for transfusion.
- Ensure early weaning from mechanical ventilation as prolonged stay could enhance the risk for AKI during the postoperative phase.

5.5.3 Further research

The researcher recommends that further research be conducted on the following topics:

- An evaluation of the use of diuretics to prevent fluid overload during the post operative phase of cardiac surgery
- An assessment of the effectiveness of preoperative use of sodium bicarbonate in reducing the incidence of CSA-AKI
- Development and/or validation of risk prediction tools in patients undergoing cardiac surgery

5.8 PERSONAL REFLECTION

This study has been a journey of discovery and growth for me. As an ICU nurse, I found that several patients developed AKI after cardiac surgery, no systematic pre-operative risk assessment was done to identify patients' risk for developing AKI, and there was uncertainty about the potential risk factors. This motivated me to conduct this study to determine the pre-operative risk and potential risk factors associated with AKI in patients that undergo cardiac surgery and categorize them as modifiable, partially modifiable and non-modifiable risk factors.

When I started with the study, I knew little about the whole research process or about CSA-AKI and its significance. My supervisors' support, guidance and encouragement helped me to grow personally and professionally. The literature review opened up a whole new world and the knowledge I gained by reading made me more confident. I

learned that CSA-AKI is still an unresolved issue and that not much information was available from the South African population related to the risk factors associated with CSA-AKI. Data collection and analysis provided further insight and assisted me to relate theory and practice.

Looking back at how far I have come makes me feel proud of my accomplishment as this knowledge is useful to me as a practitioner. Moreover, the findings should benefit other ICU nurses and assist in preventing AKI in cardiac surgery patients.

5.8 CONCLUSION

Much research has been done on the risk factors of AKI in cardiac surgery patients. To the researcher's knowledge, however, this is the first study on the South African population. This study demonstrated that anaemia, hypoalbuminemia, hyperglycaemia, use of N-acetylcysteine, and fluid overload within 48h of cardiac surgery were modifiable risk factors, while preoperative bicarbonate level <22mmol/L, preoperative use of diuretics and antibiotics, longer duration of surgery, use of fresh frozen plasma transfusion >500ml on the day of the surgery, use of red blood cell transfusion >1L on the day of the surgery and prolonged use of mechanical ventilator were partially modifiable risk factors. The study findings supports that development of AKI is cardiac surgery patients is associated with modifiable and partially modifiable risk factors.The findings suggest that identification and management of the modifiable and partially modifiable risk factors should be implemented as strategies in the prevention of CSA-AKI.

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ANNEXURE A: INSTITUTIONAL PERMISSION LETTER

Life Healthcare Head Office
Oxford Manor, 21 Chaplin Road, Illovo 2196
Private Bag X13, Northlands 2116, South Africa
Telephone: +27 11 219 9000
Telefax: +27 11 219 9001
www.lifehealthcare.co.za

National Health Research Ethics Committee registration: **REC 251015-048**

REF: 14112019/3

14 November 2019

Dear Sona Nuby

RE: APPLICATION TO CONDUCT RESEARCH:

Title of study: Risk factors associated with acute kidney injury in patients underwent cardiac surgery: A retrospective review

The Health Research Ethics Committee of Life Healthcare Group hereby grants permission with no conditions for your study to be conducted at [redacted].

1. If patient or institutional confidentiality is breached, Life Healthcare is entitled to withdraw this permission immediately. The Higher Education institution under which the research is taking place will be notified, and Life Healthcare reserves the right to take legal action against you, should the company feel that this is warranted.

2. An electronic copy of the research report must be submitted to the Life Healthcare Research Ethics Committee prior to publication. Failure to do this may result in permission to continue to examination being withdrawn. The Higher Learning institution will be notified of this withdrawal.

3. No direct reference may be made to Life Healthcare, its subsidiaries or any of its facilities or institutions in the research report or any publications thereafter. The Company and its facilities, patients and staff must be de-identified in the study, and remain so for any other studies which may utilise this information.

4. The research must be completed within the time allotted by the Higher Learning institution. If the research is being done in an individual capacity by an employee of the life Group, the research must be conducted within one year of permission being given by the Company, OR the proposed time period must be specified in the proposal, and approved. Permission may be withdrawn if the research extends beyond the approved time period.

