CONTRAST-INDUCED NEPHROPATHY IN CORONARY ANGIOGRAPHY PATIENTS WHEN USING IOVERSOL AND IOMEPROL: A META-ANALYSIS

by

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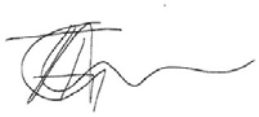
SUPERVISOR: DR DD MPHUTHI

June 2018

DECLARATION

STUDENT NUMBER: 61961981

I declare that: **Contrast-Induced Nephropathy in Coronary Angiography Patients When Using Ioversol and Iomeprol: A Meta-Analysis** is my own work and that all the sources I have used or quoted have been indicated and acknowledged by means of complete references and this work has not been submitted before for any other degree at any other institution of higher learning.



TAWANDA G.A. CHIPERE

10 June 2018
DATE

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ABSTRACT

Ioversol and Iomeprol are radiological contrast media commonly used interchangeably in many South African imaging facilities for coronary angiography. Despite differences in chemical composition, they are presumed to have similar renal safety profiles. However, no studies directly compare the renal safety of these two contrast media for coronary angiography in a predominantly healthy population. A systematic review was performed to establish which contrast medium is safer. Articles were sourced from Medline, CINAHL, Scopus, Science Direct, and PubMed Clinical Queries databases. Eligible studies were peer-reviewed articles of coronary angiography examinations carried out on a healthy adult population, where Ioversol or Iomeprol or both were administered, with contrast-induced nephropathy as an end-point. Six articles with a total population of 2431 patients were selected. The Cochrane Risk of Bias Tool was used in evaluating included articles. Pooling studies using the random effects model did not show a statistically significant reduction in contrast-induced nephropathy when Iomeprol was administered (Risk ratio 1.14, 95% confidence interval 0.797-1.643, p = 0.466). Moderate heterogeneity (I^2=54.21%) across the studies was observed. Study limitations included potential bias during data extraction because this was performed by a single reviewer, and language restrictions to include only English titles. Iomeprol may be better for use in the clinical setting because of more a predictable renal safety profile.

KEY CONCEPTS

Contrast-induced nephropathy, Ioversol, Iomeprol, coronary angiography, renal safety

KONTRASGEÏNDUSEERDE NEFROPATIE IN PASIËNTE MET KORONÊRE ANGIOGRAFIE WANNEER IOVERSOL EN IOMEPROL GEBRUIK WORD: 'N METAONTLEDING

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OPSOMMING

Ioversol en Iomeprol is radiologiese kontrasmedia wat algemeen omruilbaar in baie Suid-Afrikaanse beeldingsgeriewe vir koronêre angiografie gebruik word. Ondanks verskille in chemiese samestelling word hulle geag soortgelyke nierveiligheidsprofiele te hê. Geen studies vergelyk egter regstreeks die nierveiligheid van hierdie twee kontrasmedia vir koronêre angiografie in 'n oorwegend gesonde populasie nie. 'n Sistematiese oorsig is uitgevoer om vas te stel watter kontrasmedium die veiligste is. Artikels is uit databasisse van Medline, CINAHL, Scopus, Science Direct en PubMed Clinical Queries bekom. Geskikte studies was portuurbeoordeelde artikels oor koronêre angiografieondersoeke wat op 'n gesonde volwasse populasie uitgevoer is, waar Ioversol of Iomeprol, of albei, toegedien is, met kontrasgeïnduseerde nefropatie as 'n gevolg. Ses artikels met 'n totale populasie van 2 431 pasiënte is gekies. Die Cochrane-sydigheidsrisiko-instrument is gebruik om ingeslote artikels te evalueer. Saamvoegingstudies wat die stogastiese effektemodel gebruik het, het nie 'n statisties beduidende verlaging in kontrasgeïnduseerde nefropatie getoon wanneer Iomeprol toegedien is nie (risikoverhouding 1.14, 95% vertrouensinterval 0.797-1.643, p = 0.466). Matige heterogeniteit (I2=54.21%) oor die studies heen is waargeneem. Studiebeperkings het ingesluit potensiële sydigheid tydens dataontginning, omdat dit deur 'n enkele beoordelaar uitgevoer is, en taalbeperkings aangesien slegs Engels titels ingesluit is. Iomeprol word aanbeveel vir gebruik in die kliniese omgewing as gevolg van 'n meer voorspelbare nierveiligheidsprofiel.

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KAFUSHANE NGOCWANINGO

I-*Ioversol* kanye *Iomeprol* yiziguqulimbala zama-eksireyi neminye imisebe ezivamise ukusetshenziswa njengezinto ezenza umsebenzi ofanayo ezikhungweni eziningi zaseNingizimu Afrika ezikhiqiza izithombe zama-eksireyi emithambo yegazi eya enhliziyweni. Nakuba ukhona umehluko othile kumakhemikhali alezi ziguqulimbala, zithathwa njengeziguqulimbala ezinamaphrofayili okuphepha kwezinso afanayo. Kepha-ke, alukho ucwaningo olwenziwe oluqhathanisa ngqo ukuphepha kwezinso kwalezi ziguqulimbala ezimbili maqondana nezithombe ze-eksireyi zemithambo yegazi eya enhliziyweni kulelo qembu labantu emphakathini elakhiwe ikakhulukazi ngabantu abangumqemane futhi abaphile kahle emzimbeni. Ngenhloso yokuthola ukuthi yisiphi kulezi ziguqulimbala ezimbili esiphephile kunesinye, kwacutshungulwa futhi kwabuyekezwa imibhalo ethile ngendlela ehlelekile. Imithombo okwathathwa kuyona le mibhalo yizizindalwazi ezinjenge-Medline, CINAHL, Scopus, Science Direct, kanye ne-PubMed Clinical Queries. Izingcwaningo ezifanelekile zenziwa ngokuhlaziya leyo mibhalo eyabe ibuyekezwe ngontanga ephathelene nokuhlolwa kwama-eksireyi emithambo yegazi eya enhliziyweni, okuwukuhlolwa okwenziwa eqenjini labantu abangumqemane futhi abaphile kahle emzimbeni, ababefakwe i-*Ioversol* noma i-*Iomeprol* noma kokubili, okwaholela ekutheni bagcine sebenenkinga yokungasebenzi kahle kwezinso ngenxa yeziguqulimbala ezifakwe emizimbeni yabo (*contrast-induced nephropathy*). Kwakhethwa imibhalo eyisithupha enenani leziguli eziyizi-2431. Kwasetshenziswa i-*Cochrane Risk of Bias Tool* ukuhlola imibhalo eyabe ifakiwe ocwaningweni. Ukuhlanganiswa ndawonye kwemiphumela yezingcwaningo kusetshenziswa i-*random effects model* akubonisanga ukuncipha okukhulu kokuthembakala kwemiphumela yokulimala kwezinso okubangelwe yiziguqulimbala, ezimweni lapho kwasetshenziswa khona i-*Iomeprol* (Isilinganiso sobungozi 1.14, 95% isimo sokuthembakala [*confidence interval*] 0.797-1.643, p = 0.466). Kwabonakala ukuhlukahluka okumaphakathi (*moderate heterogeneity*) (I^2=54.21%) emiphumeleni

yazo zonke izingcwaningo. Izithiyo nemikhawulo yocwaningo kwaba wukuba khona kwamathuba okuchema okuthile ngenkathi kuqoqwa idatha ngoba lo msebenzi wawenziwa ngumbuyekezi (reviewer) oyedwa, futhi kwakhukhona nezithiyo zolimi ngenxa yesidingo sokufaka izihlokwana zesiNgisi kuphela. I-*Iomeprol* ingasebenziseka kangcono endaweni yokwelapha ngoba phela yona inephrofayili yokuphepha kwezinso ebikezeleka kangconywana kunezinye.

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Family and friends were extremely supportive and gave me the space and encouragement I needed to focus on my studies. I am grateful for their advice and re-assurance throughout the duration of my studies.

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ABBREVIATIONS

CA	Coronary angiography
CASP	Critical Appraisal Skills Programme
CI	Confidence interval
CIN	Contrast-induced nephropathy
CINAHL	Cumulative Index to Nursing and Allied Health Literature
CT	Computed tomography
eGFR	Estimated Glomerular filtration rate
et al	et alia (and others)
KDIGO	Kidney Disease: Improving Global Outcomes
mg/dL	milligrams per deciliter
mL/kg/hour	milliliters per kilogram per hour
mOsm/kg H2O	milliosmoles per kilogram of water
MRI	Magnetic resonance imaging
PCI	Percutaneous coronary intervention
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RR	Risk ratio
Sv	sub verbo (under the word)
ICMBPS	International Conference on Medical, Biological, and Pharmaceutical Sciences

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CHAPTER 1

ORIENTATION TO THE STUDY

1.1 INTRODUCTION AND CONTEXTUALISATION

This study focuses on the safety of two radiological contrast media, which are routinely used for coronary angiography (CA) examinations. The safety profiles of these contrast media are determined by the effect they have on the kidneys as determined by biomarkers, which act as indicators of any acute kidney injury. Acute kidney injury is a broad term used to describe one of a number of conditions that affect the structure and function of the kidney (Kidney Disease Improving Global Outcomes [KDIGO] 2012:19). There are many possible causative factors such as burns, trauma, and haemorrhage (Shiland 2014:228; National Kidney Foundation 2016). However, in addition to pathology, certain procedures performed in the hospital may cause acute kidney injury. One such example is exposure of the kidneys to contrast media, which is used in potentially life-saving CA examinations (Andreucci, Solomon & Tasanarong 2014:16). Acute kidney injury occurring due to contrast media exposure is known as contrast-induced nephropathy (CIN) (Hiremath 2017:291). This study will look at the said condition in greater detail.

There are several procedures performed in the radiology department where contrast media not only finds applicability, but is essential for meaningful diagnostic results. One such procedure is coronary angiography (CA). CA is a diagnostic imaging procedure used to view the coronary arteries of the heart, and it is one of the most commonly performed medical procedures worldwide (Oudkerk 2013:34). It can identify stenosis within the coronary arteries, thereby ascertaining the need for revascularisation to minimise the risk of myocardial infarction (Baveja & Sharma 2015). Iodine-based radiological contrast media is used to enhance the appearance of the coronary arteries during CA. However, intravascular exposure to contrast media is associated with acute kidney injury in some patients (Andreucci et al 2014:16). This condition is referred to as CIN (Hiremath 2017:291).

Research shows a strong correlation between CIN and poor patient outcomes, including higher mortality rates, hence the clinical importance of this condition (Lefel, Janssen, le Noble & Foudraine 2016:699; Grossman, Ali, Aronow, Boros, Nypaver, Schreiber, Park, Henke & Gurm 2017:274). In addition, patients suffer from prolonged hospital stays and increased medical costs (Lian, Liu, Liu, Li, Duan & Yu 2017:197). The increasing accessibility of healthcare and rising number of patients seeking cardiac interventional procedures has significantly increased the population size exposed to radiological contrast media, and consequently, at risk of developing CIN (Rear, Bell & Hausenloy 2016:638). According to studies conducted, CIN is now the third leading cause of hospital-acquired acute kidney injury, after impaired renal perfusion and the use of nephrotoxic drugs, representing about 14% of such cases (Fananapazir, Troppmann, Corwin, Bent, Vu & Lamba 2016:783; Kelly, Li, Stys, Thompson & Stys 2016:446).

Although exact figures fluctuate greatly across literature owing to different study populations and differing definitions of CIN, the highest incidence of the condition is seen in CA patients (Meinel, De Cecco, Schoepf & Katzberg 2014:6). This is because CIN risk increases with intravascular volume of contrast media administered and CA typically requires high volumes to be used. In addition, some comorbid conditions such as pre-existing kidney injury increase CIN risk, and these conditions frequently exist in patients who require CA (Andreucci, Faga, & Michael 2015:16).

Radiographic contrast media used for CA are classified as either ionic or non-ionic, and are further categorised as being high-, low-, or iso-osmolar (Beckett, Moriarity & Langer 2015:1738). These contrast media have varying nephrotoxic properties, and hence observed incidences of CIN because of their differing chemical structures (Andreucci et al 2015:16). Non-ionic, low/iso-osmolar contrast agents elicit the lowest levels of CIN, and are safer than their high-osmolar, ionic counterparts. For this reason, they are used for intravascular administration in preference to high-osmolar contrast agents (Beckett et al 2015:1738).

This study will focus on two commonly used drugs, namely, Ioversol and Iomeprol, which are both low-osmolar, non-ionic radiological contrast media that are used for CA in many South African imaging facilities (Seeliger, Lenhard & Persson 2014:15).

In selected medical imaging facilities within the country, these two contrast media are used interchangeably. In their research, Căldăraru, Dobreanu, Dogaru, Olariu, and Dogaru (2014:711) noted a paucity of literature that compares the safety of these two contrast media in terms of nephrotoxicity. These authors also noted that even within the same class of contrast media (low-osmolar, nonionic), the various agents have differing physiochemical properties, osmolarities and viscosities. These are qualities that ultimately impact whether the renal tubules are able to handle, or will be injured by radiological contrast media (Seeliger et al 2014:15). It can be assumed that all the radiological contrast agents in use have differing levels of nephrotoxicity, so Ioversol and Iomeprol are no exception.

Apart from patient safety, the choice of contrast medium used also has important cost implications. Cernigliaro, Haley, Adolphson, Jepperson, Crook, Thomas, and Parker (2016:902) estimated annual savings of up to R1 400 000 (US$100 000) at a single institution if they were to switch from using one contrast agent to another. However, there frequently exists a lack of consensus in literature when determining which radiocontrast medium is safer than the other (Cernigliaro et al 2016:902; Reed, Meier, Tamhane, Welch, Moscucci & Gurm 2009:645).

Non-uniformity in the determination of kidney function and diagnosis of CIN may be a cause of variability in obtained study results when evaluating nephrotoxicity of contrast media. Accepted CIN definitions determine kidney injury using either an increase in serum creatinine, or a decrease in estimated glomerular filtration rate (eGFR) (Hiremath 2017:291). There is no consensus on when these biomarkers are to be measured (Ozkok & Ozkok 2017:86). The most widely used diagnosis of CIN is informed by an increase in serum creatinine within 48-72 hours post contrast exposure (Kelly et al 2016:446). However, serum creatinine is an inconsistent marker and inferior to eGFR as a reliable predictor of kidney function (Bragadottir, Redfors, & Ricksten 2013:108). Clinical implications of these differences in determining kidney function mean a patient's kidneys may be regarded as normally functioning under one definition, or as having CIN under another (Schilp, de Blok, Langelaan, Spreeuwenberg & Wagner 2014:2).

Based on the background information discussed above, the following problem statement was formulated.

1.1.1 Problem Statement

CIN is an iatrogenic condition in which acute kidney injury occurs after intravascular administration of radiological contrast media without any other identifiable cause (Hiremath 2017:291). The condition is linked to adverse health outcomes and increased medical costs, including an increased mortality rate in some patient groups (Lefel et al 2016:699; Cernigliaro et al 2016:902). Administering high volumes of contrast media increases the likelihood of CIN development, and the potentially life-saving CA procedure requires large contrast medium volumes for optimum viewing of the coronary arteries, and hence is the procedure with the highest observed rates of CIN (Meinel et al 2014:6). The choice of contrast medium used for the CA procedure also has a bearing on the development of CIN in patients, as all contrast media have different chemical properties and are tolerated differently by the kidneys (Seeliger et al 2014:15). However, at most South African imaging centres performing CA, the contrast media Ioversol and Iomeprol are frequently administered interchangeably. It is unclear which of these two contrast media is least likely to elicit CIN in patients owing to a paucity of literature that compares their safety profiles (Căldăraru et al 2014:711). Clinicians should, in the interests of their patients, only use the safest available contrast medium but it is impossible to say which of the two commonly used contrast media is safer in the absence of comparative studies or conclusive scientific evidence.

1.2 AIM OF THE STUDY

Basing on the preceding rationale, this study aims to search literature with a focus on the observed CIN incidence in CA studies on adults where Ioversol and Iomeprol were the radiological contrast agents used, and kidney function was determined using eGFR. eGFR increases accuracy of CIN determination, fostering a more accurate representation of the condition’s incidence rate (Bragadottir et al 2013:108).

Such information will be of value to health practitioners in helping them decide on which radiographic contrast medium to use for CA examinations basing on the results of evidence-based research.
For the purpose of this study, the researcher has the following hypothesis to be tested.

1.2.1 Research Hypothesis

Johnson and Christensen (2013:560) explain that research hypothesis testing entails presuming that an effect, or occurrence in a population is not present until there is sufficient evidence to conclude otherwise. This presumption of the absence of an effect is known as the null hypothesis, represented by the symbol H_0. The null hypothesis may ultimately be rejected if the results of a hypothesis test are able to support an alternative hypothesis, which may be represented as H_1.

In this study, the null hypothesis is that there is no statistically significant difference in nephrotoxicity between Ioversol and Iomeprol. The alternative hypothesis is that a statistically significant difference in nephrotoxicity exists between the two contrast media. This is explained below.

The researcher hypothesises that:

- Iomeprol and Ioversol do not have similar nephrotoxicity because of their differing chemical structures, and hence are not interchangeable for use in clinical practice.
- Usage of Iomeprol results in a lower incidence of CIN for patients undergoing CA compared to Ioversol because commercially manufactured Iomeprol, manufactured under the trade name Iomeron, does not contain the nephrotoxic agent edetate calcium disodium, which is used to extend the shelf life of Ioversol.

The hypotheses may be represented by the following equations:

Null hypothesis: $H_0 : N_{IOV} = N_{IOM}$

Alternative hypotheses: $H_1 : N_{IOM} \neq N_{IOV}$

and $N_{IOM} < N_{IOV}$

Where N_{IOM} and N_{IOV} represent the nephrotoxicity of Iomeprol and Ioversol respectively.

The probability value, also known as the p-value, is the probability of obtaining the observed study outcome under the assumption that the null hypothesis is true. Only when the p-value is very small can the researcher reject the null hypothesis (Johnson & Christensen 2013:564). For this study, a p-value less than or equal to 0.05 was considered small enough to conclude that the obtained result was statistically significant. The statistical significance is important because it means that any observed result is not merely owing to chance or sampling error, but owing to an actual effect, which can be proven by data (Johnson & Christensen 2013:564).

1.2.2 Objectives

In order to achieve the purpose of the study, the following objectives were developed:

- To determine the extent to which Ioversol and Iomeprol elicit CIN in randomly selected adult patients undergoing CA examinations.
- To determine if Iomeprol is safer than Ioversol in terms of lower observed incidences of CIN.
- To make recommendations for improved clinical practice based on the prevalence of side effects of the contrast media.

1.2.3 Significance of study

The significance of this study will be establishing which radiological contrast media is safer for CA patients to help cardiologists, radiographers, nurses, and other clinicians make informed decisions that will result in improved practice. Such information will also be helpful in reducing the observed incidences of CIN, and the associated costs of treating this condition.