5. Life Healthcare will not take responsibility for any unforeseen circumstances within its institutions which may materially change the context and potential outcomes of a student's research. Should this occur, the student will be required to approach their Higher Learning institution for guidance around alternatives.

6. Placement of the electronic research report and any publications on the Company's research register after approval by the associated Higher Education Institution.

7. Life Healthcare will not be liable for any costs incurred during or related to this study.

Yours sincerely,

On behalf of the Health Research Ethics Committee

ANNEXURE B: CURRICULUM VITAE

ANNEXURE B:CV FORMAT

MCC Format of CV's for Principal, Co and Sub-Investigators

Curriculum Vitae

Trial:	RISK FACTORS ASSOCIATED WITH ACUTE KIDNEY INJURY IN PATIENTS WHO UNDERWENT CARDIAC SURGERY: A RETROSPECTIVE REVIEW
Protocol Number:	
Designation:	CRITICAL CARE SPECIALIZED NURSE
1. Personal details:	
Name:	MRS. SONA NUBY
Work Address:	LIFE THE GLYNNWOOD HOSPITAL HARRISON STREET BENONI
Site address(es):	
Contact information:	19 CAMERON PLACE, 40 KIMBOLTON STREET BENONI
Telephone no:	084-0872320
Fax no.:	NIL
Cell no.:	081-569-0481
E-mail address:	Sonajoseph09@gmail.com
2. Academic and Professional Qualifications:	
Date	**Qualification**
2009	BACHELORS DEGREE IN NURSING
2017	DIPLOMA IN CRITICAL CARE NURSING
2019	MCur SECOND YEAR STUDENT
3. Health Professionals Council of South Africa (HPCSA) registration number if applicable (or other health professions body registration particulars – e.g.. Nursing Council)	
SANC NO-13708417	
4. Current Personal Medical Malpractice Insurance Details:(Medical and Dental Practitioners)	

5. Relevant related work experience (brief) and current position: CRITICAL CARE SPECIALIST NURSE	
Date: 22/5/2019	**Details:** LIFE THE GLYNNWOOD HOSPITAL
	BENONI

6. Participation in clinical trials research in the last three years (title, protocol number, designation) {If multiple trials, only list those with relevance to this application, or in the last year}:

Date	Protocol No.	Title	Designation(Principal/Sub Investigator)
N/A			

7. Peer reviewed publications in the past 3 years.
NIL

8. Date of last GCP training (as a participant or presenter).
NIL

9.Any additional relevant information supporting abilities to participate in conducting this trial {briefly}

Signature: _____ Date: 29/7/19.

ANNEXURE C: COMMITMENTS AND RESPONSIBLITIES FOR PRINCIPAL AND CO-INVESTIGATORS

ANNEXURE C

COMMITMENTS AND RESPONSIBILITIES OF PRINCIPAL/CO-INVESTIGATORS REQUIRED FOR RESEARCH THROUGH THE FACULTY OF HEALTH SCIENCES RESEARCH ETHICS COMMITTEE, UNIVERSITY OF PRETORIA

DECLARATION BY INVESTIGATOR:

I agree to personally conduct or supervise the described investigation.

I understand as principal investigator that I am totally responsible for the study and am legally bound by the contract signed with the sponsor and will not inappropriately delegate my responsibilities to the rest of my study team.

I have read and understand the information in the investigator's brochure, including the potential risks and side effects of the drug.

I agree to ensure that all associates, colleagues, and employees assisting in the conduct of the study are informed about their obligations in meeting the above commitments, without relinquishing my total responsibility for the study.

I confirm that I am suitably qualified and experienced to perform and/or supervise the study proposed.

I agree to conduct the study in accordance with the relevant, current protocol and will only make changes in the protocol after approval by the sponsor and the Ethics Committee, except when urgently necessary to protect the safety, rights, or welfare of subjects.

I agree to inform any patients, or any persons used as controls, that the drugs are being used for investigational purposes and I will ensure that the ICH GCP Guidelines and Ethics Committee requirements relating to obtaining informed consent are met.

I agree to timeously reporting to the sponsor and Ethics Committee adverse experiences that occur in the course of the investigation according to the time requirements adopted by the Faculty of Health Sciences Research Ethics Committee, University of Pretoria.

I agree to maintain adequate and accurate records and to make those records available for inspection by the appropriate authorized agents, be it EC, FDA or sponsor agents.

I agree to comply with all other requirements regarding the obligations of clinical investigators and all other pertinent requirements in the Declaration of Helsinki and South African and ICH GCP Guidelines and am conversant with these guidelines.

I agree to inform the Ethics Committee in advance should I go on leave together with an agreed plan of action regarding an alternate principal investigator or sub-investigator to take responsibility in my absence.

I understand that the study may be audited at any time and that deviation from the principles in this declaration will be put before the Ethics Committee for action, which may include disqualification as an investigator and rehabilitation before being accepted as an investigator in other studies.

I confirm that there is no conflict of interest whatsoever in my participation in this study. I have no shares in the sponsoring company and my participation and interests are as defined in the financial agreement

SONA NUBY
NAME (Printed)

SIGNATURE OF PRINCIPAL INVESTIGATOR

DATE 29/7/2019

COMMITMENTS AND RESPONSIBILITIES OF SUB- INVESTIGATORS
REQUIRED FOR RESEARCH THROUGH THE FACULTY OF HEALTH SCIENCES RESEARCH ETHICS COMMITTEE, UNIVERSITY OF PRETORIA

DECLARATION BY INVESTIGATOR:

I agree to personally conduct or supervise the described investigation.

I understand as sub-investigator that I am totally responsible for aspects of the study delegated to me by the Principal Investigator and am legally bound by the contract signed with the sponsor and will not inappropriately delegate my responsibilities to the rest of my study team.

I have read and understand the information in the investigator's brochure, including the potential risks and side effects of the drug.

I agree to ensure that all associates, colleagues, and employees assisting in the conduct of the study are informed about their obligations in meeting the above commitments, without relinquishing my total responsibility for the study.

I confirm that I am suitably qualified and experienced to perform and/or supervise the study proposed.
I agree to conduct the study in accordance with the relevant, current protocol and will make changes in the protocol only after approval by the sponsor and the Ethics Committee, except when urgently necessary to protect the safety, rights, or welfare of subjects.

I agree to inform any patients, or any persons used as controls, that the drugs are being used for investigational purposes and I will ensure that the ICH GCP Guidelines and Ethics Committee requirements relating to obtaining informed consent are met.

I agree to timeously reporting to the sponsor and Ethics Committee adverse experiences that occur in the course of the investigation according to the time requirements adopted by the Faculty of Health Sciences Research Ethics Committee, University of Pretoria.

I agree to maintain adequate and accurate records and to make those records available for inspection by the appropriate authorized agents, be it EC, FDA or sponsor agents.

I agree to comply with all other requirements regarding the obligations of clinical investigators and all other pertinent requirements in the Declaration of Helsinki and South African and ICH GCP Guidelines and am conversant with these guidelines.

I agree to inform the Ethics Committee in advance should I go on leave together with an agreed plan of action regarding an alternate principal investigator or sub-investigator to take responsibility in my absence.

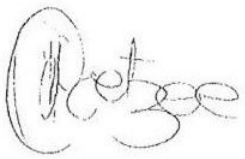
I understand that the study may be audited at any time and that deviation from the principles in this declaration will be put before the Ethics Committee for action, which may include disqualification as an investigator and rehabilitation before being accepted as an investigator in other studies.

I confirm that there is no conflict of interest whatsoever in my participation in this study. I have no shares in the sponsoring company and my participation and interests are as defined in the financial agreement.

SONA NUBY
NAME (Printed)

SIGNATURE OF PRINCIPAL INVESTIGATOR

DATE 29/7/2019



ISABEL M COETZEE
NAME (Printed)

SIGNATURE OF SUB-INVESTIGATOR

DATE 30/7/2019

ANNEXURE D: DECLARATION OF HELSINKI

SpecialCommunication

World Medical Association Declaration of Helsinki Ethical Principles for Medical Research Involving Human Subjects

World Medical Association

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, and amended by the 29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983 41st WMA General Assembly, Hong Kong, September 1989
48thWMAGeneralAssembly,SomersetWest,Republic ofSouthAfrica,October1996 52ndWMAGeneralAssembly,Edinburgh, Scotland, October2000
53rdWMAGeneralAssembly,Washington,DC,USA,October2002(Note oftClarificationadded) 55thWMAGeneralAssembly, Tokyo, Japan, October 2004 (Note of Clarification added)
59th WMA General Assembly, Seoul, Republic of Korea, October 2008 64th WMA General Assembly, Fortaleza, Brazil, October 2013

Preamble

1. The World Medical Association (WMA) has developed the Dec- laration of Helsinki as a statement of ethical principles for medi- cal research involving human subjects, including research on identifiable human material and data.