1.3 DEFINITION OF KEY CONCEPTS

The following terms will be frequently used in this research, and they have been defined and operationalised for the purposes of this study as follows:

Contrast-induced nephropathy is defined as an acute decline in kidney function which occurs within a short time interval after intravascular exposure to radiological contrast media (Meinel, et al 2014:6).

In this study, contrast-induced nephropathy will refer to the acute kidney injury resulting after either Ioversol or Iomeprol has been intra-arterially administered to patients undergoing CA.

Clinicians are individuals who have the authority to direct the delivery of personal health services to patients. They are in direct contact with the patient, and make use of recognised scientific knowledge to establish the best care pathway for the patient (Donaldson, Yordy, & Vanselow 1994:20). In this study, clinicians refer to the cardiologists, radiographers, nurses, physicians and general practitioners who are in contact with the patients undergoing CA.

Coronary angiography is a semi-invasive procedure performed to study the heart and coronary arteries. A radiological contrast agent is used during the procedure to enable visualisation of coronary arteries (Shea 2017). In this study, coronary angiography refers to a radiological diagnostic imaging examination performed on patients by catheterising the coronary arteries and injecting Ioversol or Iomeprol for evaluation of the coronary arteries.

Mosby's Medical Dictionary (2016 sv "patient") defines the recipient of a health care service who may be ill or hospitalised as a **patient**. In this study, a patient is an individual who undergoes a CA examination.

Ioversol is an intravenous, non-ionic, iodine-based radiological contrast medium. Its trade name is Optiray (Hale & Rowe 2017:505). In this study, Ioversol refers to a contrast medium used for CA.

Iomeprol is a non-ionic iodine-based radiological contrast medium. It is sold under the trade name Iomeron (Hale & Rowe 2017:505-506). In this study, Iomeprol is a contrast medium used for CA.

1.4 RESEARCH DESIGN AND METHODS

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) standard was developed for systematic reviews and meta-analyses of studies that use aggregate data, generally extracted from published reports (Stewart, Clarke, Rovers, Riley, Simmonds, Stewart, & Tierney 2015:1657). Compliance with this standard ensures the completeness and transparency of a systematic review, and hence the researcher adhered to the outlined guidelines in the research design and methods.

1.4.1 Research methodology

The methodology used for research is the steps, procedures and strategies employed to gather and analyse data (Polit & Beck 2014:385). Methodology outlines a systematic plan that describes which methods are best suited to the intended research type. This study made use of systematic review methodology, which is concerned with combining information from various sources to provide data so a research question may be answered (Jesson, Matheson & Lacey 2011:105).

1.4.2 Systematic review approach

A systematic review entails identifying relevant studies regarding a specific topic, appraising their quality, and then using a scientific methodology to summarise the findings obtained (Khan, Kunz, Kleijnen & Antes 2011:1). Such an approach was necessary in this study because numerous prior studies have been performed to assess the safety profiles of radiographic contrast media. However, owing to the sheer volume of these studies and the varying patient populations as well as potential study biases, it is difficult to tell which contrast medium has the best safety profile, hence the need for a systematic review.

1.4.2.1 Appraisal of the systematic review

Not all systematic reviews produce reliable conclusions because of bias that may be introduced into the final result. Study authors may improve reporting by adhering to widely agreed standards (Hoffmann, Bennett & Mar 2013:296). As discussed in section 1.4, the standard used for this research is the PRISMA statement. Further

analysis of the results of a systematic review can be done by using tools or checklists to check if the results produced are indeed trustworthy. One such checklist is known as the Critical Appraisal Skills Programme (CASP) (Hoffmann, Bennett & Mar 2013:296). This checklist consists of 10 questions that identify issues requiring consideration when appraising a systematic review study (CASP Systematic Review Checklist 2018). The CASP checklist was used to appraise this systematic review, and has been included as Appendix 6.

1.4.3 Research design

A research design is a strategy of enquiry within the qualitative, quantitative and mixed methods approaches that provides specific direction for procedures to be followed (Creswell 2014:12). This study utilises a quantitative approach, and adopted a meta-analysis design. Meta-analysis is a quantitative epidemiological study design, used for systematic assessment of previous studies to derive conclusions about a body of research (Haidich 2010:29).

1.4.4 Setting and population

Polit and Beck (2010:568) define a study setting as the physical location and conditions where data collection takes place when conducting a research study. This study will be conducted using information obtained online from journal databases as well as scientific search engines. The following databases will be searched for information: PubMed Clinical Queries, Science Direct, CINAHL, Medline, and Scopus. Only records involving standard CA examinations where Ioversol and Iomeprol were used on a randomly selected population will be included in the study.

1.4.5 Sample and sampling methods

A sample is a subset of the population, selected to be representative of the whole, in situations where the population is too large to effectively study owing to time or budget constraints (Acharya, Prakash, Saxena & Nigam 2013:330). In this study, all eligible scientific papers evaluating the incidence of CIN in adult CA patients when using Ioversol and when using Iomeprol were considered.

Eligibility Criteria:

- Studies involving patients above the age of 18 who underwent standard CA examinations.
- Studies where eGFR was used as a measure of renal function.
- Studies detailing the nephrotoxicity of Ioversol and Iomeprol.
- Studies where patients were considered to be in general good health prior to the coronary angiogram.
- Data sourced from journals from the following databases: PubMed Clinical Queries, Science Direct, CINAHL, Medline, and Scopus.
- Studies performed from inception of databases to the last search date, which was 11 April 2018.

Exclusion Criteria:

- Studies involving coronary angiograms where non-standard prophylactic measures against CIN were used.
- Studies of patients below the age of 18.
- Studies involving patients who were critically ill or unstable.
- Studies performed on animals.
- Studies with incomplete or dubious data.
- Studies conducted in languages other than English, without an official English translation.
- Data from books, other print media, non-medical websites or other electronic databases not mentioned above.

1.4.6 Data extraction method

Data extraction is the precise and systematic way of gathering information which is specific to the research purpose, and /or objectives, questions, and hypothesis of a study (Grove, Burns & Gray 2014:47) To extract data for this research study, the researcher will perform an internet search for relevant scientific papers, as per guidelines specified within the inclusion and exclusion criteria. These will be organised

and stored using Zotero (version 4.0.29.17 George Mason University, USA) citation and bibliography processing software.

1.4.7 Data management and analysis

Data analysis involves looking for patterns, differences and other features that help to address the questions at hand (Downey 2014:2). Articles earmarked for inclusion in the study will be reviewed and individually appraised, with the final selection of articles being analysed for quality, and their data included in the study. A data collection form (Appendix 2) will be used to organise the data collected (adapted from Cochrane: Data collection form for intervention reviews: RCTs and non-RCTs 2014). Included studies will be assessed for risk of bias as recommended by the PRISMA statement (Moher, Liberati, Tetzlaff & Altman 2009:2). Statistical analysis will also be carried out and specific statistical methods will be determined by the nature of data obtained.

1.5 ETHICAL CONSIDERATIONS

Ethical clearance was sought from the University of South Africa (Unisa) Higher Degrees Ethics Committee, and has been included in this document as Appendix 1. In addition, the researcher ensured all sources are referenced correctly as per Unisa guidelines to avoid plagiarism.

1.6 CONCLUSION

This chapter gave an orientation to the study with a focus on acute kidney injury, followed by a brief background of CIN and its significance. This led to the problem statement, as well as the hypothesis and aims of this research study. A description of the significance of the study followed, and an explanation of the key terms, which will appear repeatedly throughout the text. Reference was made to the research method, and this will be explored in further detail in Chapter 3. The next chapter will explore available background knowledge related to coronary angiography, development of CIN, and the two radiological contrast agents under comparison.

1.7 STRUCTURE OF THE DISSERTATION CHAPTERS

The chapters of this dissertation are structured as outlined below:

Chapter 1 Orientation of the study

Chapter 2 Background and key concepts

Chapter 3 Research methodology

Chapter 4 Results and interpretations

Chapter 5 Discussion and recommendations

CHAPTER 2

BACKGROUND AND KEY CONCEPTS

2.1 INTRODUCTION

The previous chapter presented an outline of the study and gave a brief overview of what CIN is and its clinical significance. An explanation was given of how this research is structured to gather and analyse data pertaining to CIN incidence rates when two commonly used radiological contrast media are used. This chapter will discuss the existing knowledge relevant to this research and explain key concepts in greater detail. This is important because it fosters an understanding of the accumulated knowledge regarding the topic at hand. The goal of exploring existing literature on a topic is to base any conclusions made on many different studies (Garrard 2016:4-5).

The search engines used in generating the materials to write this chapter were the Unisa online library, Medline and Google Scholar. The relevant data was extracted from articles in scientific journals, webpages, and books.

2.1.1 Kidney function

As mentioned in the preceding chapter, CIN is acute injury to the kidneys, which occurs due to contrast media exposure (Hiremath 2017:291). Before the condition can be explored in greater detail, this section will delve deeper into the normal function and structure of the kidneys.

The basic function of the kidneys is to filter blood, and remove wastes in the form of urine, which is then excreted from the body (Patton & Thibodeau 2015:967). The kidneys can be regarded as the most important organs for homeostasis because in addition to controlling the concentration of the waste products of metabolism, they are also involved in the osmolarity, volume, acid-base status, and ionic composition of the blood plasma. They also control these same variables indirectly within the cells of the body (Lote 2012:1). The anatomy of the kidney is as described below.

2.1.2 Kidney anatomy

The general shape of a kidney may be likened to that of a lima bean, that is, oval in shape, and with a central indentation. The size of an average kidney is 11cm by 7cm by 3cm. The two kidneys lie in the retroperitoneal position, and each is positioned on either side of the lumbar portion of the vertebral column. A heavy cushion of fat encases each kidney, and this cushion together with connective tissue ensures that both kidneys are anchored to their surrounding structures and maintain normal positions (Patton & Thibodeau 2015:967). The basic functional unit of the kidney is the nephron, and each kidney has up to 1.5 million of them (Lote 2012:22). The structure of a kidney and nephron are as shown in Figure 2.1 below:

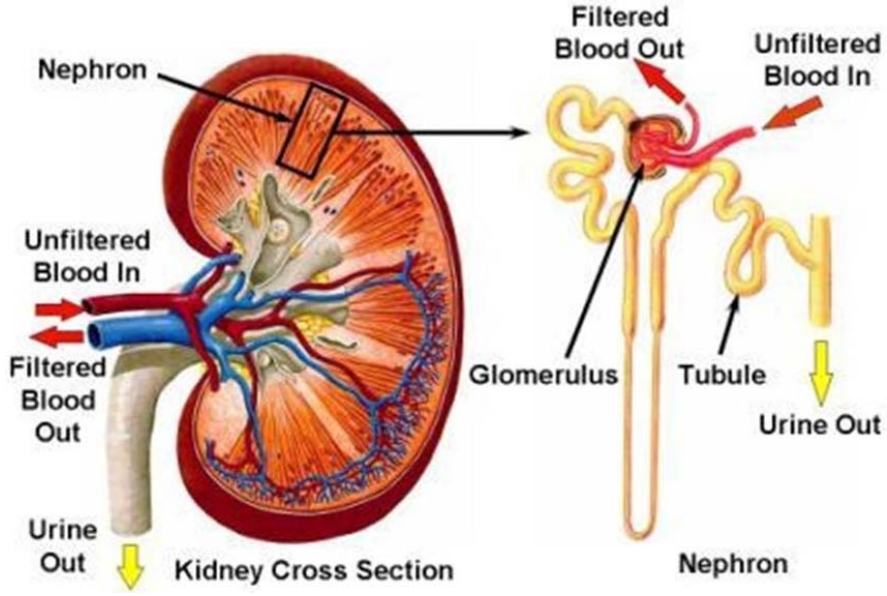


Figure 2.1: Kidney cross section and nephron (UNC Kidney Centre 2016)

The nephron receives a supply of blood for filtration, which occurs on its proximal end in a region known as the renal corpuscle. The blood vessel which supplies the unfiltered blood to the nephron branches to form a complex network of leaky capillaries known as the glomerulus from which fluid seeps out, and enters the lumen of the nephron. However, larger molecules such as serum albumin are unable to pass through membranes lining the glomerulus and hence they remain in the blood, leaving the smaller molecules to proceed in entering the nephron. Inside the nephron, the fluid is further filtered, with essential small molecules such as glucose and amino acids being reabsorbed as the fluid moves along the length of the tubule.

Reabsorption of multiple elements such as water and sodium also occurs, and the quantities of elements reabsorbed or remaining in the lumen largely depend on complex hormonal mechanisms. The fluid that remains after all filtration and reabsorption have occurred is urine, and its composition is final when it reaches the end of the nephron at the point where it joins to the collecting duct. The collecting duct system funnels all the urine from the individual nephrons through a ureter to the bladder (McMahon 2016:33-34).

Substances that are not needed by the body are usually filtered out of the blood by the nephrons and excreted as urine (Patton & Thibodeau 2015:967). This is also true for contrast media which are used in angiography examinations (Adam, Dixon, Gillard, Schaefer-Prokop, Grainger & Allison 2014:28). The necessity of angiograms as well as contrast media will now be explored in greater detail.

2.2 A HISTORY OF ANGIOGRAPHY

Angiography is a diagnostic imaging procedure which is performed to view the lumen of blood vessels. This procedure allows the diagnosis of intravascular disease (Toy & Faulx 2014:48). The concept of imaging blood vessels was first explored in January 1986, barely a month after the discovery of X-rays. This was done by injecting calcium carbonate into the blood vessels of an amputated hand, and subsequently taking X-ray images. Calcium carbonate is opaque to X-rays, and as a result, its distribution within the blood vessels was visible on the resultant X-ray image. This was the first ever recorded angiogram. Angiograms at this point were limited to cadavers because substances that were opaque to X-rays and yet safe to be injected into the blood stream had not yet been discovered (Wake, Yoshiyama, Iida, Takeshita, Kusuyama, Kanamitsu, Mitsui, Yamada, Shimodozono & Haze 2014:69).

Figure 2.2: The first ever recorded angiogram (Wake et al 2014:69)

As early as 1910, Franek and Alwens injected a mixture of bismuth and oil into the large blood vessels of live dogs and rabbits. Using fluoroscopic imaging equipment, they were able to observe the movement of the substance to the heart, and subsequently, the lungs. More experimentation continued, and in 1922, Sicard and Forestier injected living human subjects with Lipiodol to successfully study the bronchial tree and spinal subarachnoid space. Lipiodol was an early oil-based substance which is opaque to X-rays. A year later, they injected Lipiodol into the femoral vein of a dog, and were able to observe movement of the liquid all the way to the heart, out of it, and up to the small vessels of the lungs. Shortly after, this experiment was repeated with human subjects. They reported that the subjects coughed as the Lipidol reached the lungs, but they did not observe any other side effects. In 1923, other scientists carried out successful experiments where they imaged blood vessels in living humans using strontium bromide, and in 1924, more successful experiments using sodium iodide were performed.

These different chemicals which were used to visualise the blood vessels, namely, calcium carbonate, Lipiodol, strontium bromide, and sodium iodide, effectively became the early versions of radiographic contrast media (Wake et al 2014:69).

Radiological contrast media, also known as radiographic contrast agents, are a group of medical drugs that are used to increase the visibility of internal structures and organs when imaging is being performed. The most common use for them is to differentiate between normal and pathological areas within the body (Andreucci et al 2014:1).

2.2.1 Coronary angiography

When an angiogram is performed to view the coronary arteries of the heart, it becomes known as a coronary angiogram (American Heart Association 2015). This examination is the recognised standard clinical imaging method used to diagnose coronary arterial narrowing (Nicholls & Crowe 2014:51). Should there be any coronary arteries that are narrowed, coronary angioplasty is usually carried out if the narrowing is not too severe, and this is done as part of the same examination (Zhou & Brahme 2008:137). Coronary angioplasty is a percutaneous intervention involving the implantation of one or more stents at the site of arterial stenosis within a coronary artery. It is also known as percutaneous coronary intervention (PCI) (Hiremath 2017:107). Coronary artery disease is the current leading cause of mortality and morbidity in the world, more so in industrialised countries, and because of this, the importance of CA has greatly increased such that it has become one of the most commonly performed medical procedures (Oudkerk 2013:34; Tu, Holm, Janssen, & Reiber 2014:151).

2.2.2 Coronary angiography indications

As discussed above, the main reason for performing CA is to determine if any narrowing or blockage exists in the coronary arteries, and if so, to pinpoint the location and extent of the pathology (Chatterjee, Anderson, Heistad & Kerber 2014:778). Multiple conditions may present in patients where CA may be of benefit, and these are known as indications for the procedure.

An indication is defined as a condition for which a specified approach would benefit the patient for the enhancement of their health or treatment of a disorder (Fritz 2013:200).

Patients presenting with chest pain, which is suspicious of coronary artery disease, may need CA performed to exclude the suspected pathology. In addition, unstable angina pectoris as well as having had a recent heart attack are also common indications for CA. This is because the examination results will allow for PCI to be performed as a therapeutic measure, thereby decreasing the chances of repeat heart attacks, and in the case of angina pectoris, the condition may be treated and go away altogether (Sundareson 2014).

In some patients, PCI may not be possible for various reasons, and so more invasive measures are required such as coronary artery bypass surgery. In this case, CA would be necessary as a precursor to such surgery to ensure correct localisation of the stenotic region(s). Abnormal treadmill test results may also be suggestive of coronary artery disease and hence warrant a CA examination for a conclusive diagnosis to be made. For patients in whom clinicians are aware of pre-existing coronary artery disease, it may be necessary to determine the extent of their condition, and this is yet another indication for CA. The procedure may also assist in monitoring any possible rejection in heart transplant patients (Sundareson 2014).

2.2.3 Coronary angiography contraindications

Not all patients can safely have coronary angiograms performed on them even though the diagnosis from this procedure may be lifesaving. For some patients, the CA procedure is contraindicated. A contraindication is defined as a condition or situation that makes the procedure in question inadvisable for the patient (Misch & Resnik 2017:13).

Patients with allergies to contrast media are a good example, as exposure may result in life-threatening reactions (Sundareson 2014; Siddiqi 2017). In addition, some conditions such as uncontrolled hypertension, electrolyte imbalance, severe anaemia, and coagulopathy are typically contraindicated for the angiography procedure.

Kidney problems like renal failure and dysfunction; and heart conditions, namely, arrhythmias and uncompensated heart failure; as well as fever, transient ischemic attacks, and active systemic infections all add to the list of contraindications (Sundareson 2014). That said, the indications and contraindications discussed here are only the common ones and are by no means exhaustive.

2.2.4 The coronary angiography procedure

As is the requirement prior to performing any medical procedure, before CA can be performed, patient informed consent needs to be obtained. The patient must have the procedure clearly outlined to them in simple terms they can understand, as well as any risks and benefits of the procedure. The dangers and potential benefits of the examination are entirely dependent on the patient in question, meaning that explanation of the procedure must be tailored to the situation being addressed (Chatterjee et al 2014:781).

Patients who have diabetes mellitus, kidney injury, or previous hypersensitivity to iodinated contrast media are considered high-risk, and will need special precautions to ensure the safety of the procedure. These precautions will include measures such as premedication, or in other cases, dosage adjustment of any chronic medication the patient is receiving, and measures are determined on an individual basis. The patient is then brought to the catheterisation laboratory and given sedatives to help keep them comfortable throughout the procedure (Chatterjee et al 2014:781).

The next step is to insert a catheter into an artery. The skin on the arm or leg is punctured under local anaesthesia for access to either the radial artery, or the femoral artery (Chatterjee et al 2014:781; Kulick 2015). The choice of artery used depends on several factors, such as comorbidities, as well as personal preferences and expertise of the clinician, but the femoral artery route is the most popular (Schwalm, Stacey, Pericak & Natarajan 2012:260). The catheter is pushed up the selected artery, and fluoroscopic imaging equipment is used to guide the catheter tip to the heart at the level of the coronary ostia (Kulick 2015). Figure 2.3 below shows the catheterisation of the heart via femoral artery entry.

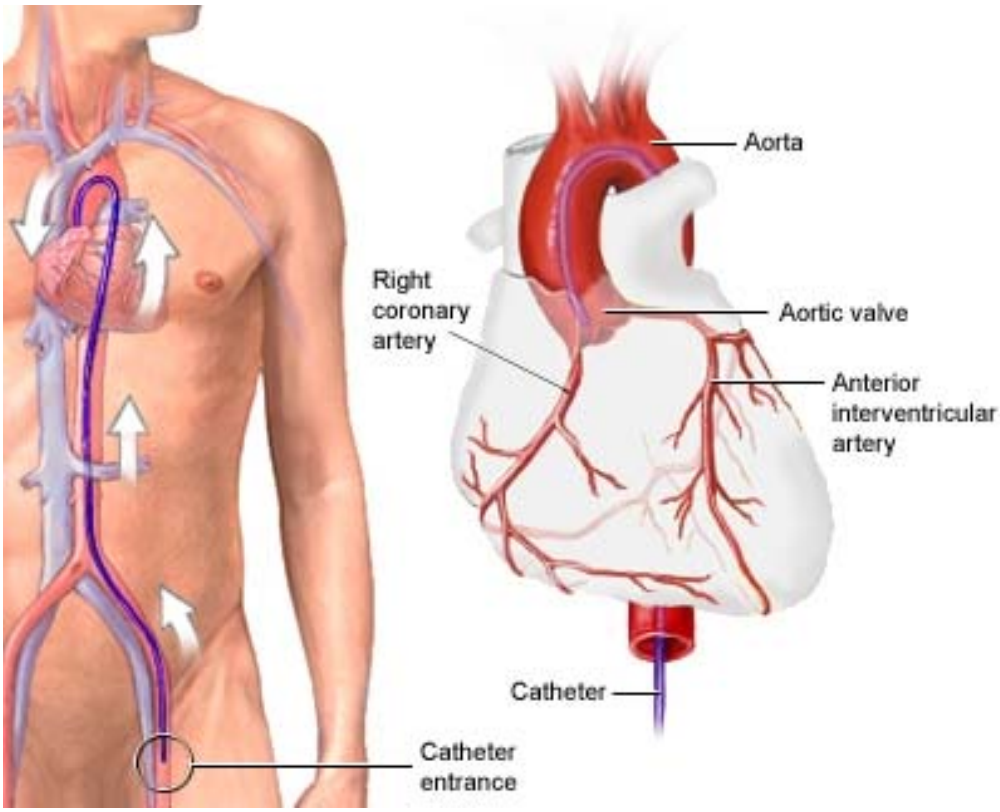


Figure 2.3. Illustration showing catherization of the heart for CA (MedlinePlus 2015)

The contrast medium is then injected via the catheter into each of the coronary arteries. This requires considerable precision to ensure that the catheter is at the desired coronary artery, and the injection of contrast medium must not be too weak, as this may result in inadequate filling of the coronary lumen which may lead to false diagnosis of coronary stenosis where only a contrast-filling defect exists. If the contrast medium is injected too forcefully, coronary dissection may occur (Čaluk 2011:109). For this reason, electronically controlled pumps are generally used to ensure a standard, known injection rate as well as easily determinable contrast medium quantity (Oudkerk 2013:28).

The fluoroscopic equipment is then angled around the patient in order to obtain multiple views of the coronary arteries at different segments without foreshortening or overlap. This is essential to enable accurate diagnosis of a stenosis (Shah 2013:230). Figure 2.4 (A) below shows an angiogram where there is stenosis within coronary artery, and complete occlusion of blood flow has occurred.

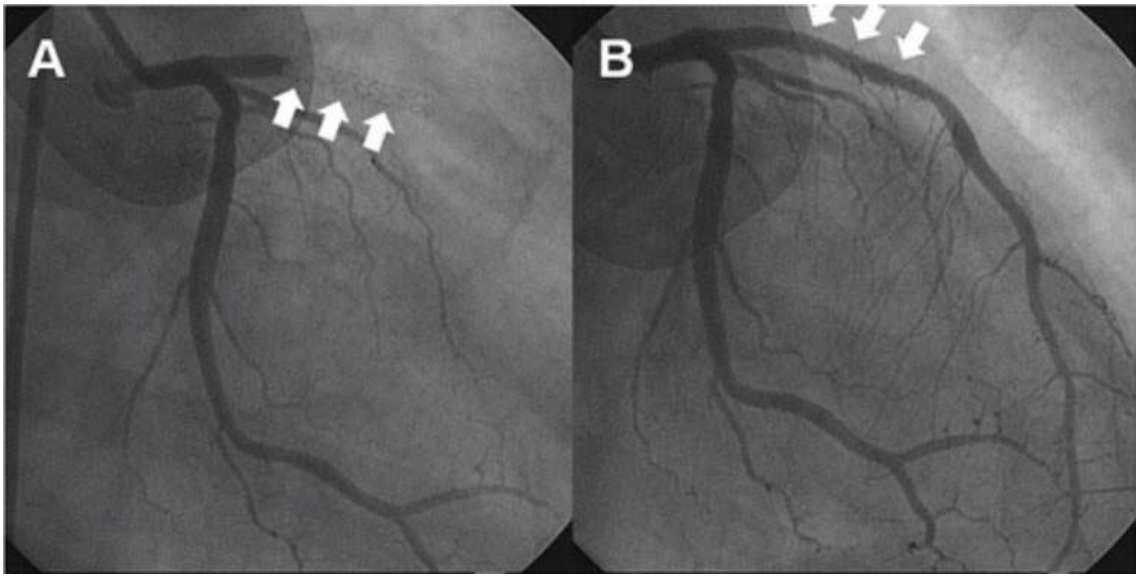


Figure 2.4: Image obtained from a coronary angiogram. (A) Angiogram showing a completely occluded coronary artery, typically associated with a heart attack. The arrows depict the point of stenosis; (B) The same coronary artery after angioplasty, showing restored perfusion (Banks 2017).

A confirmed stenosis paves the way for catheter-based surgical revascularisation to be carried out (Nicholls & Crowe 2014:51). Revascularisation after diagnosis of stenosis minimises the risk of the patient developing myocardial infarction, and this is usually combined with the angiogram examination as part of the same procedure (Baveja & Sharma 2015; Kulick 2015). The angiogram in Figure 4. (B) above shows restored blood flow to a coronary artery after revascularisation, in this case, angioplasty, has been carried out (Banks 2017).

The entire examination usually takes about 20-30 minutes. When the procedure is complete, the catheter is then withdrawn, and the puncture site of the artery is either sutured, sealed, or compressed manually to prevent excessive bleeding (Kulick 2015). CA is invasive as it involves puncturing an artery and subsequent insertion of a catheter and possibly other instruments, which may be used for treating observed stenosis. Less invasive alternatives to viewing the coronary arteries are available in the form of cardiac computed tomography (cardiac CT), as well as cardiac magnetic resonance imaging (cardiac MRI).

To perform these examinations, contrast medium is injected intravenously and the heart is imaged using the chosen modality without any need for catheterisation of the heart. However, CA performed via cardiac catheterisation still remains the 'gold standard' of viewing the coronary arteries as cardiac CT and MRI produce images of inferior quality in this regard, although they may be superior when viewing other anatomy (Weil 2014:20).

2.2.5 Risks associated with coronary angiography

CA is considered to be a safe procedure with a low associated risk of death. One of the early studies conducted over 40 years ago, which investigated mortality directly linked to CA, demonstrated a rate of 0.44%. When the same authors repeated the study just two years later, the rate had dropped to 0.17% (Oudkerk 2013:31). However, like any other invasive procedure, there are other patient-related and procedure-related risks, which are inherent to the examination. Apart from mortality, one of the risks of the procedure is myocardial infarction. This condition, also known as a heart attack, is defined as the severe compromise of blood supply to an area of heart muscle, which results in death of the affected muscle (Oudkerk 2013:31; Akram, Zaidi, Bansal & Kishore 2015:2678, Merritt, de Zoysa, & Hutton 2017:589). Arguably, the most important risk associated with CA is nephropathy, and this is discussed extensively in section 2.4. There is also the risk of patients developing a stroke owing to the procedure (Oudkerk 2013:31). Sub-optimal contrast media injection techniques may result in coronary dissection or an air embolism (Čaluk 2011:109; Oudkerk 2013:31). Iatrogenic vascular injury is also possible, and is more common when catherization is performed via the femoral artery route. The puncture site may not close fully, resulting in extraversion of blood into the surrounding perivascular space thereby forming a hematoma. This condition is known as a pseudoaneurism (Oudkerk 2013:31; Vraniæ, Haxhibeqiri-Karabdiæ & Hadžimehmedagiæ 2014:51).

Other negative consequences of the CA procedure have been reported, but are less common. These include cortical blindness, spinal cord infarction, lactic acidosis (in diabetic patients taking Metformin), radiation injury, allergic reactions, and infections (Oudkerk 2013:31).

The risks discussed in this study are by no means exhaustive, but it is worth noting that the overall risk of complications developing in patients undergoing coronary angiography is usually less than 1%, although it may be as high as 50% for some high-risk patient categories (Oudkerk 2013:31).

Owing to continual advances in equipment design, improvements in peri-procedural management, and increased experience of diagnostic centres and operators, the risk of adverse events occurring owing to CA is continually decreasing. The contrast medium used in the coronary angiography procedure is also a factor to be considered when looking at the risks of the examination because some patients develop adverse reactions when exposed to certain contrast media. This has prompted the introduction of improved contrast media, which have been shown to elicit lower levels of adverse reactions (Tavakol, Ashraf & Brener 2012:65-66).

2.3 RADIOLOGICAL CONTRAST MEDIA

Iodine is the only element that has been proven to be satisfactory as a general contrast medium that can be administered intravascularly for radiological imaging. It is opaque to X-ray radiation, and it is bound to other elements, which not only help to reduce the toxicity of iodine, but also act as carriers which increase solubility (Adam et al 2014:27). Since their introduction, iodinated contrast media have been among the most commonly administered drugs in the history of modern medicine. More than 75 million procedures with intravascular iodinated contrast media are performed worldwide each year (Siddiqi 2017; Nijssen, Rennenberg, Nelemans, Essers, Janssen, Vermeeren, Van Ommen & Wildberger 2017:1313).

Iodinated contrast media have evolved greatly over the years and the ones used now are primarily based on a chemically modified tri-iodinated benzene ring (Andreucci et al 2014:1). These contrast media are used in a multitude of imaging examinations, and may be administered intravascularly, intrathecally, directly into anatomical structures such as the urinary tract or joint spaces, and even into abnormal structures, such as fistulae. However, intravascular administration is the most common method used (Thomsen, Muller & Mattrey 2012:75).

The ideal contrast medium would be one that can achieve a very high concentration in the tissues but without producing any adverse effects. This is yet to be achieved because all contrast media are known to have adverse side effects and may cause kidney injury (Thomsen & Webb 2014:4; Hiremath 2017:291).

Several different iodine-based contrast media have been developed to date, and they are classified based on their ionicity (ionic and non-ionic), viscosity (monomers and dimers), and osmolarity (high- low- and iso-osmolar), which is measured relative to the osmolarity of blood plasma (Beckett et al 2015:1739). These differences in their physical properties exist because of the different modifications to the organic molecule to which the iodine is bound.

Over the past two decades, contrast media have evolved from ionic monomers to non-ionic monomers to non-ionic dimers, and the number of iodine atoms per molecule has also increased from one and a half to six (Solomon 2014:1). The currently used non-ionic dimers have two benzene rings, which means that the molecule size has increased from the monomers, which had only a single one, and this has the effect of increasing the viscosity. However, because these larger molecules now carry six iodine atoms each (compared to the previous one and a half), the total number of molecules required to deliver a sufficient amount of iodine for radiological imaging has decreased, effectively lowering the osmolarity of the resultant contrast medium (Solomon 2014:2). The chemical structures and some examples of the different types of contrast media that have been developed over the years are shown in the figure below:

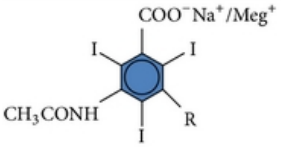
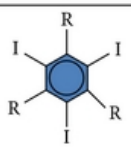
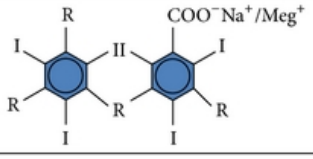
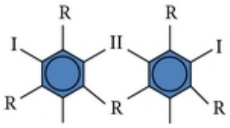
Molecular structure	Era	Examples	Comment
	1950s	Ionic monomer Diatrizoate Iothalamate	High osmolality, 5–8*x* blood
	1980s	Nonionic monomer Iopamidol Iohexol Ioversol	Low osmolality, 2–3*x* blood, improved hydrophilicity
	1980s	Ionic dimer Ioxaglate	Low osmolality, ~2*x* blood
	1990s	Nonionic dimer Iodixanol (iotrolan)	Isoosmolality Osmolality = blood

Figure 2.5: The structure of iodinated contrast media (Solomon 2014:2)

Contrast media that are ionic with high osmolarity are associated with allergic and adverse reactions in patients. Studies have shown that the numbers of patients likely to have adverse reactions may even be in excess of 50% post exposure to this class of radiological contrast media. Observed adverse reactions range from mild constitutional symptoms, which are typically self-limiting, such as chest tightness, pain, vomiting, and nausea, to more serious complications requiring intervention such as hypotension, bradyarrhythmias, and pulmonary congestion (Tavakol et al 2012:66). For this reason, high-osmolar contrast media are no longer recommended for intravascular use (Mruk 2016:161).

The high adverse reaction rates fuelled the development of contrast media which would be safer for patients. Lowering the osmolarity of contrast media has helped to achieve this (Tavakol et al 2012:66). Low-osmolar contrast media elicit adverse reactions in about 3.7% of patients who have it administered intravenously (Thomsen et al 2012:117). It was also observed after multiple studies that non-ionic contrast media produced fewer mild, moderate, and severe adverse reactions than did their ionic counterparts (Thomsen et al 2012:118).

There is strong scientific evidence that has confirmed these low incidence rates, and hence only non-ionic low-osmolar and iso-osmolar contrast agents are currently used for intravascular administration. Table 2.1 below lists some of the contrast media and their different classifications:

Contrast Medium	Trade name	Structure	Charge	Class
Diatrizoate	Renografin	Monomer	Ionic	HOCM
Amidotrizoate	Urografin	Monomer	Ionic	HOCM
Iothalamate	Conray	Monomer	Ionic	HOCM
Ioxithalamate	Telebrix	Monomer	Ionic	HOCM
Ioxaglate	Hebarix	Dimer	Ionic	LOCM
Iopamidol	Isovue	Monomer	Non-ionic	LOCM
Iohexol	Omnipaque	Monomer	Non-ionic	LOCM
Iomeprol*	Iomeron	Monomer	Non-ionic	LOCM
Iopentol	Imagopaque	Monomer	Non-ionic	LOCM
Ioxilan	Oxilan	Monomer	Non-ionic	LOCM
Ioversol*	Optiray	Monomer	Non-ionic	LOCM
Iopromide	Ultravist	Monomer	Non-ionic	LOCM
Iotrolan	Isovist	Dimer	Non-ionic	IOCM
Iodixanol	Visipaque	Dimer	Non-ionic	IOCM

HOCM *High-osmolar contrast media,* ***LOCM*** *Low-osmolar contrast media,* ***IOCM*** *Iso-osmolar contrast media.*

**The highlighted contrast media with an asterisk are the ones being investigated in this study*

Table 2.1: Iodine-based contrast agents (Thomasen & Webb 2014:6)

Although they are within the same classification, low-osmolar contrast media are a heterogeneous group of compounds, each with different physiochemical parameters. The group has contrast media with varying osmolarities, which range from 300 to 900 mOsm/kg H_2O. On the other hand, iso-osmolar contrast media have an osmolarity of 290 mOsm/kg H_2O, which is similar to that of blood (Mruk 2016:161).

Once injected intravascularly, contrast media are distributed rapidly because of high capillary permeability. They do not enter the interior of blood/tissue cells but stay within the extravascular and extracellular space, without any marked pharmacological action.

After a period of 24 hours, 98% of the contrast medium will have been excreted by glomerular filtration in patients with a normal glomerular filtration rate (Adam et al 2014:28). However, in some patients, contrast media are observed to have toxic effects on the glomeruli and results in kidney injury. This condition is known as CIN (Redahan & Reddan 2010:382).

2.4 CONTRAST-INDUCED NEPHROPATHY

2.4.1 Definition

CIN is recognised as one of the most important post-operative adverse events that can occur after CA (Golshahi, Nasri & Gharipour 2014:52). CIN is iatrogenic acute kidney injury occurring 24-72 hours after the intravascular administration of iodinated contrast media that cannot be attributed to other causes. In its milder form, the kidney injury may manifest as a slight increase in serum creatinine, but in extreme cases, it presents as severe acute kidney failure with anuria. More commonly, CIN is observed as a non-oliguric transient decline in kidney function and is asymptomatic. The decline in kidney function is often detected by an increase in serum creatinine of 0.5 mg/dL or more; or by a 25% (or more) increase in serum creatinine from baseline. This peaks on the third to the fifth day, and returns to baseline within 10 to 14 days (Andreucci, Faga, Pisani, Sabbatini & Michael 2014:1).

However, defining CIN in this way does pose potential problems owing to serum creatinine fluctuations which may occur naturally, or fluctuations which may arise because of acute medical instability. For this reason, it is better to consider the decrease in creatinine clearance as calculated by considering serum creatinine, age, body weight, and sex to produce an estimated glomerular filtration rate, abbreviated as eGFR (Andreucci et al 2014:1). Using this method as a more reliable indicator of kidney function, CIN can then be defined as having occurred when eGFR drops to 30-60mL/min, within 72 hours post-intravenous contrast exposure (Hiremath 2017:291).

The KDIGO definition of contrast-induced acute kidney injury also includes the measurement of urine output as one of the means that can be used to define CIN, in addition to the methods that have been outlined above.