   The Declaration is intended to be read as a whole and each of its constituent paragraphs should be applied with consider- ation of all other relevant paragraphs.

2. Consistent with the mandate of the WMA, the Declaration is ad- dressed primarily to physicians. The WMA encou ages others who are involved in medical research involving human subjects to adopt these principles.

General Principles

3. The Declaration of Geneva of the WMA binds the physician with the words, "The health of my patient will be my first consider- ation," and the International Code of Medical Ethics declares that, "A physician shall act in the patient's best interest when provid- ing medical care."

4. It is the duty of the physician to promote and safeguard the health, well-being and rights of patients, including those who are involved in medical research. The physician's knowledge and con- science are dedicated to the fulfilment of this duty.

5. Medical progress is based on research that ultimately must in- clude studies involving human subjects.

6. The primary purpose of medical research involving human sub- jects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic in- terventions (methods, procedures and treatments). Even the

   best proven interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.

7. Medical research is subject to ethical standards that promote and ensure respect for all human subjects and protect their health and rights.

8. While the primary purpose of medical research is to generate new knowledge, this goal can never take precedence over the rights and interests of individual research subjects.

9. It is the duty of physicians who are involved in medical research to protect the life, health, dignity, integrity, right to self- determination, privacy, and confidentiality of personal informa- tion of research subjects. The responsibility for the protection of research subjects must always rest with the physician or other health care professionals and never with the research subjects, even though they have given consent.

10. Physicians must consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and stan- dards. No national or international ethical, legal or regulatory re- quirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.

11. Medical research should be conducted in a manner that mini- mises possible harm to the environment.

12. Medical research involving human subjects must be conducted only by individuals with the appropriate ethics and scientific edu- cation, training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care profes- sional.

ANNEXURE E: LETTER OF STATISTICAL SUPPORT

UNIVERSITEIT VAN PRETORIA
UNIVERSITY OF PRETORIA
YUNIBESITHI YA PRETORIA
Denkleiers • Leading Minds • Dikgopolo tša Dihlalefi

DEPARTMENT OF STATISTICS

LETTER OF STATISTICAL SUPPORT

Date: ***01/03/2019***

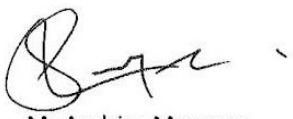
This letter is to confirm that **Ms. S Nuby** studying at the University of Pretoria discussed the project with the title **RISK FACTORS CONTRIBUTING TO ACUTE KIDNEY INJURY IN CARDIAC SURGERY PATIENTS A RETROSPECTIVE STUDY** with me.

I hereby confirm that I am aware of the project and undertake to assist with the statistical analysis of the data generated from the project.

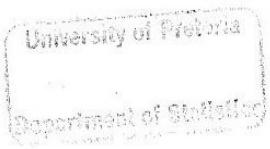
The statistical software SAS 9.4 will be used to analyze the data .The data analysis will consist of: descriptive statistics (frequencies tables for categorical variables and means, medians and standard deviations for continuous variables) which will be used to describe the data. **Inferential statistics**: The Pearson chi-square test will be performed to test association between the categories of risk factors (modifiable, partially modifiable and non-modifiable) and Pre, Intra, Post-operative risk factors. If the number of counts within the categories is less than 5 the Fisher exact test will be performed to test for association.

The sample will consist of approximately 350 records of patients that had undergone cardiac surgery from January 2014 to December 2018.

NAME



Mr Andries Masenge
Department of Statistics
Internal Consultation Service
Tel 012 420 3645



ANNEXURE F: DECLARATION OF THE STORAGE

ANNEXURE F

Principal Investigator's Declaration for the storage of research data and/or documents

I, the Principal Investigator(s), SONA NUBY of the following trial/study titled RISK FACTORS ASSOCIATED WITH ACUTE KIDNEY INJURY IN PATIENTS WHO UNDERWENT CARDIAC SURGERY: A RETROSPECTIVE STUDY will be storing all the research data and/or documents referring to the above mentioned trial/study at the following non-residential address: Life the Glynnwood, Third flocr ICU, 33-35 Harrison Street, Benoni. I understand that the storage for the above mentioned data and/or documents must be maintained for a minimum of 15 years from the end of this trial/study.