By this definition, CIN will have occurred if intravascular contrast exposure results in a urine output of less than 0.5mL/kg/hour for more than six consecutive hours (Hiremath 2017:291).

2.4.2 Pathophysiology of contrast induced nephropathy

Administration of contrast media into the blood vessels results in transient vasodilation, which can be followed by several minutes of arteriolar vasoconstriction. However, within the renal circulation, this vasoconstriction can last several hours. In patients with reduced renal parenchymal mass and reduced overall nephron quantities, this vasoconstriction may result in ischemia to the renal tubules. Patients with chronic kidney disease and diabetes usually have reduced renal parenchymal mass and are particularly susceptible to this ischemic reaction (McCullough, Choi, Feghali, Schussler, Stoler, Vallabahn & Mehta 2016:1466).

In addition to the ischemic reaction, cells of the nephrons absorb the contrast media, causing them to swell, and blebbing occurs, followed by cell death. As such, the contrast media is not filtered out of the body, but rather remains in the kidneys after the CA procedure has long been completed. This high concentration of contrast media within and surrounding renal tubular cells results in cellular toxicity and loss of cell membrane integrity. In some patients, the contrast medium has been shown to persist in the kidneys for as long as eight days post-administration (McCullough et al 2016:1466).

This combination of ischemic and chemotoxic injury to the nephrons triggers a process known as tubuloglomerular feedback, which signals the glomerulus to decrease filtration and thereby cause an increase in plasma creatinine. A significant decrease in filtration will increase the levels of plasma creatinine, which can be detected clinically within 24-48 hours (McCullough et al 2016:1466). Figure 2.6 shows an illustration of a patient whose heart is catheterised for the purposes of CA, and receives iodinated contrast media, which then injures the kidneys.

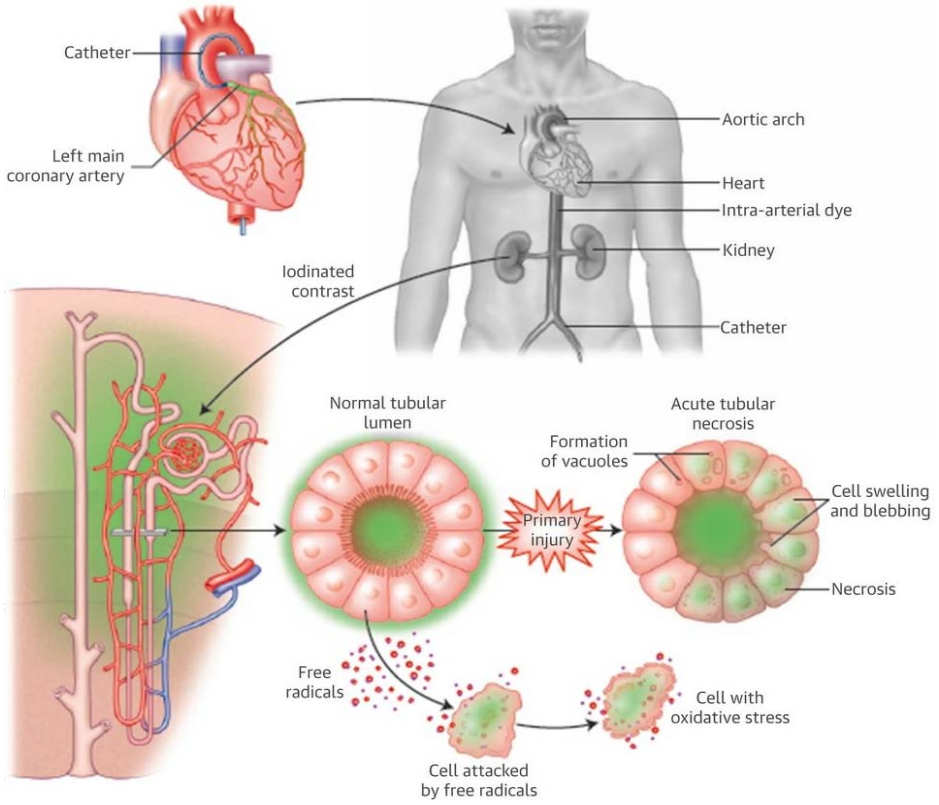


Figure 2.6: The development of contrast-induced nephropathy after coronary angiography (McCullough et al 2016:1468)

2.4.3 Incidence of contrast-induced nephropathy

Incidence refers to the number of new cases of a disease that occur (Brunicardi, Andersen, Billiar, Dunn, Hunter, Matthews & Pollock 2014:274). It is frequently linked to epidemiology, which is the study of disease distribution within populations, and the factors affecting or determining the distribution. Epidemiology is based on the premise that distribution of disease is not random, but rather there are factors and characteristics that predispose us to, or protect us from certain conditions (Gordis 2013:2).

The worldwide incidence of CIN has increased in recent years owing to several factors. One of the major reasons is that the number of contrast media examinations performed is continually increasing because of improvements in accessibility to healthcare.

In addition, more patients who are classified as being at a high-risk of developing adverse reactions to contrast media are having examinations done, despite the possible dangers of side effects developing. Yet another reason is that patients who are exposed to contrast media are increasing in age, in line with the global increase in mature populations (Quiros, Sánchez-González, López-Hernández, Morales & López-Novoa 2013:493; Halter, Ouslander, Studenski, High, Asthana, Woolard, Ritchie & Supiano 2016:57).

About 10-12% of acute kidney injury which occurs in the hospital setting can be attributed to CIN, making it a fairly common condition (Redahan & Reddan 2010:382). It is the third most common cause of hospital-acquired acute kidney injury (Golshahi et al 2014:52). The observed incidence of CIN varies greatly depending on factors such as the population under study, definition used to classify patients as having CIN, as well as the type of contrast medium used. However, it ranges from less than 5% in patients exhibiting normal kidney function prior to contrast media exposure, to over 50% in some high-risk groups, which are discussed further in section 2.4.5 (Redahan & Reddan 2010:382; Andreucci et al 2014:2). There are preventative measures that are frequently employed in imaging centres to reduce the incidence of CIN, such as prophylactic intravenous hydration, or the administration of different prophylactic drugs. This makes it difficult to establish the true incidence of CIN as the baseline incidence in an untreated population is unknown. In addition, it effectively means that the extent to which prophylaxis is effective as a means of reducing the incidence of CIN is also not truly known (Nijssen et al 2017:1314).

2.4.4 Significance of contrast induced nephropathy

CIN is reversible in most cases, and can easily go undetected because patients are frequently asymptomatic, making it seem clinically inconsequential and insignificant. However, it should by no means be considered a trivial complication. Research shows a strong correlation (adjusted Odds Ratio 18.1, Confidence Interval 10.7-30.6, $P<0.001$) between CIN and poor patient outcomes including higher mortality rates (Lefel et al 2016:2; Grossman et al 2017:274-280).

According to a large retrospective study involving 16000 hospitalised patients who were all exposed to intravenous iodinated contrast media, the risk of in-hospital mortality in subjects who developed CIN was 34% while it was 7% for those who did not have the condition (McCullough 2008:1420).

CIN is linked to an increased incidence of chronic kidney disease, and some patients may develop irreversible kidney injury, thereby necessitating dialysis (Wang, Zhang, Yue, You & Zeng 2016:2957). After a period of two years, the mortality rate rose to 81.2% for patients who required dialysis post-CIN development (McCullough 2008:1420). Quiros et al (2013:493) suggested that an association might exist between CIN and later cardiovascular events.

Patients who develop CIN suffer from prolonged hospital stays and hence increased medical costs (Lian et al 2017:197). In addition to increased length of hospital stay, studies have also shown that these patients have a more complicated clinical course (McCullough 2008:1420). Subramanian, Tumlin, Bapat and Zyczynski (2007:119) calculated the average cost of treating CIN at over R154 000 ($11 000) per patient over the duration of a year. The same authors estimated that annually, about R63 billion ($4.5 billion) is spent in the USA and Europe treating the sequelae of CIN. Owing to the rise in the usage of intravenous contrast media as well as increases in high-risk populations who undergo interventional procedures, the incidence of CIN and associated costs of treating the condition are only set to increase.

There are no effective therapies that can be used to treat CIN, and hence prevention is the best strategy (Wang et al 2016:2960). One of the commonly used strategies used in the prevention of CIN is to identify risk factors, which are associated with increased occurrence of the condition, and making decisions based on a patient's risk profile.

2.4.5 Contrast-induced nephropathy risk factors

Pre-existing kidney injury is the primary predisposing factor for the development of CIN. Diabetes and increasing age-particularly for patients above 75, are also known risk factors.

These factors are inherent in the profile of a patient and are non-modifiable, but modifiable risk factors also exist, such as the type, and volume of contrast medium used (Kaul 2012:35). CIN risk is observed to increase with the usage of high-osmolar contrast media, and the same is true when larger volumes of contrast media are administered, such as when performing CA. The CA examination typically requires large volumes of contrast media to produce images of satisfactory diagnostic quality, and hence this imaging examination has the highest observed incidence of CIN (Meinel et al 2014:6).

Table 2.2 shows a summary of commonly encountered modifiable and non-modifiable risk factors:

Modifiable Risk Factors	Non-Modifiable Risk Factors
Contrast volume	Diabetes, multiple myeloma
Patient hydration	Chronic kidney disease
Type of contrast medium used	Shock, hypotension
Recent contrast administration	Advanced age
Concomitant nephrotoxic agents	Congestive heart failure

Table 2.2: Common pre-procedural risk factors for CIN (Kaul 2012:35)

The effect of these risk factors is additive. This means that the risk of CIN developing rises sharply with the increase of simultaneously present risk factors. For patients with chronic kidney disease and who are on dialysis, the likelihood of developing CIN is approximately 50% (McCullough 2008:1423).

2.5 CONTRAST MEDIA TYPES AND CONTRAST-INDUCED NEPHROPATHY

The contrast medium used is a modifiable risk factor for the development of CIN, as can be seen in Table 2.2. Because of this, a plethora of research attention has been focused on the types of contrast media used for coronary angiography, and how safe they are. Osmolality has generally been viewed as the most important chemical property of contrast media affecting renal safety.

High-osmolar contrast media are no longer approved to be injected intravascularly owing to increased levels of adverse reactions, and so only low- and iso-osmolar contrast agents are used for this purpose in medical practice (Mruk 2016:161). Many studies predominantly compare the safety levels of contrast media between the different classes, namely, low- and iso-osmolar contrast media. However, a consensus has yet to be reached over which class of radiopharmaceutical is safer owing to conflicting results that are frequently obtained (Bucher, Cecco, Schoepf, Meinel, Krazinski, Spearman, McQuiston, Wang, Bucher, Vogl & Katzberg 2014:6; Biondi-Zoccai, Lotrionte, Thomsen, Romagnoli, D'Ascenzo, Giordano & Frati 2014:375).

In an ideal situation, only the safest contrast medium should be administered to patients, but with the existing lack of consensus over which low-osmolar or iso-osmolar contrast medium satisfies this condition, other factors may become more important, such as the associated cost and ease of use. Cernigliaro et al (2016:902) estimated annual savings of up to R1 400 000 (US$100 000) at a single institution if they were to switch from using the more expensive, iso-osmolar contrast medium iodixanol to low-osmolar iohexol. Iso-osmolar contrast agents also tend to have much higher viscosities, which makes them more difficult to inject. This may make low-osmolar contrast media preferable (Tomsick, Foster, Liebeskind, Hill, Carrozella, Goyal, von Kummer, Demchuk, Dzialowski, Puetz, Jovin, Morales, Palesch, Broderick, Khatri & Yeatts 2015:2).

2.6 CONTRAST-INDUCED NEPHROPATHY IN AFRICA

Extensive research on CIN has been carried out predominantly in developed countries, with very few studies performed within the African continent (Banda, Duarte, Dickens, Dix-Peek, Muteba, Paget, Mngomezulu, Manga & Naicker 2016:699). However, it is worth noting that for most papers that investigated CIN using data from patients who had medical examinations undertaken in Africa, the observed rates of CIN are higher than those for similar populations within the developed world. Okoye, Ojogwu, Unuigbe and Oviasu (2013:23) conducted a study at a centre in Nigeria and attained a CIN rate of 38.4% for an in-patient population, higher than their expected percentages of 3.3%, 1.4%, and 6.6%, which were obtained from comparative studies conducted in developed countries.

Banda et al (2016:702) measured CIN rates at a South African centre, and they too found that their obtained CIN rate of 16.4% was higher than comparative studies performed in first-world countries (Banda et al 2016:702). A prospective study in Sudan similarly produced a high CIN percentage of 16.9% (Shigidi, Ahmed, Suliman & Taha 2013:73).

The authors of these different studies did note that their observed incidences of CIN were higher. As a result, they suggested that differences in the definition of CIN, high numbers of subjects with existing comorbidities in their patient populations, and inconsistencies in the administration of prophylactic measures at their respective imaging centres may have been responsible for this anomaly (Okoye et al 2013:23; Banda et al 2016:702). However, although yet to be investigated, it is also a possibility that CIN has a higher incidence within African populations and therefore deserves more attention than is currently given to the condition on the African continent as a whole.

2.7 CONTRAST INDUCED NEPHROPATHY IN SOUTH AFRICA

A literature search for studies that detail the impact of CIN in South African institutions revealed that almost all studies base their knowledge on data from developed countries, and only a single primary study (Banda et al 2016) was identified where the patient population was from a South African institution. No similar studies were identified, and any other identified studies that mentioned CIN only did so briefly.

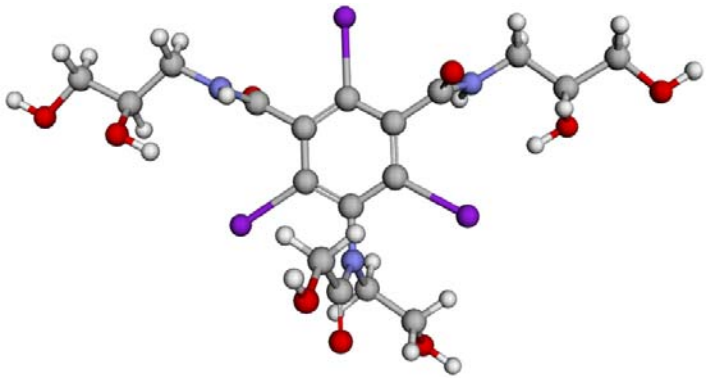
2.8 IOVERSOL AND IOMEPROL USE

At most South African institutions, Ioversol and Iomeprol are the available radiological contrast media which are used for coronary angiography, and they are typically used interchangeably. Ioversol and Iomeprol are both within the same class of low-osmolar, non-ionic radiological contrast media (Seeliger et al 2014:15). In their research, Căldăraru et al (2014:711) noted that almost no literature exists which compares the safety of these two contrast media in terms of nephrotoxicity. As mentioned in section 2.3, even within the same class of contrast media (low-osmolar, non-ionic), the various agents have differing physiochemical properties, osmolarities and viscosities.

These physiochemical properties are the ones that ultimately determine whether the renal tubules are able to handle, or will be harmed by the administered radiological contrast medium (Seeliger et al 2014:15). This means that all the radiological contrast agents in use have differing levels of nephrotoxicity, and Ioversol and Iomeprol are no exception. Using this logic, it may be presumed that Ioversol and Iomeprol have differing safety profiles, and therefore may not necessarily be interchangeable as one may be safer for use than the other. Their individual properties and chemical profiles are described below.

2.8.1 Ioversol (optiray)

Ioversol is a radiological contrast agent that was released for distribution by the French pharmaceutical company, Guerbet in 1989 (Guerbet [s.a.]). It is a non-ionic molecule that contains 47.2% organically bound iodine (Mallinckrodt 2015:1). Each Ioversol molecule contains three iodine atoms that are responsible for its radiological opacity, and it is highly water soluble (Wang & He 2011:295).



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Purple = iodine; Blue = nitrogen; & Red = oxygen atoms

Figure 2.7: Three-dimensional chemical structure for Ioversol (Drugbank 2018)

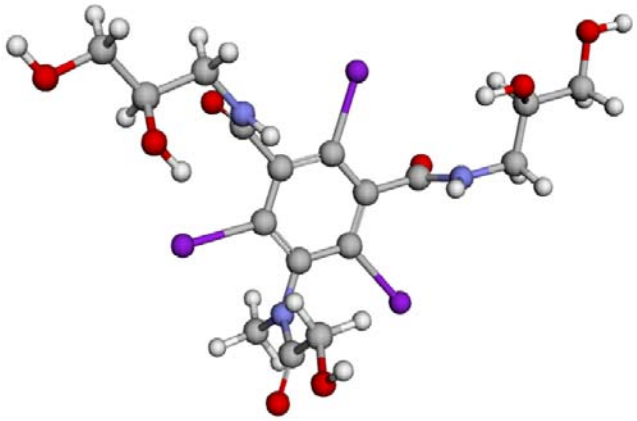
Figure 2.7 above shows the spatial atomic structure of an Ioversol molecule. To make a solution that can be used in the clinical setting, Ioversol is bound to tromethamine as a buffer and the chelating agent, edetate calcium disodium as a chemical stabiliser. These chemicals prolong the shelf life and increase chemical stability of the contrast medium. It is sterilised by autoclaving, and no preservatives are added.

The resulting solution is a radiocontrast formulation sold and distributed under the trade name Optiray, and it is manufactured in four different concentrations, namely Optiray 350, 320, 300, and 240. Optiray is a clear, colourless to pale yellow solution and its osmolarity is 1.8 to 2.8 times that of blood plasma, depending on the concentration used (Mallinckrodt 2015:1).

The different concentrations of Optiray have different applications, with certain concentrations being optimal for use in specific imaging modalities. As an example, some concentrations are ideal for paediatric administration, while others are ideal for adult peripheral arteriography. For the purposes of coronary angiography in adults, Optiray 350 and 320 are indicated for use. The importance of hydration is underscored when using Optiray and this must be maintained prior to and following intravascular administration (Mallinckrodt 2015: 5).

2.8.2 Iomeprol (iomeron)

The radiocontrast medium Iomeprol was developed by pharmaceutical giant Bracco at their Milan, Italy laboratories in 1995 (Radiological Sciences Dictionary, 2009 sv “Iomeprol”; Achenbach, Paul, Laurent, Becker, Rengo, Caudron, Leschka, Vignaux, Knobloch, Benea, Schlosser, Andreu, Cabeza, Jacquier, Souto, Revel, Qanadli & Cademartiri 2017:822). It is a monomeric, non-ionic, tri-iodinated, water soluble radiological contrast medium (Andreucci 2002). The molecular structure for Iomeprol is depicted in Figure 2.8 below.



Purple = iodine; Blue = nitrogen; & Red = oxygen atoms

Figure 2.8. Three-dimensional chemical structure for Iomeprol (Drugbank 2017)

Iomeprol is combined with trometamol, hydrochloric acid, and water to make a solution suitable for intravenous for injection that is known as Iomeron (Medsafe 2006:1-2). Unlike other contrast media formulations such as Optiray, Iomeron does not require a chelator to remain stable. Chelating agents are normally added to contrast media to mask trace levels of metals such as iron, which may initiate de-iodination and thereby shorten the shelf life of the product (Lanzer & Lipton 2012:100). This is a notable advantage for Iomeprol because an important side effect of the chelator edetate calcium disodium, which is used as a stabiliser in the manufacture of Optiray, is its potential for nephrotoxicity (Gahart & Nazareno 2017:525). Section 2.4.2 discussed the pathophysiology of CIN, and how intravascular administration of contrast media initially causes vasodilation, which is followed by vasoconstriction that may last for hours within the renal circulation and eventually result in an ischemic reaction. This reaction may be owing to the presence of chelating agents. When considering the volumes used for diagnostic imaging procedures such as CA, the other compounds added to Iomeprol, namely, trometamol and hydrochloric acid, have no known renal side effects (National Centre for Biotechnology Information online [s.a.]).

Iomeron easily withstands heat sterilisation as well as prolonged room temperature storage (Patheon 2015:1). It is identified as a clear, colourless solution, which is manufactured in concentrations of 300, 350, and 400mg iodine/ml. All three concentrations may be used for coronary angiography in adults (Medsafe 2006:1-2).

It is also worth noting that Iomeron's 400mg iodine/ml formulation is currently the highest iodine concentration available for contrast media on the market. This is useful for providing stronger radiological contrast enhancement, and thereby improving visualisation of the smaller peripheral arteries. In addition, stronger contrast enhancement allows for lower volumes of contrast media to be administered without compromising the resultant image quality. As stated in section 2.4.5, larger volumes of contrast medium increase the risk of CIN, making this high iodine formulation advantageous by permitting the usage of lower volumes.

Another unique quality of Iomeron is that when compared to other non-ionic contrast media, it exhibits the lowest viscosity at all concentrations.

This is important because reduced viscosity translates to improved glomerular filtration, and consequently, improved renal tolerance of the contrast media. Even at higher concentrations, Iomeron is able to maintain a low viscosity because viscosity is dependent on molecular features, which remain unaltered despite varying the concentration (Esposito 2013:3). As with all contrast media, hydration of the patient should be maintained prior to, and post-administration of Iomeron (Medsafe 2006:1).

2.9 THE NEED FOR SYSTEMATIC REVIEWS

The increasing number of research papers addressing the problem of CIN in CA patients has resulted in a vast wealth of valuable information. However, it is impractical to expect health care practitioners to find, appraise, interpret, and incorporate into practice all the information available to them, hence the need for systematic reviews (Green, Higgins, Alderson, Clarke, Mulrow & Oxman 2011:121). A systematic review is a review of existing research, which uses explicit, accountable, and rigorous research methods. It brings together the findings of primary research, and is a second level of analysis (Gough, Oliver & Thomas 2017:2). Although individual studies may have been undertaken with care to ensure the accuracy of findings, it is possible that by chance, atypical findings will have been obtained and reported. For this reason, it is much better to base medical decisions upon all the available and reliable research which has been undertaken within that area, as opposed to an individual study, or a small group of studies, making a systematic review ideal.

2.10 CONCLUSION

This chapter explored the development of angiography from a historical perspective, briefly explaining how the procedure has evolved up until present day. The development of contrast media was outlined, as well as why it is essential for use in CA, and its increasing prevalence of use in the clinical setting. This then led to a discussion of the side effects of contrast media, the chief one being CIN. This condition is closely linked to the type of contrast medium used. Unfortunately, it is unclear which contrast medium elicits the lowest levels of CIN owing to heterogeneity in studies investigating this condition.

The end of the chapter notes the paucity of literature focused on CIN on the African continent, and how the few primary studies carried out on African populations find that the prevalence is higher than expected using data from comparative studies from developed countries. In South Africa, Iomeprol and Ioversol are the contrast media of choice in many centres. They are used interchangeably despite them having different physiochemical properties, hence the need to investigate which of these two commonly used contrast media is safer for use when performing coronary angiography. This is best done by means of a systematic review because such a method pools together all the available data pertaining to the subject at hand, and produces information that is more reliable than an individual study.

The following chapter will discuss how the research was designed and the associated methods used to address the research problem, as well as related topics.

CHAPTER 3

RESEARCH METHODOLOGY

3.1 INTRODUCTION

The previous chapter discussed the available knowledge relating to CIN, exploring the different aspects relating to the condition such as its incidence and pathophysiology, as well as a discussion on the properties of the contrast media which will be reviewed in this study. This chapter focuses on the design of the research study and methodology that was used to address the research question and fulfil the stated aims.

The purpose of this research study was to search literature and determine the extent to which Ioversol and Iomeprol elicited CIN in adult patients who underwent CA examinations in order to make recommendations for improved clinical practice. To this end, this chapter describes the study design, target population, participant selection criteria, data collection methods, analysis of the collected data, and the ethical considerations pertinent to this research study.

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement was developed for systematic reviews and meta-analyses of trials that use aggregate data, generally extracted from published reports (Stewart et al 2015:1657). It is an internationally recognised standard for the reporting of systematic reviews and meta-analyses for healthcare interventions, and was used to direct the writing of this research report. Compliance with this standard ensures the completeness and transparency of a systematic review, and hence the researcher adhered to the outlined guidelines when this research was carried out. A completed PRISMA checklist is included in the appendices as evidence of adherence to the stated requirements (Appendix 3).

3.1.1 Protocol

The first stage in conducting a systematic review involves developing the aims and methods, and this is done in advance of identifying the relevant literature. The research question is defined, the scope of research is outlined, inclusion and exclusion criteria, methods for quality appraisal, and synthesis of the data is specified. This plan for the intended research is known as the review protocol (Torgerson 2003:26). Gough, Oliver and Thomas (2017:7) explain that a protocol is important for the avoidance of bias and maintenance of scientific rigour.

In this systematic review, a protocol with methods of analyses, inclusion, and exclusion criteria was designed in advance, assessed and approved by the Unisa Scientific Review Committee and the Higher Degrees Ethical Committee.

3.2 RESEARCH METHODOLOGY

The methodology of research describes the reasons that underlie the choice and usage of specific methods during the research process. In addition, it describes how the researcher will go about acquiring the knowledge they desire (Kuada 2012:59). Furthermore, Polit and Beck (2014:385) describe methodology as the steps, procedures and strategies that are used for the gathering and analysis of data. There are two main types of research methodology, namely, qualitative and quantitative, although a third type, known as mixed methods research, is now widely recognised (Gray, Grove & Sutherland 2016:192). This research adopted a quantitative, systematic review approach. Quantitative research counts or measures in order to answer a research question (Gray et al 2016:37). Such a method was ideal for this research because numerical data on patient numbers exposed to contrast media were used to determine which contrast medium was safer for use in CA patients.

The research methodology should not be confused with the research methods. The methods employed during research are the various techniques, indices, and tests, and so on, which a researcher employs in the research. On the contrary, the methodology is more concerned with which of these techniques and tests are relevant, and the reasons and implications of using each technique and test (Kumar 2014:5).

In essence, the scope of the research methodology is wide, and it includes in it the research methods, as well as the logic and explanations behind the choice of methods selected (Kumar 2014:5). In this study, a systematic review method was selected, and this is described in the section that follows.

3.2.1 Systematic review method

A systematic review is defined as a research method that is used to make sense of large bodies of information, and this is done to answer the question of what works, and what does not (Jesson et al 2011:12). In addition, Khan et al (2011:1) explain that a systematic review entails identifying relevant studies, appraising their quality, and then using a scientific methodology to summarise the findings obtained. This method of enquiry has gained importance owing to the large volumes of new research studies that are constantly being released and made available to health-care practitioners, policy makers, and researchers. Systematic reviews tackle this problem of information overload by condensing the available knowledge on a subject so that interested parties may know what practices are currently useful (Jesson et al 2011:105). In practice, there are five key steps that are followed when employing this method of scientific enquiry, and these are outlined in Figure 3.1 below.

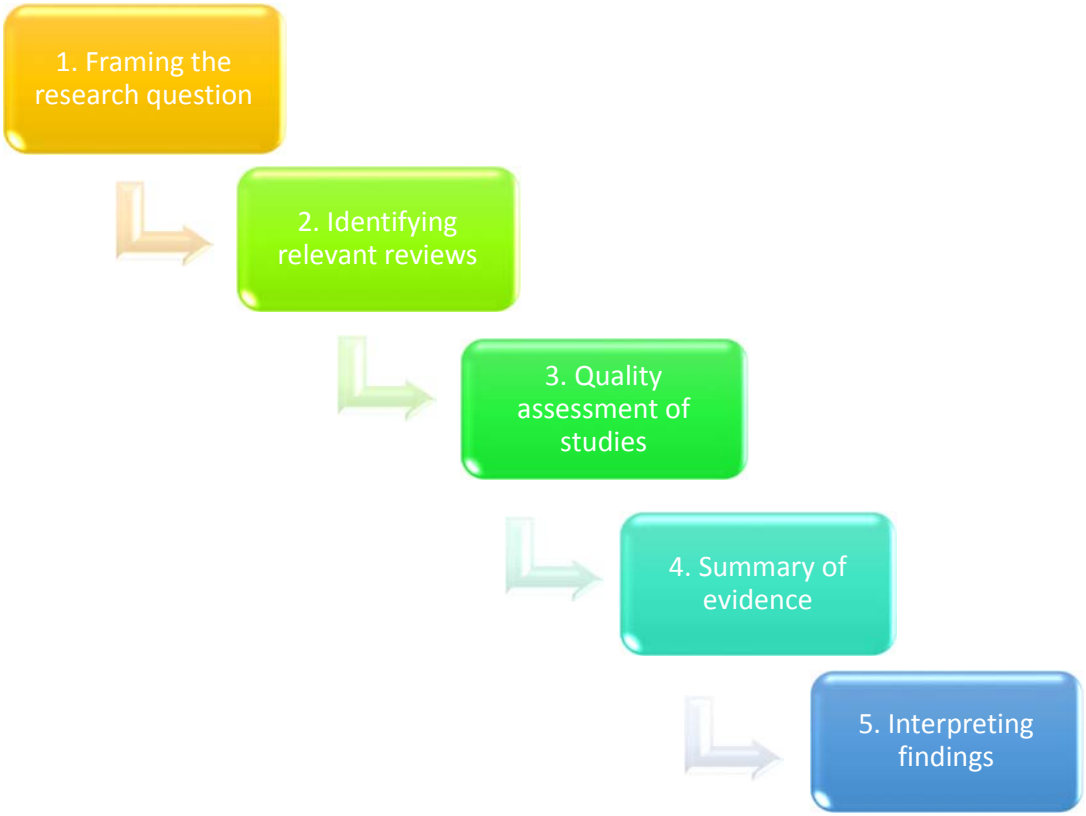


Figure 3.1: Steps involved in conducting a systematic review.
(Adapted from Khan et al 2011:2)

The steps outlined in Figure 3.1 above were followed in order to prepare this research document. First, the research question was framed and stated in a clear, concise sentence. The research question for this study was: *'What is the incidence of contrast-induced nephropathy in randomly-selected coronary angiography patients when Iomeprol is used versus when Ioversol is used?'* Along with the question, the rationale was explained, and the aims and objectives of the study were stated.

Next, a thorough literature search was done to identify potentially relevant peer-reviewed articles, which investigated the prevalence of CIN in adult patients when Ioversol and/or Iomeprol were the contrast media used to perform CA examinations. This was an essential step that made the review a systematic one (Khan et al 2011:5).

The third step was to assess quality and suitability for inclusion of the studies based on predetermined criteria. These criteria and quality assessment methods are given in detail in sections 3.3.2.3, 3.3.2.4, and 3.5.1.

In step four, studies which had been deemed to be of a suitable quality and which were of relevance to the study were combined for statistical analysis to be performed, and the results were summarised and presented in visual form by means of graphs and tables before being interpreted.

In the last step, the researcher drew conclusions regarding the safety profiles of Ioversol and Iomeprol when administered to adults for the CA procedure, and gave a detailed interpretation. The design of the research will now be considered.

3.3 META-ANALYSIS RESEARCH DESIGN

David and Sutton (2004:134) describe research design as a logical framework upon which research is conducted. It allows the researcher to gather evidence that will enable the answering of a research question. Its role is to ensure that the data collected enable the researcher to answer the original research question as unambiguously as possible. A research design may also be described as the strategy of enquiry that provides direction for the procedures that must be followed when conducting research (Creswell 2014:12). This research adopted a meta-analysis design to address the study question of which contrast medium was safer than the other. A meta-analysis is a quantitative, formal and epidemiological type of study design, which is used for the systematic assessment of previous research so as to derive conclusions regarding that particular body of research. The outcomes produced by meta-analyses may include more precise estimates regarding the effects of a treatment, or risk factors of a disease as compared to the individual research studies, which contribute to the pooled analysis (Haidich 2010:30).

3.3.1 Comparative design

A comparative design compares data from different groups (Grove et al 2014:216). LoBiondo-Wood and Haber (2014:32) suggest that comparative designs may be explained by looking at dependent and independent variables. If Y is the dependent variable and X is an independent variable, a comparative design looks at the difference in Y between people who have been exposed to X_1 and X_2 variables. By this explanation, Ioversol and Iomeprol can be identified as the independent variables X_1 and X_2, and the development of CIN was the dependent variable, Y. The comparative nature of the research design means the research study compared the effects of exposure to Ioversol (X_1) and Iomeprol (X_2) on the prevalence of CIN (Y) development in study participants.

3.3.2 Population

A population is defined by Hartas (2015:67) as a group of individuals who share the same characteristics that are of interest to the research study. For every study, there is a theoretical population, also known as the population universum as well as a pragmatic, or target population (Hartas 2015:67). These concepts are explained below.

3.3.2.1 Population universum

The population universum is defined as a complete set of elements with specified characteristics, which are of interest to the researcher (Hulley, Cummings, Browner, Grady, & Newman 2013:55; Rasinger 2013:45). For this research, all peer-reviewed studies, which investigated incidence of CIN development in adult CA patients when Ioversol or Iomeprol were the contrast media used formed the population universum.

3.3.2.2 Target population

The target population is the population for whom access is feasible after the scope and limitations of the study have been considered (Hartas 2015:67).

When the population universum for a study has been identified, owing to resource limitations, it is not always possible or feasible to access every member of the population who possesses the characteristic of interest (Hartas 2015:67). For this reason, the research then needs to be carried out with the target population.

In this research study, it was not feasible to include studies that were conducted in other languages but did not have an official English translation. In addition, the researcher had access to limited electronic databases, which impacted the researcher's database selection. Therefore, the target population was comprised of articles within the population universum, which were written in English or had an official English translation, and which were accessible to the researcher. Once the target population had been identified, it was necessary to define desirable parameters of articles, which would find relevance within this study.

3.3.2.3 Eligibility criteria

The following criteria were specified *a priori* to determine which studies would be relevant for incorporation into this research:

- Peer-reviewed studies performed on CA patients aged 18 years or above – This research focused exclusively on an adult population and individuals at least 18 years or older in this study satisfied this condition.
- Studies focused on standard CA examinations, with or without PCI, and without modification to departmental protocol – No studies involving alteration to technique/protocol, as may have been necessitated by certain patient conditions or co-morbidities were considered. This was done to ensure uniformity and comparability of the examinations and attempt to control for confounding factors. PCI patients were included because stenoses identified by CA are typically treated by this procedure, as a continuation of the CA examination (Zhou & Brahme 2008:137).
- Studies where either Ioversol or Iomeprol were administered for CA were included in this research as these are the two contrast media whose safety profiles are being investigated.
- Studies performed on randomly selected patient populations considered to be in general good health prior to the CA exam were considered.

- Studies where CIN was the primary end-point used to ascertain the safety of the contrast media administered.
- Studies that mentioned eGFR as an indicator of kidney function.
- Data sourced from journals from the following databases: PubMed Clinical Queries, Science Direct, CINAHL, Medline, and Scopus. No time restriction was placed, meaning all relevant articles were considered from inception of the databases up till the date of the literature search.
- Studies performed from inception of databases to the last search date, which was 11 April 2018.

3.3.2.4 Exclusion criteria

Studies that were undesirable for the purposes of this study and the explanation for their lack of suitability are detailed below.

- Studies where non-standard prophylactic measures against CIN were used were excluded. Standard CIN prophylactic treatment is hydration prior to, during, and after the CA procedure (Medsafe 2006:1). Additional or alternative prophylaxis may alter resultant obtained CIN rates.
- Studies using data from patients below the age of 18 years – these patients were not classified as adults in this study and were beyond the focus of this research.
- Studies performed exclusively on patients who were critically ill, unstable, or with a known pathology. Critically ill and medically unstable patients on average receive more medication and interventions than their healthier counterparts. Rear et al (2016:638) point out that the effect of certain medications on the development of CIN is not well documented in literature, hence the exclusion of such records.
- Studies were Ioversol and Iomeprol were not used were excluded because this study is focused on the aforementioned contrast media.
- Any studies with incomplete, poor quality or dubious data were omitted from this research as the contents of such records were potentially misleading and prone to introduce errors into the research findings.

- Studies conducted in languages other than English without an official English translation were excluded.
- Data from books, case reports, other print media, non-medical websites, or other electronic databases not mentioned above were not included in order to preserve the overall scientific integrity of the research, and studies that were inaccessible to the researcher were also excluded.

3.3.3 Sampling

Once the population has been defined, a sample may be selected. A sample is defined as a subset of the population, selected to be representative of the whole in situations where the population is too large to effectively study owing to resource constraints. However, if possible, the best strategy is to investigate the entire population (Acharya et al 2013:330).

In this study, all available peer-reviewed articles whose content was deemed relevant as specified within the eligibility criteria were selected for inclusion. This was necessary because of the use of the systematic review method, which aims to be as comprehensive as possible and representative of all relevant literature within the chosen field (Siddaway [s.a.]:5).

3.4 INFORMATION SOURCES

Information sources comprise of all physical, written, oral, and figurative sources, which enables knowledge of the nature, specificities, and meaning of a subject (The Georgia State University World Heritage Initiative [Sa]:1). Data for this study were sought from electronic databases, which had peer-reviewed articles related to the research topic. Information was retrieved from the following databases: Science Direct; PubMed Clinical Queries; Medline; Scopus; and CINHAL. Any titles identified from the reference lists of an article which appeared to be of relevance were also included. No publication date restriction was imposed on the search, meaning all relevant articles since database inception up to and including the last search date were included. The final database search was performed on 11 April 2018.

3.4.1 Information search

To find the relevant articles on these databases, the keywords “Iomeprol,” “Ioversol,” “nephropathy,” “coronary angiography,” “eGFR,” and “kidney injury” were used. Synonyms and similar or alternative words to the key words were also used, such as “Iomeron,” “Optiray,” “cardiac catheterization,” and “renal injury.” The similar key words were grouped within parentheses and combined using the Boolean operator OR, and different search concepts were separated by the operator AND. The Boolean operator NOT was avoided to prevent elimination of potentially useful studies. Where applicable, the truncation symbol (*) and the wild card symbol (?) were used in the different databases to search for all word and spelling variations of the key concepts. The search techniques and concepts were accordingly modified to suit the parameters of the different databases. No restriction on the years in which studies were published was imposed on the search results.