START DATE OF TRIAL/STUDY: 1/10/ 2019
END DATE OF TRIAL/STUDY: 1/11/ 2019

SPECIFIC PERIOD OF DATA STORAGE AMOUNTING TO NO LESS THAN 15 YEARS: 1/10/2019 until 30/7/2033

Name: SONA NUBY

Signature _____ **Date 29/7/2019**

ANNEXURE G: AUDIT TOOL

ANNEXURE G

UNIVERSITEIT VAN PRETORIA
UNIVERSITY OF PRETORIA
YUNIBESITHI YA PRETORIA

Section A: Demographic profile

					For office use
	FILE CODE NO:			A0	
1	Age	.....yrs		A1	
2	Gender				
	Female	1	Male 2	A2	
3	Ethnicity				
	African		1	A3	
	Caucasian		2		
	Asian		3		
	Mixed		4		
4	Body Mass Index (BMI)				
	Body weight ..... KG				
	Height .....M	Yes	No		
	BMI > 30			A4	
	Co-morbidities	Yes	No		
5	Diabetes mellitus			A5	
6	Hypertension			A8	
7	High cholesterol			A7	
8	Smoking			A8	
9	Peripheral vascular disease			A9	
10	COPD			A10	
11	CVA			A11	

Section B: Cleveland Clinic Score

	Risk factors	Points	Patient score	For office use only	
1	Female gender	1		B1	
2	Congestive heart failure	1		B2	
3	Left ventricular ejection fraction <35%	1		B3	
4	Preoperative use of IABP	2		B4	
5	COPD	1		B5	
6	Insulin dependent diabetes	1		B6	
7	Previous cardiac surgery	1		B7	
8	Valve surgery only	1		B8	
9	CABG + Valve surgery	2		B9	
10	Other cardiac surgery	2		B10	
11	Preoperative creatinine (106.08-185.6µmol/l)	2		B11	
12	Preoperative creatinine (≥185.6µmol/l	5		B12	
13	Total score			B13	
14	Risk category	Total score	Tick	B14	
14.1	Low risk	0 - 2	1	B14.1	
14.2	Moderate risk	3 - 5	2	B14.2	
14.3	Intermediate risk	6 - 8	3	B14.3	
14.4	Severe risk	9 - 13	4	B14.4	

Adapted from (Thakar, et al., 2005:165).

Section C: Risk factors					
	Preoperative	Yes	No		
1	Anemia (<12g/dl)			C1	
2	Hypoalbuminemia (<34g/l)			C2	
3	Bicarbonate level <22mmol/l			C3	
4	Hyperglycemia (>8mmol/l)			C4	
5	Angiogram within 72hrs of surgery			C5	
6	Contrast use with 72hrs of surgery			C6	
7	Hyperuricemia (>7gm/dL)			C7	
8	Hyponatremia (<135 mmol/l)			C8	
	Intraoperative				
9	Cardiopulmonary bypass (CPB)	Yes	No	C9	
	If yes:				
9.1	CPB time <60mnts			C9.1	
9.2	CPB time 60 - 89mnts			C9.2	
9.3	CPB time 90 - 119mnts			C9.3	
9.4	CPB time 120 - 149mnts			C9.4	
9.5	CPB time >150mnts			C9.5	
10	Cross clamp time			C10	
11	Total duration of surgery >7hrs			C11	
12	Mean arterial pressure <65mmhg			C12	
	Postoperative				
13	Extra corporeal membranous oxygenation (ECMO)			C13	
	If yes specify the type-				
13.1	Veno-arterial			C13.1	
13.2	Veno-venous			C13.2	
14	Mechanically ventilated for > 72hrs			C14	
15	Administration of voluven / volulyte			C15	
16	Hyperchloremia within 72hrs (>106mEq/L)			C16	
17	FFP>500ML on the day of the surgery			C17	
18	RBC transfusion >1000ml on the day of surgery			C18	
19	Hypercalcemia within 48hrs of sugery (>2.5mmol/L)			C19	
20	Fluid overload within 48hrs after surgery			C20	
20.1	>2000- 3000ml			C20.1	
20.2	>3000ml			C20.2	
21	Hyperthermia with in 72hrs of surgery (>37.2°c)			C21	
22	hypothermia with in 24hrs of surgery (<35.5°c)			C22	
23	Hypoxemia <80mmhg with in 48hrs of surgery			C23	
24	CVP >12mmhg within 24hrs of surgery			C24	