An example search that was performed on Medline using the EBSCOhost interface on 10 April 2018 covering the period from 1994 to 2016 utilised the search string depicted below:
(coronary angiography OR coronary angiogram OR coronary catheterisation) AND (nephropathy OR kidney injury OR renal injury OR cin OR ciaki OR renal OR kidney) AND (iomeprol OR ioversol OR iomeprolum OR iomeron OR iomeprolo OR imeron OR optiray OR loversol OR 8777-40-2 OR loversolum OR mp-328). To ensure that a comprehensive search was carried out, assistance in searching was sought from the institutional librarian, who peer-reviewed the search strategy.

3.4.2 Study selection

The results obtained after this keyword search were converted into BibTeX file format. Thereafter, they were imported into Zotero (version 4.0.29.17, George Mason University, USA) citation and bibliography software for ease of management. They were screened manually by examining titles for suitability for inclusion in the study as per eligibility criteria detailed in sections 3.3.2.3 and 3.3.2.4. A Microsoft Excel spreadsheet was utilised in addition to Zotero to further organise the data and record the search parameters and numbers of articles eliminated or included.

The abstracts/full text articles of studies that remained after this initial screening were analysed to further check for suitability for inclusion in the review. Research articles that were deemed to be unsuitable were eliminated. The full-text articles that appeared to be suitable were then downloaded from the respective databases and assessed for quality. This is discussed in the following section.

3.4.3 Data extraction process

Data extraction involves the retrieving of information that is specific to the research objectives and purpose for further processing such as clustering, or segmentation analysis (Grove et al 2015:47; Mena 2016:77). The actual steps of extracting data are specific to each study, but in most cases, unstructured data is extracted for analysis with a structured tool. This may involve a transformation of the extracted data, and possibly the addition of metadata (Mena 2016:77).

A data extraction form was used to extract, then organise and appraise the final data collected. The form was adapted from the template by Cochrane: Data collection form for intervention reviews: RCTs and non-RCTs (2014). This study was not limited to randomised controlled trials (RCTs), but all peer-reviewed study types were eligible. Therefore, RCT-specific sections of the template were either modified or excluded. The data collection form was pilot-tested on two included randomly-selected studies and adapted accordingly before it was used in this study. It is included as Appendix 2. The form was used to obtain information from each article, and extracted information is detailed in the section that follows.

3.4.4 Data items

Data were extracted from each included article by means of the data collection form. The PICOT method was adapted and used to define the important data items for each study. PICOT is a structured approach that looks at the characteristics of a research question, and the acronym is expanded as follows.

P – Population of interest; I – Intervention that is applied to the population; C – Comparison for the intervention; O – Outcome that will be studied, based on the intervention; T – Time frame (Roussel 2015:369). An extra 'I', 'C' and 'S' for Identification, Conflict of interest, and Study type respectively were added by the researcher to make it PIICCOTS. These parameters were adapted to the domains of this study as explained below:

- Population: The size of the population, average age, comorbidities, inclusion, and exclusion criteria.
- Identification: The first author, year of publishing, and country were recorded.
- Intervention: Whether CA or PCI or a combination of the two were performed, average volume of contrast medium used, which contrast medium / media were used.
- Comparison: The contrast media which were used as comparators within the studies, where applicable.
- Conflict of interest: Any declared funding sources, or other stated conflicts of interest.
- Outcomes: The observed rates of CIN, any other outcomes determined by the different studies which were relevant to this research.
- Time: The time at which the biomarkers which were used to determine the presence of CIN were measured.
- Study type: The design of the study adopted by the authors.

3.5 DATA ANALYSIS

Data analysis reduces, organises and gives meaning to the information collected during the research process. Quantitative research has a variety of data analysis techniques that may be employed, but the choice of analysis methods employed depends on the objectives and questions posed by the research (Grove et al 2015:47). This step of the research process involves looking for patterns, differences, and other features that may assist in addressing the research problem (Downey 2014:2). Techniques for analysing data employed in this study are as specified below.

3.5.1 Risk of bias in individual studies

The PRISMA statement requires that individual studies which are included in a systematic review be assessed for risk of bias (Moher, Liberati, Tetzlaff, & Altman 2009:2). The Cochrane Risk of Bias Tool (Cochrane Methods 2018) was adapted to the parameters of this study for this purpose. Six questions were formulated to check for risk of bias, namely, selection, performance, detection, attrition, and reporting biases.

These are explained as follows:

Selection bias arises when the study population is atypical of the general population, meaning that the sample selected is non-representative (Bruce, Pope & Stanistreet 2008: 134).

Performance and **detection bias**es arise from differences in the care rendered to different groups of study participants other than the intervention under study, and systematic differences in outcome assessment of comparison groups, respectively. Performance bias can be countered by blinding of those rendering and receiving care. Detection bias may similarly be avoided by blinding those who will detect the outcome of an intervention (Athanasiou, Debas & Darzi 2010: 432).

Attrition bias refers to systematic differences in comparison groups with regards to loss of participants from the study. Mortality, withdrawals, and dropouts may result in reporting inadequacies, which may lead to biased results (Athanasiou, et al 2010: 432).

Reporting bias refers to systematic differences between reported and unreported findings. Statistically significant differences between intervention groups are more likely to be reported than non-significant differences (Godbole, Koyle & Wilcox 2015: 18).

Additional questions were added to this tool by the researcher to evaluate the strength of evidence contributed by each study. This is explained in the following section.

3.5.2 Quality assessment of studies

In addition to risk of bias, individual studies in systematic reviews must be assessed for quality. However, there is no single ‘correct’ way of evaluating quality, and the

researcher must employ the principles of evidence-based medicine to define a unique system for this purpose (Talley, Locke & Saito 2008:68). To this end, six questions that looked at the strength of evidence of each study with respect to the aims of this specific research paper were formulated. Parameters that were considered were the study type, population size, population screening for removal of high-risk patients, average contrast media dosage, CIN definition, and time at which biomarkers were measured.

The risk of bias and the quality assessment questions were combined to make a single tool with two sections and a total of 12 questions that were used in evaluation of individual studies. At least three pre-determined answers to each question on the tool were formulated. For each question, each answer was classified as being Strong, Medium, or Weak. The overall rating for the risk of bias within a study, and the strength of evidence provided by an individual study in relation to this research's aims was based on the number of Strong or Medium ratings each study scored.

A study that was strongly relevant to this research with low risk of bias and high quality of evidence would have had to score at least eight Strong ratings; a study with a medium level of evidence required either at least six Strong ratings or at least eight Medium ratings, while all studies below these levels were considered to have a weak level of evidence.

3.5.3 Characteristics of an ideal study

The above measures for risk of bias detection and quality evaluation were developed in a bid to objectively identify studies that exhibit ideal characteristics aimed at answering the study question. The characteristics of an ideal study are as follows.
An ideal study would have had randomly selected patients (low selection bias), randomly allocated (low selection bias) to two or more treatment groups, which would each receive a different contrast medium for the CA examination. Alternatively, all the randomly selected patients could have received the same contrast medium for CA, and/or PCI. Studies comparing two or more contrast media should have had blinding of practitioners, patients (low performance bias), and personnel measuring biomarkers (low detection bias).

Any participant withdrawals or exclusions from the study need to be explained and adjusted for equitably in the statistical analyses (low attrition bias), and all findings reported, regardless of whether they were significant or not (low reporting bias).

The study should have been a systematic review, with a population size of 1000 or more CA and/or PCI patients, and high CIN-risk patients excluded. Dose of contrast medium for the examination ideally had to be between 100mls and 150mls. The most sensitive, and accurate definition of CIN was considered to be a reduction in eGFR of 50% or more within 72 hours of contrast exposure. An increase of 25% or more in serum creatinine within the same time frame was also considered suitable as an accurate CIN definition.

3.5.4 Summary measures

Curran, Aaronson, Standaert, Molenberghs, Therasse, Ramirez, Koopmanschap, Erder and Piccart (2000:835) explain that in research, summary measures collapse the complete set of measurements for an individual to a single number. A summary measure is chosen to reflect an important aspect of repeated measurements. For example, multiple toxicity data for a group of patients may be summarised by considering only the worst value obtained for each patient throughout a specified period. The relative risk (RR) of CIN development with a 95% confidence interval (CI) was used in this study as the primary measure of contrast medium safety. For this study, RR is the ratio of the risk of CIN development in CA patients who received one contrast medium, to the risk for patients who did not receive that contrast medium (Andrikopoulou & Morgan 2015:188). Values for RR were computed from data supplied in the individual studies using MedCalc statistical software package (MedCalc Software Version 18.2.1, Belgium).

Sample sizes across studies were preserved by intention-to-treat analysis to control for bias, and eliminate the effect of observed minor CA exam protocol violations for individual patients. This type of analysis includes all the subjects that were originally selected to be treated in the final study result, even if some of the subjects were treated differently than what the study intended (Gauch 2008:124).

For example, a researcher may select 100 patients for a study and intend to perform standard CA examinations to determine the incidence of CIN. Within that patient cohort, five patients present with certain co-morbidities, which necessitate modification to the CA protocol by means of administration of CIN prophylactic medication. Intention-to-treat analysis will include all 100 patients in the final study result, and not eliminate the five because they were treated differently. In practical scenarios, it may be near impossible to treat all 100 patients identically because of variables such as contrast volume administered, which depends on patient body size, as an example. Bias can be introduced in a study when a researcher decides to eliminate certain patients and leave others (Gauch 2008:124). In light of this explanation, Redmond and Colton (2001:184) explain the intention-to-treat approach as essential when reporting the results of trials.

3.5.5 Synthesis of results

To synthesise the extracted data, a meta-analysis of the study results was performed. This is a statistical approach used to integrate quantitative findings from separate, but similar studies. It supplies a numerical estimate of the overall effect of interest as the outcome (Petrie, Bulman & Osborn 2003:74). To perform the meta-analysis, RRs for each included study were pooled together to obtain a summary effect using the random effects model and MedCalc statistical software. The random effects model assumes that all studies in the analysis are fundamentally different, meaning each study will estimate its own unique outcome. It is used when there is some statistical heterogeneity between studies (Petrie et al 2003:74). The random effects model was selected for this study because all the included studies had methodical differences, which may have in turn affected the observed incidences of CIN. These differences existed because no limits were included in the eligibility criteria with respect to study type or methodology used. This in turn was done to include as many relevant articles as possible into the analysis.

3.5.5.1 Heterogeneity

Heterogeneity in systematic reviews and meta-analyses is used to refer to differences between observations, populations, or studies.

If included studies are too heterogeneous, this may preclude the data from being pooled together (Lewis, Sheringham, Bernal & Crayford 2014:113). This means that only studies with acceptable levels of heterogeneity should be included in a meta-analysis, and the appraisal of the similarity of studies and the ultimate decision on whether to include or exclude a certain study is ultimately the responsibility of the meta-analyst(s) (Melsen, Bootsma, Rovers & Bonten 2014:124).

For this study, Cochran's Q test was used to check the included studies for heterogeneity. This test can detect significant disagreement in all of the included studies in a meta-analysis simultaneously (Looney & Hagan 2015:318). Additionally, the I^2 test was also used. This test measures the proportion of observed dispersion in study results that is owing to heterogeneity and presents it as a percentage. Generally, I^2 values of 25%, 50%, and 75% correspond to low, moderate, and high levels of heterogeneity (Lewis et al 2014:113).

3.5.6 Risk of bias across studies

Studies whose results are 'positive' and statistically significant are more likely to be published, as opposed to those that produce non-significant results. This is known as publication bias. Authors may filter, manipulate, or present results in such a way that they become positive and more likely to be published. This affects a meta-analysis by making relevant data either unavailable or hard to find, because useful data may not be presented in easily usable formats (Sterne, Sutton, Ioannidis, Terrin, Jones, Lau, Carpenter, Rücker, Harbord, Schmid, Tetzlaff, Deeks, Peters, Macaskill, Schwarzer, Duval, Altman, Moher & Higgins 2011:2).

To check for the absence of bias and between-study heterogeneity, a funnel plot may be used. This is a scatter plot of the effect estimates from individual studies, plotted against a measure of the study's size, or precision (Sterne et al 2011:2). This plot is based on precision in the estimation of an underlying treatment effect increasing in tandem with sample size (Sterne & Harbord 2004:128). This means that smaller studies will scatter widely at the bottom of the graph, and less spread will be observed for larger studies.

In the absence of bias, the plot is symmetrical, but publication and other biases will result in a skewed funnel, with a gap in the right bottom side. This occurs owing to smaller, non-statistically significant studies remaining unpublished. However, other reasons for asymmetry are possible, such as overestimation of treatment effects in smaller studies, chance, and language bias (Sterne & Harbord 2004:128,132).

The logarithm RRs were plotted against the standard error of the population sizes of individual studies to create a funnel plot. This was then assessed for symmetry.

3.5.7 Additional analysis

Meta-analyses must be investigated to see how sensitive their results are to the inclusion of studies with varying size, quality and methodical differences. This is known as a sensitivity analysis (Bruce et al 2008:417). In this study, it was performed by including a study that had initially been excluded from the meta-analysis because it used a different definition of CIN relative to the rest of the included studies.

3.6 RELIABILITY

Reliability is defined as the probability of getting the same results on two different occasions with different researchers (McLeod 2011:265). It relates to the consistency of a measure (Heale & Twycross 2015:67). The results of a research study need to be replicable, and the study methods need to be prepared in a detailed manner to allow this to be possible. Reliability is a pre-requisite for validity, which is explained in the section that follows (Dempster & Hanna 2015:25-26).

To ensure reliability in this research study, the study methods have been described clearly in this chapter, in a detailed manner with reasons to justify why those specific methods were employed. Alignment of a systematic review to the PRISMA reporting standard ensures the transparency of a study, which in turn improves the validity of results obtained. As a result, this standard was adhered to for the purposes of this research study (Stewart et al 2015:1657).

3.7 VALIDITY

The validity of a quantitative study is a measure of the quality of the research which looks at the extent to which a concept is accurately measured (Heale & Twycross 2015:66). Bolarinwa (2015:195) describes four different types of validity which may apply to research studies, namely, construct validity; content validity; criterion validity; and face validity. Validity tests may be categorised into two components, namely, internal and external validity. The types of validity that apply to this study are construct, internal, and external validity. These are discussed further in the sections that follow.

3.7.1 Construct validity

This entails the extent to which theory and evidence support a particular test as a measure of the construct that the test is designed to measure. The construct in question may either be a latent variable, or a characteristic or concept regarding people that is inferred from test scores (Weiner 2003:433). Construct validity within a study allows us to draw inferences from test results because of their direct relation to the concept under study (Heale & Twycross 2015:66).

The construct that was measured in this study was the development of CIN in adult patients who had a CA examination performed. To ensure construct validity, theory and evidence need to support that the test employed to ascertain the presence of CIN was appropriate and accurate. Therefore, the researcher presented a background of existing knowledge regarding the different definitions that are used to determine the presence of CIN, and how this ultimately can affect the observed incidence of the condition. According to this study, the most appropriate definition for CIN was that which was suggested by the KDIGO guidelines (2012:69), namely, a 25% or more increase in serum creatinine from a patient's baseline values, assessed at 48 hours after a radiological procedure.

3.7.2 Internal validity

Internal validity refers to how accurately the measures obtained from a research quantify what they were designed to measure (Bolarinwa 2015:195). Stated differently, this type of validity is concerned with the degree to which it can conclusively be deduced that changes in a variable, X, caused changes in another variable, Y. When variable X is associated with, and precedes variable Y, and no other plausible alternate explanations can explain the changes in Y besides the effect of the variable X, it can be logically claimed that X causes Y. In such a scenario, a study may be said to have a high level of internal validity (Seltman 2013:193).

However, if X happens to vary along with a real cause of change in Y, confounding is said to have occurred, and this is a threat to internal validity. In a research study, it is not possible to have absolutely no differences between two treatment groups as some level of difference will always be present, but on average, the two groups must have similar characteristics. Confounding occurs when more than one element is different on average between two experimental groups which are being compared. Ideally, the only major difference in the two comparison groups must be the treatment, or intervention the groups receive (Seltman 2013:194).

This study made use of a structured data collection form to organise the data received from the institution where the study was carried out. Usage of such a form lowered the impact of extraneous variables by organising the data in a systematic way. This enabled ready identification of confounders, such as additional prophylactic treatments that may have been administered to patients, or high levels of comorbidities which are directly linked to the development of CIN.

The data collection form ensured reliability and consistency of procedures during the data gathering process, which also increased the internal validity of this study.

3.7.3 External validity

External validity refers to the extent to which the study results can be applied to the population that the sample represents.

This means that if the results of the study are only applicable to the selected sample and not the population, there is no external validity (Blankenship 2010:91). Therefore, sample selection is extremely important for the external validity of a study. In order to ensure external validity, the sample needs to be representative of the population from which it was selected. When a sample is said to be representative, it means that the individuals chosen or units of analysis have the characteristics and attributes that are typical of that population (Hartas 2015:67).

The study populations in the records included within this research were representative of the general population as they were extracted from consecutive participants who visited imaging centres for elective or emergency CA and / or PCI. As such, the deductions made can be applied to the general populace of patients who will undergo these same examinations, meaning the study has good external validity.

3.8 ETHICAL ISSUES RELATING TO THE STUDY

Ethical considerations entail a set of moral principles or values that bind a society together (Rodgers 2011:186). Poudel, Newlands and Simkhada (2016:8) describe research ethics as rules of morally good conduct for researchers. They further explain that ethics are based on moral and political beliefs, which are frequently external to the actual research itself. Ethics may also be defined as the standard practices for privacy and confidentiality protection of any human subject participants in a research study. The ethical considerations for this study are elaborated below.

3.8.1 Permission to conduct the study

Ethical clearance was sought from the University of South Africa (Unisa) Higher Degrees Ethics Committee (Annexure A). In addition to this, the researcher ensured that all sources consulted for the writing of the research document were appropriately referenced as per Unisa guidelines to avoid plagiarism. The UNISA librarian was consulted about the use of the search engines for the extraction of the articles. This is because the university has got the indemnity to use these engines.

3.8.2 Study participants

No direct contact with human subjects was required in order to obtain data for use in this study. As a consequence, it was not necessary to obtain informed consent from the specific participants.

3.9 CONCLUSION

This chapter described how the research study has been designed to address the research question, and details the methodology employed. Each of the methods that were selected to address the different components of the research question were defined, and an explanation given of how the respective method was suited to this particular study. The research adopted a quantitative approach, and this means after systematically reviewing related literature, a meta-analysis was carried out to obtain an estimate of the summary effect once all the included studies had been pooled together using statistical methods. Included studies were scrutinised for quality and bias, and adherence to the PRISMA method of reporting is underscored. The chapter ends with a discussion of reliability, validity and the ethical obligations that were observed in the undertaking of this research. The next chapter will look at the processes used in the analysis of data obtained during the data collection process, as well as a detailed description of the results obtained.