Section D: Medications					
	Preoperative	Yes	No		
1	N acetyl cystein			D1	
2	Diuretics			D2	
	If yes				
2.1	Bolus			D2.1	
2.2	Infusion			D2.2	
3	Inotropes			D3	
	If yes specify……				
3.1	dobutrex			D3.1	
4	Vasopressors			D4	
	If yes specify……				
4.1	noradrenalin			D4.1	
4.2	adrenalin			D4.2	
4.3	vasopressin			D4.3	
4.4	phenyleprine			D4.4	
5	Antibiotics			D5	

	If yes specify				
5.1	vancomycin			D5.1	
5.2	gentamycin			D5.2	
5.3	amphotericin			D5.3	
5.4	aminoglycoside			D5.4	
	Intraoperative				
6	Diuretics			D6	
	Postoperative				
7	Inotropes			D7	
	if yes specify				
7.1	dobutrex			D7.1	
8	Vasopressors			D8	
	if yes specify				
8.1	noradrenalin			D8.1	
8.2	vasopressin			D8.2	
8.3	adrenalin			D8.3	
8.4	phenylephrine			D8.4	
9	Nephrotoxins			D9	
	If yes specify				
9.1	vancomycin			D9.1	
9.2	gentamycin			D9.2	
9.3	amphotericin			D9.3	
9.4	aminoglycoside			D9.4	
10	Diuretics			D10	
	If yes specify				
10.1	Bolus			D10.1	
10.2	Infusion			D10.2	

	Section E: Patient outcome				
	Patient outcome	Yes	No		
1	Normal renal fuction			E1	
2	Developed acute kidney injury (creatinine ≥26.5µmol/l)			E2	
3	Discharged			E3	
4	Deceased			E4	
5	Total days in ICU……			E5	
6	Total days of hospitalisation……			E6	

ANNEXURE H PERMISSION TO USE CLEVELAND CLINIC SCORE

The researcher have attached below the copy of the email requesting for permission to use Cleveland Clinic Score from the developer Dr.Charuhas V. Thakar and his response granting the permission to use the Cleveland Clinic Score.

On Mar 11, 2019, at 7:32 AM, Isabel Coetzee <u09032657@up.ac.za> wrote:

> Good day,
>
> I hereby want to humble ask permission to utilize the Cleveland tool to assess the predictors of AKI. I have a masters student Ms S Nuby who want to do a retrospective study on post cardiac bypass patients to see it we could have predicated the AKI by using the Cleveland scoring tool. We aim to audit 200 case files of patient who developed AKI following cardiac surgery.
>
> We would highly appreciate permission to use and if necessary adapt the tool please.
>
> Kind regards
>
> Isabel Coetzee

Prof Isabel Coetzee
Associated Professor
BCur (I et A) Education and Management (UP), Diploma Critical Care, PGCHE (UP),MCur (UJ), PhD (UNISA) FANSA
Board member of the World Federation for Critical Care Nurses (WFCCN)
Executive member of the Critical Care Society of Southern Africa (CCSSA)
Tel +27 (0)12 356 3173, Fax +27 (0)12 354 1490
Cell +27 (0)711 589 045
Email isabel.coetzee@up.ac.za
www.up.ac.za
Faculty of Health Sciences

Department of Nursing Science
Room 8-32, Level 8, HW Snyman North Building
University of Pretoria, Private Bag X323
Arcadia, 0007, Gauteng, South Africa

From: **Thakar, Charuhas (thakarcv)** <thakarcv@ucmail.uc.edu>
Date: Mon, 11 Mar 2019 at 13:37
Subject: Re: Permission to use the Cleveland score
To: Isabel Coetzee <u09032657@up.ac.za>

Sure
Thanks for asking
It's a publicly available tool - we would of course ask that any publications be properly cited.
If I can be of any assistance let me know
Ps-200 patient audit - the sample size for the event rate seems low - one can possibly conduct an audit but the predictive power will be inadequate
Thanks
Charuhas

Charuhas V. Thakar, MD, FASN
Professor of Medicine
Director, Division of Nephrology
Kidney C.A.R.E. Program
(*Clinical Advancement, Research & Education*)
ML 0585
231 Albert B Sabin Way
Cincinnati, OH 45267

Phone: 513-558-5471

Fax: 513-558-4309

ANNEXURE I UNIVERSITY OF PRETORIA ETHICS CLEARANCE LETTERS

UNIVERSITEIT VAN PRETORIA
UNIVERSITY OF PRETORIA
YUNIBESITHI YA PRETORIA

Faculty of Health Sciences

Institution: The Research Ethics Committee, Faculty Health Sciences, University of Pretoria complies with ICH-GCP guidelines and has US Federal wide Assurance.

- FWA 00002567, Approved dd 22 May 2002 and Expires 03/20/2022.
- IORG #: IORG0001762 OMB No. 0990-0279 Approved for use through February 28, 2022 and Expires: 03/04/2023.

6 November 2020

Approval Certificate
Annual Renewal

Ethics Reference No.: 586/2019
Title: Risk factors associated with acute kidney injury in patients who underwent cardiac surgery :a retrospective review

Dear Mrs S Nuby

The **Annual Renewal** as supported by documents received between 2020-10-14 and 2020-11-04 for your research, was approved by the Faculty of Health Sciences Research Ethics Committee on 2020-11-04 as resolved by its quorate meeting.

Please note the following about your ethics approval:

- Renewal of ethics approval is valid for 1 year, subsequent annual renewal will become due on 2021-11-06.
- Please remember to use your protocol number (586/2019) on any documents or correspondence with the Research Ethics Committee regarding your research.
- Please note that the Research Ethics Committee may ask further questions, seek additional information, require further modification, monitor the conduct of your research, or suspend or withdraw ethics approval.

Ethics approval is subject to the following:

- The ethics approval is conditional on the research being conducted as stipulated by the details of all documents submitted to the Committee. In the event that a further need arises to change who the investigators are, the methods or any other aspect, such changes must be submitted as an Amendment for approval by the Committee.

We wish you the best with your research.

Yours sincerely

Dr R Sommers
MBChB MMed (Int) MPharmMed PhD
Deputy Chairperson of the Faculty of Health Sciences Research Ethics Committee, University of Pretoria

The Faculty of Health Sciences Research Ethics Committee complies with the SA National Act 61 of 2003 as it pertains to health research and the United States Code of Federal Regulations Title 45 and 46. This committee abides by the ethical norms and principles for research, established by the Declaration of Helsinki, the South African Medical Research Council Guidelines as well as the Guidelines for Ethical Research: Principles Structures and Processes, Second Edition 2015 (Department of Health)

Research Ethics Committee
Room 4-60, Level 4, Tswelopele Building
University of Pretoria, Private Bag x323
Gezina 0031, South Africa
Tel +27 (0)12 356 3084
Email: deepeka.behari@up.ac.za
www.up.ac.za

Fakulteit Gesondheidswetenskappe
Lefapha la Disaense tša Maphelo

UNIVERSITEIT VAN PRETORIA
UNIVERSITY OF PRETORIA
YUNIBESITHI YA PRETORIA

Faculty of Health Sciences

The Research Ethics Committee, Faculty Health Sciences, University of Pretoria complies with ICH-GCP guidelines and has US Federal wide Assurance.

- FWA 00002567, Approved dd 22 May 2002 and Expires 03/20/2022.
- IRB 0000 2235 IORG0001762 Approved dd 22/04/2014 and Expires 03/14/2020.

29 August 2019

Approval Certificate
New Application

Ethics Reference No.: 586/2019
Title: Risk factors associated with acute kidney injury in patients who underwent cardiac surgery :a retrospective review

Dear Mrs S Nuby

The **New Application** as supported by documents received between 2019-07-30 and 2019-08-28 for your research, was approved by the Faculty of Health Sciences Research Ethics Committee on its quorate meeting of 2019-08-28.

Please note the following about your ethics approval:

- Ethics Approval is valid for 1 year and needs to be renewed annually by 2020-08-29.
- Please remember to use your protocol number (586/2019) on any documents or correspondence with the Research Ethics Committee regarding your research.
- Please note that the Research Ethics Committee may ask further questions, seek additional information, require further modification, monitor the conduct of your research, or suspend or withdraw ethics approval.