CHAPTER FOUR

RESULTS AND INTERPRETATIONS

4.1 INTRODUCTION

Chapter 3 gave a detailed description of the way in which the study was designed and the methods employed, together with explanations of the rationale behind the methodical choices made. This chapter presents the findings of the research and gives an analysis and description of these findings. The analysis of results is tailored to address the following research objectives:

- To determine the extents to which Ioversol and Iomeprol elicit CIN in CA patients.
- To investigate if Iomeprol is safer to use.
- To make recommendations to clinicians for improved practice based on the results of evidence-based medicine.

The process by which relevant studies were identified is outlined below.

4.2 STUDY SELECTION

A literature search for peer-reviewed articles was conducted on five scientific databases, namely, CINAHL, Medline, Scopus, PubMed Clinical Queries, and Science Direct. The information search process was explained in detail in section 3.4.1. A total of 199 studies were retrieved when the databases were searched for information, and nine additional studies were found in the reference lists of the retrieved articles. This gave a total of 208 articles, and these were screened by looking at their titles so that any articles that did not appear to be of relevance could be eliminated. Articles in which studies were performed on paediatrics, animal populations, or exclusively on high-risk adult populations such as diabetics and kidney injury patients were excluded. In addition, articles that involved angiographic exams other than CA or PCI were also excluded. This resulted in the elimination of 82 records, leaving 126 for further scrutiny. The abstracts, and in some cases, full-text articles of these remaining studies were retrieved and evaluated for suitability.

Eventually, 11 articles remained after this additional scrutiny. These were further evaluated making use of the data collection form, and four studies were deemed unsuitable, leaving seven studies for inclusion within the study.

A PRISMA flow diagram illustrating the above-mentioned search process is shown in Figure 4.1. below:

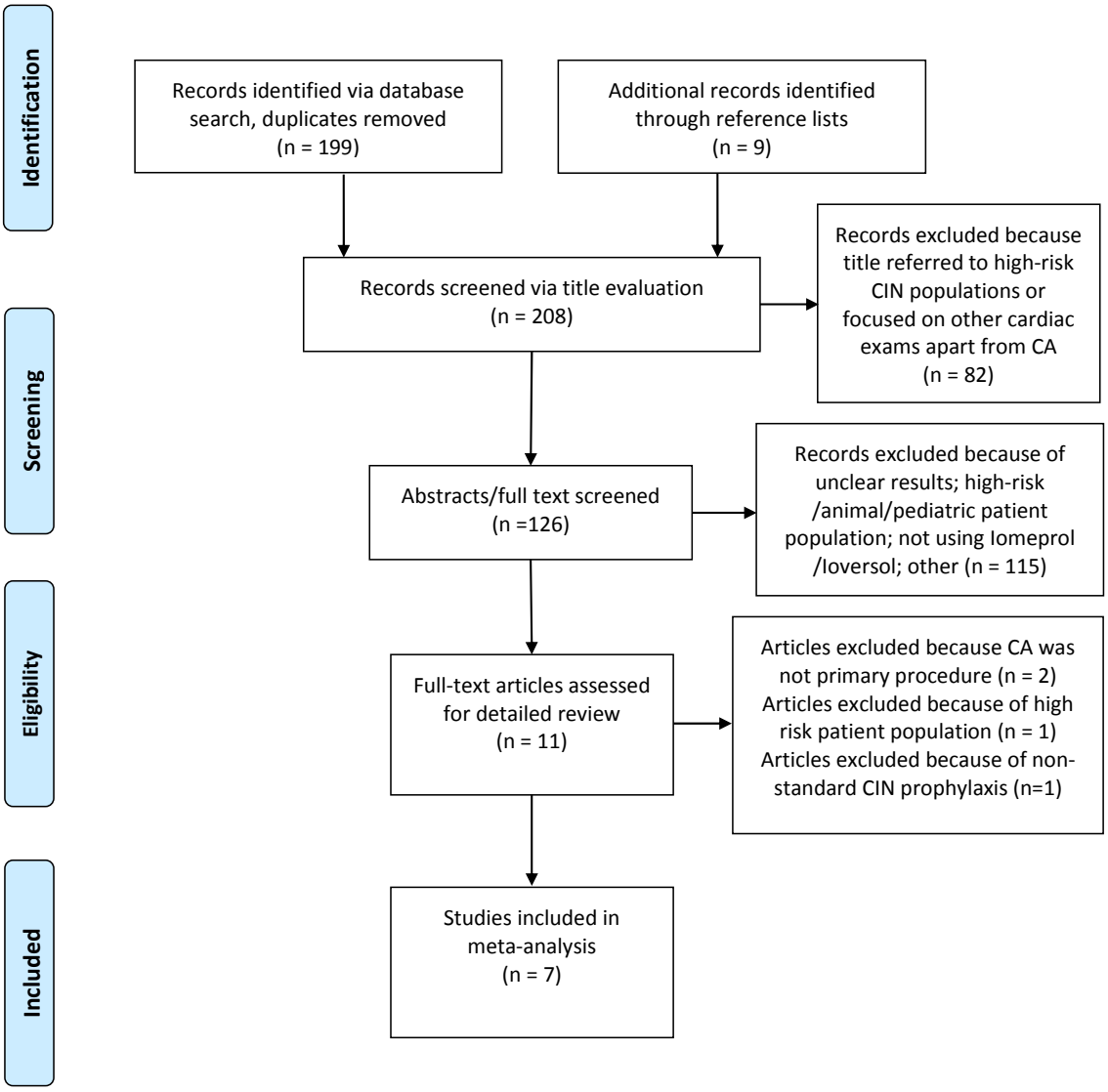


Figure 4.1: PRISMA flow diagram (adapted from Moher et al 2009:e1000097)

The data collection form collected comprehensive information that was of use in this study, using the PIICCOTS format aforementioned in Section 3.3.2.3. The section that follows details the information that was extracted from each study.

4.3 STUDY CHARACTERISTICS

The characteristics of the articles included in the analysis are shown in Table 4.1. Two studies included were performed in Asia (China and Japan), four were from Europe (Italy, France, Switzerland and Greece), and one study was from the USA. No relevant studies performed on the African continent were identified, and no two studies were performed in the same country. The oldest study included was published in 2001 (Donaldio et al 2001:385-396), and the two most recent were published in 2018 (Cao et al 2018:369-375 & Gullion et al 2018:818-824).

4.3.1 Population

With the exception of the study by LaBounty et al (2012:1594-1599) who performed a retrospective multi-centre study, all the included studies recruited participants from a single healthcare centre. In all cases, patients were subjected to either CA or PCI, or both. LaBounty et al (2012:1594-1599) used a total of 107994 patient records for their study, and these patients were each exposed to any one of three selected contrast media. The number of patients in their research exposed to Ioversol was 66319, and this was the patient population of relevance to this study. Patient details were extracted from a database whose records are populated by over 600 geographically disperse hospitals within the USA. Records were included if patients were ≥18 years, hospitalised, undergoing CA or PCI or both, and exposed to either Iomeprol, or Ioversol. Haemodialysis and exposure to multiple contrast media during the index hospitalisation were listed as exclusion criteria. LaBounty et al (2012:1594-1599) state that 43.4% of the Ioversol study population was ≥ 65 years, but the mean age of the entire population is not explicitly given in the study. The identified comorbidities in the patient population were diabetes, kidney injury, cardiovascular pathology, and cancer.

In a similar fashion to LaBounty et al (2012:1594-1599), Abe et al (2007:1-5) performed a retrospective study, but patient records were recruited from a single hospital in Kyoto, Japan. All patients who had either CA or CA and PCI performed were included, and the exclusion criteria was haemodialysis and missing laboratory data. The mean age was 68.4 years, which was the highest for the studies included. Comorbidities noted in the patient population were cardiovascular compromise/pathology, kidney injury, and diabetes.

The remaining records (Cao et al 2018:369-375; Donaldio et al 2001:385-396; Gullion et al 2018:818-824; Perrin et al 2013:1-10 & Tziakas et al 2013:46-55) were all prospective, single centre studies, and consecutive patients presenting for CA or PCI were included in the studies. Cao et al (2018:369-375) performed a randomised controlled study in China where 35 CA patients who were over 18 and had chest pain suspicious of cardiac pathology were recruited for their research. Exclusion criteria were pregnancy, kidney injury, coma, cardiovascular pathology / surgery, and exposure to certain medications. Mean age for included patients was 59.37 years, which was the lowest of all included studies.

Donaldio et al (2001:385-396) recruited 45 patients for their study, which was performed in Italy. Patients were split into three groups, and each group received either Iopromide, Ioxaglate or Ioversol. The Ioversol group, which was the one of interest in this research, had 15 patients, and the average age was 62.2 years. Comorbidities noted in this group were cardiovascular pathology, diabetes and elevated plasma creatinine. All patients requiring CA met the inclusion criteria, and they were only excluded if they had any contraindications to contrast media.

The studies by Gullion et al (2018:818-824) and Perrin et al (2013:1-10) were performed at hospitals in France and Switzerland, respectively. Admitted CA patients with mean ages of 68 and 66.6 years respectively were included in the studies. Cardiogenic shock, cardio-circulatory arrest and kidney injury patients were excluded by Gullion et al (2018:818-824), while Perrin et al (2013:1-10) excluded kidney injury patients and any patients who withheld consent for study inclusion. The comorbidities present in both patient populations were diabetes and cardiovascular pathology.

The last record was from Greece by Tziakas et al (2013:46-55). They recruited all consecutive PCI patients at their facility. Kidney injury, heart surgery and repeat PCI patients were excluded, and a total cohort of 488 patients whose mean age was 64 years were included into the study. Comorbidities in the population were kidney injury and cardiovascular pathology.

4.3.2 Intervention

As per eligibility criteria stated in sections 3.3.2.3 and 3.3.2.4, all included studies focused on patients who either had CA, PCI, or both exams performed, with either Ioversol or Iomeprol administered. Four records with a total population of 66857 patients used Ioversol, and the remaining three (Abe et al 2007:1-5; Gullion et al 2018:818-824 & Perrin et al 2013:1-10) made use of Iomeprol, and total population exposed was 1893 patients. LaBounty et al (2012:1594-1599) were unable to determine the average volume of contrast media used in their study, and Donaldio et al (2001:385-396) measured their contrast media dosages in grams of contrast medium/kg bodyweight, while all other studies measured dosages in millilitres.

4.3.3 Comparison

The study design for four of the included studies was such that only one contrast medium was used on all patients. The remaining three records compared the safety profiles of different contrast media on CA patients. Abe et al (2007:1-5) compared Iomeprol to Iopamidol; Donaldio et al (2001:385-396) compared Ioversol, Iopromide, and Ioxaglate; and LaBounty et al (2012:1594-1599) compared Ioversol, Iohexol, and Iopamidol.

4.3.4 Outcome and time biomarkers were measured

The primary outcome measurement in this research was the development of CIN. With the exception of LaBounty et al (2012:1594-1599), all included studies measured biomarkers two to three days post contrast exposure, although Abe et al (2007:1-5) were unclear on when exactly biomarkers were determined, but stated that it was within five days post-contrast exposure.

In addition, LaBounty et al (2012:1594-1599) considered re-admission for CIN within 30 days post exposure as the primary outcome measurement. Other outcomes of importance were derived by the individual studies but they were not the primary focus of this research.

4.3.5 Conflicts of interest and study type

Two studies, namely Donaldio et al (2001:385-396) and Perrin et al (2013:1-10) declared receipt of funding for their researches. The study by Perrin et al (2013:1-10) received support from three different sources, namely “Schweizerische Herzstiftung” (Bern, Switzerland), the “Fondation Lausannoise pour la Recherche en Hypertension” (Lausanne, Switzerland) and the “Fonds Scientifique Cardiovasculaire” (Fribourg, Switzerland), and Donaldio et al (2001:385-396) received a research fund from “Ministero dell’Universita` e della Ricerca Scientifica e Tecnologica,” Italy. The rest of the included studies did not declare any potentially conflicting financial interests.

With regards to study type, three of the included studies (Donaldio et al 2001:385-396; Perrin et al 2013:1-10 & Gullion et al 2018:818-824) were prospective cross-sectional studies, two were retrospective cohort studies (Abe et al 2007:1-5 & LaBounty et al 2012:1594-1599), and there was a single randomized controlled trial (Cao et al 2018:369-375).

Table 4.1 below shows the characteristics of the included studies and the data which was extracted.

1st Author Year Country	POPULATION Inclusion/Exclusion, Size, Mean age, Comorbidities			INTERVENTION		COMPARISON	CONFLICT of interest declared	OUTCOME		TIME outcome is determined	STUDY design
	Inclusion/Exclusion criteria, Comorbidities	Size	Mean age	Exam done	Contrast type, mean volume			CIN definition; other study outcomes	Observed CIN incidence		
Abe 2007 **Japan**	Incl.: All consecutive CA patients. Excl.: Dialysis; lack of lab data.68.4 years Kidney injury 22.6%; Diabetes 32.9%	n = 647	68.4 years	CA	Iomeprol 185 ml	Iopimadol	None	Increase in serum creatinine of ≥ 0.5mg/dl after contrast exposure. CIN rates increased with contrast volume, female sex, kidney injury	15.3%	Within 5 days of CA.	Single centre, retrospective cohort
Cao 2018 **China**	Incl.: Patients over 18; chest pain Excl.: Kidney injury, comma, pregnancy, nephrotoxic medications, previous myocardial infarction, peripheral arterial disease. Hypertension, diabetes, dyslipidemia	n = 35	59.37 years	CA + PCI	Ioversol, 91.5 ± 20.02 ml	None	None	≥25% increase in serum creatinine, or increase of 44 µmol/L post CA. Remote ischemic conditioning reduced CIN rates	31.4%	At 1 day, and 3 days post exam.	Single centre, randomized controlled trial
Donadio, 2001 **Italy**	Incl.: Patients for CA Excl.: Contraindications to contrast media, recent exposure to CA, nephrotoxic drugs Diabetes, high plasma creatinine	n = 15	62.2 years	CA	Ioversol, 1.8±0.4g contrast /kg body weight	Iopromide and Ioxaglate	Funded study	≥50% increase in plasma creatinine, or ≥ 50% reduction in GFR after contrast administration. Increase in urinary enzyme excretion is a sensitive marker to depict contrast media effect on kidneys	0%	3 days post CA.	Single centre prospective cross sectional
Gullion 2018 **France**	Incl.: CA patients. Excl.: Kidney injury patients excluded. Hypertension, diabetes, dyslipidemia	n=1002	68 years	CA (+PCI in some cases)	Iomeprol, 135 ml	None	None	≥25% increase in serum creatinine or ≥0.3 mg/dl post CA. Relative serum creatinine increase of 25% should be abandoned in favour of an absolute increase	15.7%	3 days post CA contrast exam.	Single centre, prospective, cross sectional

LaBounty 2012 **USA**	Incl.: Hospitalised patient records, ≥ 18 years, exposure to one of 3 selected contrast media Excl.: Dialysis, prior contrast exposure during hospitalization. Diabetes, kidney injury, congestive cardiac failure, myocardial infarction, hypertension, anaemia, cancer.	n= 66319	Not clear	CA and / or PCI	Ioversol, volume unknown	Iohexol and Iopamidol	None	New renal insufficiency post contrast exam requiring re-admission to the hospital, or a need for new dialysis. Iohexol, Ioversol, Iopamidol have similar safety profiles when used for CA and/or PCI	0.1%	Within 30 days of exam.	Multi-centre retrospective cohort
Perrin, 2013 **Switzerland**	Incl.: Patients ≥ 18 years Excl.: Kidney injury, lack of consent. Hypotension, diabetes, known cardiac compromise, high cholesterol	n = 244	66.6 years	CA and/or PCI	Iomeprol, 122 ml	None	Funded study	≥25% or ≥26.5 µmol/L increase in serum creatinine post CA; or oliguria of ≤0.5ml/kg/hour for 6 hours or more. Urinary neutrophil gelatinase-associated lipocalin is not a sensitive marker for CIN in CA	10%	2 and 3 days after contrast exam.	Single centre, prospective, cross sectional
Tziakas 2013 **Greece**	Incl.: All consecutive patients Excl.: Kidney injury, repeated PCI, mortality, coronary artery bypass graft patients. Kidney injury, hypertension, dyslipidemia	n = 488	64 years	CA + PCI	Ioversol, 277ml	None	None	≥ 25% or ≥ 0.5 mg/dl increase in serum creatinine post CA examination. A model for predicting risk of CIN development in patients	10.2%	At the 1st, 2nd, and 7th days post exam.	Single centre, prospective, cohort

Table 4.1: Characteristics of studies included in the meta-analysis. The studies where Iomeprol was used are shaded blue for ease of identification, and those where Ioversol was used are unshaded.

4.4 RISK OF BIAS WITHIN STUDIES

Risk of bias was assessed for each study using the tool adapted from the Cochrane Collaboration (Appendix 4). A Strong rating meant that there was low risk of bias. On the contrary, a Medium rating was indicative of moderate risk, while a Weak rating was suggestive of high risk of bias. The different categories of bias that were assessed will now be discussed.

4.4.1 Risk of selection bias

Risk of selection bias was low in most of the included studies. Patient populations were composed of consecutive patients who presented for CA, PCI, or both over a specified time period, which ranged from three months (Perrin et al 2013:1-10) to two years (Abe et al 2007:1-5; Donaldio et al 2001:385-396 & LaBounty et al 2012:1594-1599). Such study participant recruitment was considered representative of the general population of CA and PCI patients. Donaldio et al (2001:385-396) was the only study to score a Medium rating in this section because their patient selection method was unclear.

Risk of selection bias also involved patient allocation to contrast media treatment groups. All studies scored strongly in this section except for Abe et al (2007:1-5) and LaBounty et al (2012:1594-1599) who had Weak scores because these studies made use of retrospective data where patients were allocated to different contrast media treatment groups with no mention of randomisation. Purposeful allocation to a specific contrast media treatment group based on comorbidities or any other reason was therefore a possibility in these studies, hence the Weak rating. The remaining studies all had Strong scores because they either made use of a single contrast medium or mentioned randomised allocation of patients to different contrast medium treatment groups.

4.4.2 Risk of performance and detection bias

Three studies (Abe et al 2007:1-5; Donaldio et al 2001:385-396 & LaBounty et al 2012:1594-1599) divided patients into two or more contrast media treatment groups

but blinding was not mentioned in any of these studies, hence their Weak risk of performance and detection bias ratings. The remaining studies only had a single contrast medium treatment group and so blinding was not applicable to these studies. By default, they were ranked Strong in both bias categories.

4.4.3 Risk of attrition bias

All studies with the exception of Donaldio et al (2001:385-396) ranked strongly for risk of attrition bias. In their analyses, Donaldio et al (2001:385-396) had inconsistent patient population numbers that were not clearly accounted for and explained, suggestive of high attrition bias risk. This resulted in their study obtaining a Weak rating. In the remaining studies, patient populations were consistent in all calculations and analyses and no evidence of risk of attrition bias was observed.