Ethics approval is subject to the following:

- The ethics approval is conditional on the research being conducted as stipulated by the details of all documents submitted to the Committee. In the event that a further need arises to change who the investigators are, the methods or any other aspect, such changes must be submitted as an Amendment for approval by the Committee.

We wish you the best with your research.

Yours sincerely

Dr R Sommers
MBChB MMed (Int) MPharmMed PhD
Deputy Chairperson of the Faculty of Health Sciences Research Ethics Committee, University of Pretoria

The Faculty of Health Sciences Research Ethics Committee complies with the SA National Act 61 of 2003 as it pertains to health research and the United States Code of Federal Regulations Title 45 and 46. This committee abides by the ethical norms and principles for research, established by the Declaration of Helsinki, the South African Medical Research Council Guidelines as well as the Guidelines for Ethical Research: Principles Structures and Processes, Second Edition 2015 (Department of Health)

Research Ethics Committee
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www.up.ac.za

ANNEXURE J PERMISSION FROM HOSPITAL MANAGER

UNIVERSITEIT VAN PRETORIA
UNIVERSITY OF PRETORIA
YUNIBESITHI YA PRETORIA

November 15th 2019

Mr. Mathews Moavodi
Hospital Manager
[redacted]
Benoni

Dear Mr. Moavodi,

Re: Permission to conduct research

I am Sona Nuby, working in 3rd floor ICU is currently a student at the University of Pretoria. I am conducting a research entitled **"RISK FACTORS ASSOCIATED WITH ACUTE KIDNEY INJURY IN PATIENTS WHO UNDERWENT CARDIAC SURGERY: A RETROSPECTIVE REVIEW"** for the fulfillment of requirement for Masters in Critical Care Nursing. I herewith request permission to conduct a study on the above mentioned topic on the hospital ground. I humbly request access to the following information: admission assessment document, doctors notes, ward prescription chart, ICU chart and laboratory results.

We intent to publish the findings in a professional journal and/or to present them at professional meetings like symposia, congresses or other meetings of such nature. We noted to protect the personal identity of the patients by assigning each individual a specific numeric code. Ethical clearance letter from University of Pretoria and Life Health care Ethics committee are attached with this letter.

I humbly request you to grant me the permission to conduct the proposed research. I would greatly appreciate your support and assistance. Please don't hesitate to contact me if there is any query.

With regards
Sona nuby.

18/11/2019

ANNEXURE K: PERMISSION FROM NURSING SERVICE MANAGER

UNIVERSITEIT VAN PRETORIA
UNIVERSITY OF PRETORIA
YUNIBESITHI YA PRETORIA

November 15th 2019

Mrs. Dot Putzier
Nursing Service Manager
[redacted]
Benoni

Dear Mrs. Putzier,

Re: Permission to conduct research

I am Sona Nuby, working in 3rd floor ICU is currently a student at the University of Pretoria. I am conducting a research entitled **"RISK FACTORS ASSOCIATED WITH ACUTE KIDNEY INJURY IN PATIENTS WHO UNDERWENT CARDIAC SURGERY: A RETROSPECTIVE REVIEW"** for the fulfillment of requirement for Masters in Critical Care Nursing. I herewith request permission to conduct a study on the above mentioned topic on the hospital ground. I humbly request access to the following information: admission assessment document, doctors notes, ward prescription chart, ICU chart and laboratory results.

We intent to publish the findings in a professional journal and/or to present them at professional meetings like symposia, congresses or other meetings of such nature. We noted to protect the personal identity of the patients by assigning each individual a specific numeric code. Ethical clearance letter from University of Pretoria and Life Health care Ethics committee are attached with this letter.

I humbly request you to grant me the permission to conduct the proposed research. I would greatly appreciate your support and assistance. Please don't hesitate to contact me if there is any query.

With regards
Sona nuby.

ANNEXURE L: LETTER FROM THE EDITOR

Cell/Mobile: 073-782-3923

53 Glover Avenue
Doringkloof
0157 Centurion

17 November 2020

TO WHOM IT MAY CONCERN

I hereby certify that I have edited Sona Nuby's master's dissertation, **Risk factors associated with acute kidney injury in patients who underwent cardiac surgery: a retrospective review**, for language and content.

IM Cooper

IM Cooper

Iauma M Cooper
192-290-4