4.4.5 Risk of reporting bias

All studies received a Strong rating in the risk of reporting bias section. Results and measurements were accounted for whether statistically significant or not, and these were clearly stated and presented. There was no evidence noted of non-statistically significant results being omitted in any of the included studies.

4.5 QUALITY ASSESSMENT OF STUDIES

This section assessed the strength of evidence provided by each study based on the study methods selected by the authors, as well as inherent characteristics of the study.

4.5.1 Study type

In the Study Type section, only systematic reviews with meta-analyses would have scored a Strong rating because they provide information whose strength is placed at the highest tier of evidence-based medicine (Burns, Rohrich & Chung 2011:9). None were included in this research. Hence, all included studies either received Medium, or Weak ratings depending on the trustworthiness of level of evidence provided by the study design.

Cohort studies and randomised controlled trials (Abe et al 2007:1-5; Cao et al 2018:369-375; LaBounty et al 2012:1594-1599 & Tziakas et al 2013:46-55) had Medium ratings, while cross-sectional studies (Donaldio et al 2001:385-396; Gullion et al 2018:818-824 & Perrin et al 2013:1-10) scored Weak ratings.

4.5.2 Population size

Under population size, larger trials were considered as providing stronger levels of evidence than smaller ones owing to greater statistical power (Button, Ioannidis, Mokrysz, Nosek, Flint, Robinson & Munafò 2013:365). Gullion et al (2018:818-824) and LaBounty et al (2012:1594-1599) scored strongly in this section as they both had patient populations over 1000, Abe et al (2007:1-5) had a Medium rating with a patient population of 647, whilst four studies (Cao et al 2018:369-375; Donaldio et al 2001:385-396; Perin et al & Tziakas et al 2013:46-55) had Weak scores as none of them individually had more than 499 patients exposed to either Ioversol or Iomeprol.

4.5.3 Population screening

Studies with clear eligibility criteria and which excluded patients who were contraindicated for the CA procedure ranked highly on the Population Screening scale. Inclusion of patients for whom CA is contraindicated may have potentially skewed obtained results in favour of high levels of CIN. All studies scored Medium ratings in this section, except for Donaldio et al (2001:385-396) who had a Strong rating. Medium ratings were owing to the inclusion of some high-risk patients and exclusion of others; a strong rating was owing to the exclusion of all patients for whom CA was contraindicated.

4.5.4 Contrast medium dosage

Dosage of contrast medium was an important measure affecting the strength of evidence provided by a study because of the association of high contrast medium dosages with increasing CIN rates (KDIGO 2012:76). This means studies in which high contrast media dosages were used would have exaggerated the observed CIN rates, thereby decreasing the strength of the evidence supplied.

Acceptable clinical practice is to use the minimum possible contrast dosage which is sufficient to produce images of diagnostic quality (KDIGO 2012:76).

No authoritative body of literature provides exact figures for how much contrast administration is acceptable for CA. However, the study by Solomon, Biguori, and Bettmann (2006:S40) presented mean volumes of contrast media that have been presented as 'low' or 'acceptable' according to a literature search they performed, and this information was adopted for the domains of this research to determine ideal contrast volumes for use in CA and or PCI. In this study, 100-150ml of contrast medium was deemed an ideal dosage. A total of three studies (Cao et al 2018:369-375; Gullion et al 2018:818-824 & Perrin et al 2013:1-10) using this dosage were awarded a Strong rating. Next, 151-250ml of contrast was determined as intermediate, and one study (Abe et al 2007:1-5) fulfilled this criterion. Studies where more than 251ml of contrast were used (Tziakas et al 2013:46-55) were given a Weak rating.

LaBounty et al (2012:1594-1599) failed to report a mean contrast dosage and so by default were awarded a Weak scoring. Donaldio et al (2001:385-396) reported dosage in grams of contrast medium per kilogram of body weight but did not mention how much this was in millilitres as recommended by the KDIGO Work Group (2012:76), making the dosage data they provided unusable for this study. They were also awarded a Weak score.

4.5.5 Definition of contrast-induced nephropathy

The last two points on the quality scoresheet looked at the definition of CIN each paper used, and the time in which biomarkers were measured. The KDIGO (2012:69) guidelines suggest that CIN be defined as "a ≥25% increase in serum creatinine from baseline values assessed at 48 hours after a radiological procedure." However, as outlined in section 1.1, eGFR is a more reliable predictor of kidney function as serum creatinine is prone to erroneous conclusions owing to naturally occurring fluctuations, which may be unrelated to kidney function. For this research study, records that defined CIN by evaluation of eGFR were considered as providing a Strong level of evidence, and this was done by Donaldio et al (2001:385-396) only.

The remaining records except for LaBounty et al (2012:1594-1599) received medium ratings as they either used the less robust KDIGO definition for CIN, or they defined the condition by an absolute increase in serum creatinine of 0.3mg/dl. LaBounty et al (2012:1594-1599) received a weak rating because their definition involved re-admission for CIN within 30 days, meaning patients who developed CIN but did not get re-admitted were not accounted for.

LaBounty et al's (2012:1594-1599) study was the only record to receive a Weak rating with regards to the time biomarkers were measured because of the 30-day period in which CIN was considered to have occurred. Abe et al (2007:1-5) scored a Medium rating as biomarkers were measured within five days. The remaining records all had Strong ratings in this section as biomarkers were measured one to three days after contrast media exposure.

Appendix 4 shows the tool that was used to score the articles for bias and quality. Table 4.2 shows a visual representation of the risk of bias scoring, as well as the quality assessment that was done for the individual studies.

First Author	Abe			Cao			Donaldio			Gullion			LaBounty			Perrin			Tziakas		
Blinding to practitioners and patients (Performance bias)			●	●					●	●				●		●			●		
Blinding of personnel measuring biomarkers (Detection bias)		●		●					●	●					●	●			●		
Missing data accounted for equitably (Attrition bias)	●			●					●	●			●			●			●		
All findings reported (Reporting bias)	●			●			●			●			●			●			●		
Study type		●			●				●			●		●				●		●	
Population size		●				●			●	●			●					●			●
Population screening		●			●		●				●			●			●			●	
Dose of contrast medium		●		●					●	●					●	●					●
Definition of CIN		●			●		●				●				●		●			●	
Time biomarkers measured		●		●			●			●					●	●			●		
Overall Rating	Weak			Strong			Weak			Strong			Weak			Strong			Medium		

Table 4.2: Quality and bias assessment of the individual studies included (researcher made, 2018).

4.6 RESULTS OF INDIVIDUAL STUDIES

The RR was the selected measure of effect for this research. MedCalc statistical software was used to calculate values for RR for each study using the supplied CIN incidence data. This was done by means of 2x2 contingency tables. In cases where zeros caused problems or errors in calculating RR or the confidence intervals, 0.5 was added to all four cells as suggested by Pagano and Gauvreau (2000:325), and Higgins and Green (2008:521). In order to populate the 2x2 table and compute the RR for each study, patients exposed to Ioversol were considered as the 'exposed' group, and the pooled patient population exposed to Iomeprol was the 'unexposed', or 'control' group. The reverse was done for the patient population exposed to Iomeprol in each study to calculate the RRs.

The primary outcome considered in this research was the development of CIN, and so a true 'unexposed' population cannot exist (because there cannot be CIN development without exposure to contrast medium). Therefore, the 'unexposed' population was considered to be that which was exposed to the alternative contrast medium, namely Ioversol, in the calculation of Iomeprol RRs, and vice versa. This assumption was considered sufficient owing to the comparative nature of this study, which sought to compare Iomeprol with Ioversol. Table 4.3 below shows the calculated RRs for six of the seven included studies. The study by LaBounty et al (2012:1594-1599) was excluded, and the reason for this is explained in Section 4.6.1.

Iomeprol					**Ioversol**				
Author	**RR**	**%**	**No CIN**	**CIN**	**CIN**	**No CIN**	**%**	**RR**	**Author**
Abe	1.35	15.30%	548	99	11	24	31.43%	2.12	Cao
Gullion	1.38	15.67%	845	157	0	15	0.00%	0.21	Donaldio
Perrin	0.90	10.25%	219	25	50	438	10.25%	0.69	Tziakas
		14.84%	**1612**	**281**	**61**	**477**	**11.34%**		

Table 4.3: Results of individual studies showing CIN incidence rates and risk ratios

Figure 4.2 shows the RR for CIN development obtained for each study and the mean age of participants while Figure 4.3 shows the RR and volume of contrast medium used. The mean volume of contrast medium administered in the study by Donaldio et al (2001:385-396) was not included because the study authors expressed the average dosage in grams of contrast medium per kilogram of body weight. The given value could not be converted to millilitres, and so it was effectively not useful for comparison to the other included studies who all supplied average dosages in millilitres.

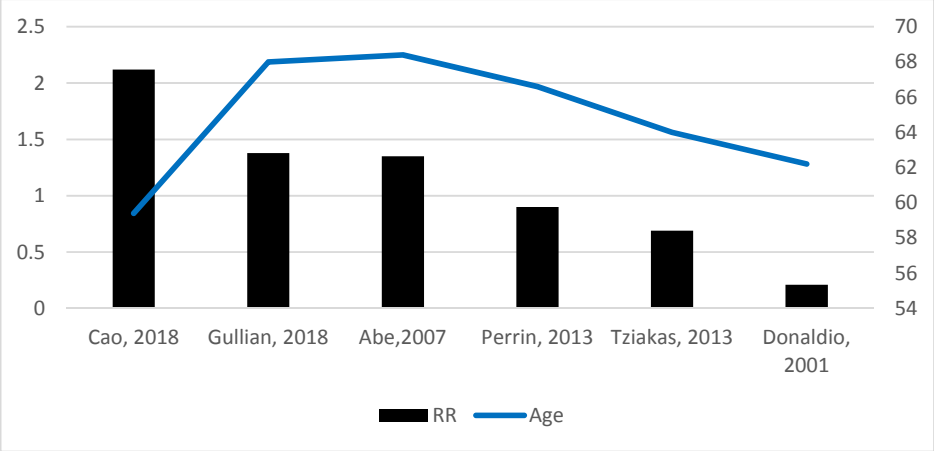


Figure 4.2: Association between age and RR for each included study

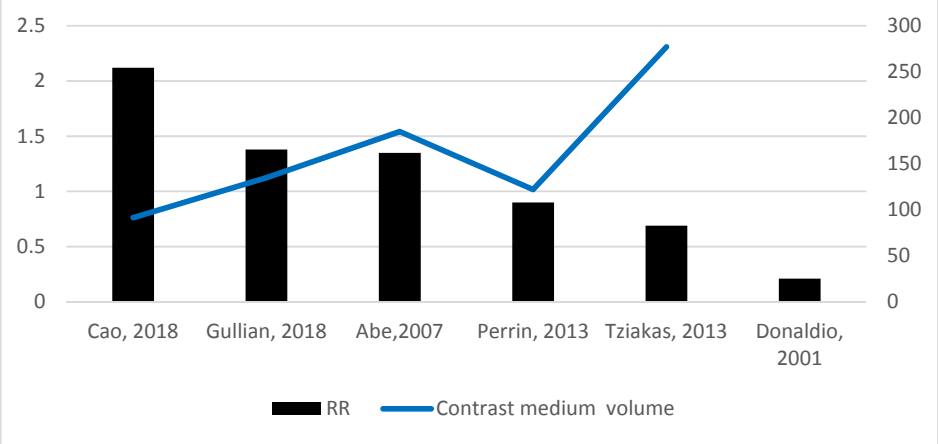


Figure 4.3: Association between average contrast medium volume administered and RR for each included study

4.6.1 CIN incidence with Ioversol use

The four included studies which considered CIN development in CA patients when Ioversol was used had a wide range of disease incidences, ranging from 0% to 31.43%. LaBounty et al (2012:1594-1599) had the largest patient population of 66319, and this study reported a CIN incidence of 0.1%. The exact numbers of patients who developed CIN were not explicitly stated in the study, but the supplied percentage corresponds to 66 patients. This was also the only study that did not measure biomarkers to determine the presence of CIN, thereby weakening the strength of evidence provided by the study. Inclusion of this study's findings into the pooled analysis produced skewed data and unrealistic RR calculations and so it was excluded from the meta-analysis.

From the remaining three articles, Donaldio et al (2001:385-396) were the only authors not to detect any cases of CIN in their patient cohort, and their study also had the smallest patient population (n=15). This study consequently had the lowest RR of 0.21. The study by Tziakas et al (2013:46-55) reported a CIN incidence of 10.25% with a RR of 0.69. Cao et al (2018:369-375) observed the highest CIN incidence of 31.43% and the risk of CIN with Ioversol use was more than twice as likely according to this study. The obtained RR was 2.12.

4.6.2 CIN incidence with Iomeprol use

A relatively narrower range of CIN percentage incidence was noted with Iomeprol use. The smallest study was performed by Perrin et al (2013:1-10) (n = 244) and an observed CIN incidence of 10.25% was obtained, with a RR of 0.90. The remaining two studies which looked at Iomeprol use were performed by Abe et al (2007:1-5) and Gullion et al (2018:818-824) and they observed near-identical CIN rates of 15.30% (RR = 1.35) and 15.67% (RR = 1.38) respectively.

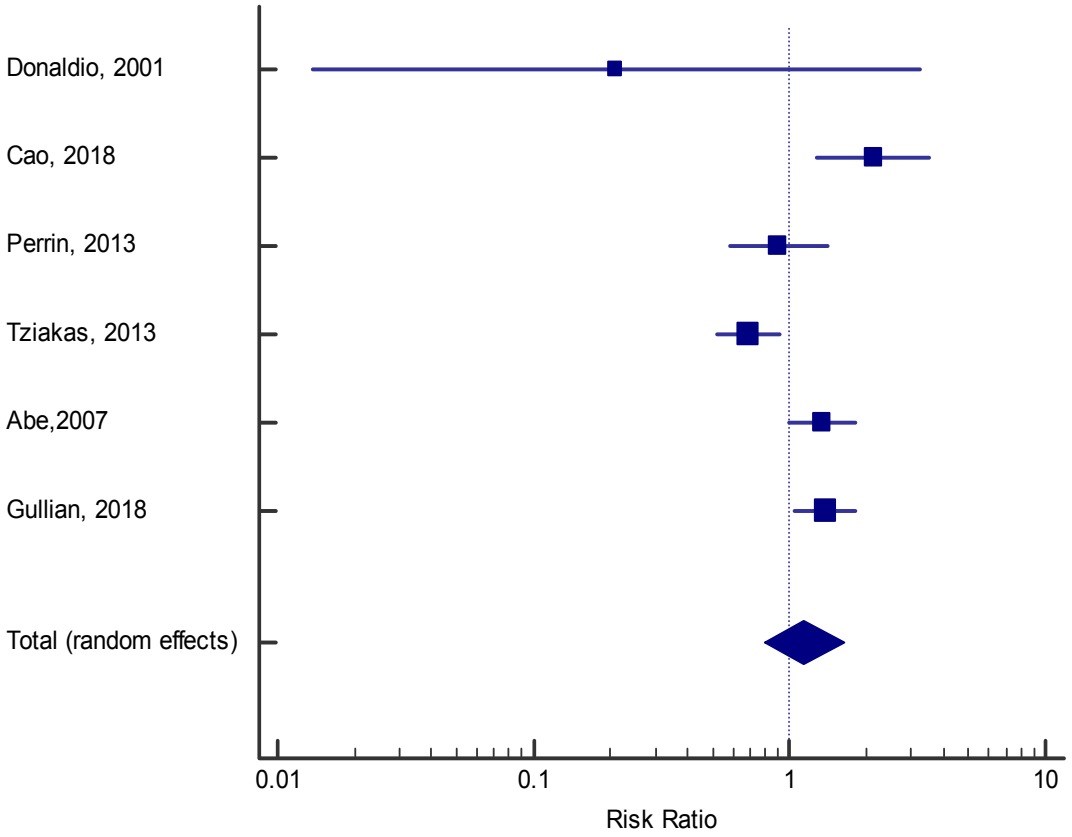
The next section describes the synthesis of the included studies and the results obtained.

4.7 SYNTHESIS OF RESULTS

MedCalc statistical software package was used to perform the meta-analysis of the six included studies. A total of 1893 CA patients from three studies were exposed to Iomeprol, and from these, 281 developed CIN (RR = 1.31, 95%CI = 1.01-1.70). The remaining three studies had a total population of 538, and from this number, 61 patients had CIN development after exposure to Ioversol (RR = 0.76; 95%CI = 0.59-0.99). The RRs of all six studies were pooled together and each study was weighted using the random effects model.

The I^2 test was used to check for heterogeneity of the included studies and this was found to be moderate (I^2 = 54.21%). In addition, Cochran's Q test for heterogeneity was also performed. The critical value of Q for five degrees of freedom on a chi square distribution table is 11.070, and the Q value obtained for this study was 10.91, meaning heterogeneity was acceptable. Therefore, the results of the individual studies were deemed suitable for meta-analysis.

A forest plot was used to depict the results of the meta-analysis conducted. The analysis showed that the summary effect of the pooled RRs of included studies intersected the line of no effect, meaning the null hypothesis that there was no statistically significant difference in the relative risk of CIN development when either Iomeprol or Ioversol was used in CA patients could not be rejected (RR = 1.14, 95%CI = 0.797-1.643, p = 0.466).
Figure 4.4 below shows the forest plot with the results of the meta-analysis.



	Risk Ratio	95% CI	P	Weight %
Donaldio, 2001	0.21	0.014-3.225	0.263	1.64
Cao, 2018	2.12	1.283-3.495	0.003	16.66
Perrin, 2013	0.90	0.582-1.403	0.652	17.98
Tziakas, 2013	0.69	0.520-0.917	0.011	21.29
Abe,2007	1.35	1.002-1.818	0.049	21.01
Gullian, 2018	1.38	1.048-1.822	0.022	21.43
Total (random effects)	1.14	0.797-1.643	0.466	100

I^2=54.21% Q=10.91

Figure 4.4. Meta-analysis of Risk Ratios from six out of the seven included studies showing CIN prevalence in CA examinations

4.8 RISK OF BIAS ACROSS STUDIES

A funnel plot was used to assess the risk of bias across all the studies included in the meta-analysis. This is a scatter plot of the measures of effect size under consideration from the different sources, plotted against the size of the sample. An asymmetric shape obtained in a funnel plot for a meta-analysis is suggestive of potential publication bias, which may favour higher or lower effect sizes (Indrayan & Holt 2016:249).

In this study, the measure of effect size was the RR, and the logarithm of the RR was plotted against its log standard error, as a measure of the study size. The resultant funnel plot is depicted in Figure 4.3. Diagonal dotted lines represent the pseudo 95% confidence limits around the summary treatment effect, which is depicted by the solid horizontal line. The blue dots represent each of the studies included in the meta-analysis. Visual inspection of the plot suggested symmetrical distribution, suggestive of the absence of publication bias.

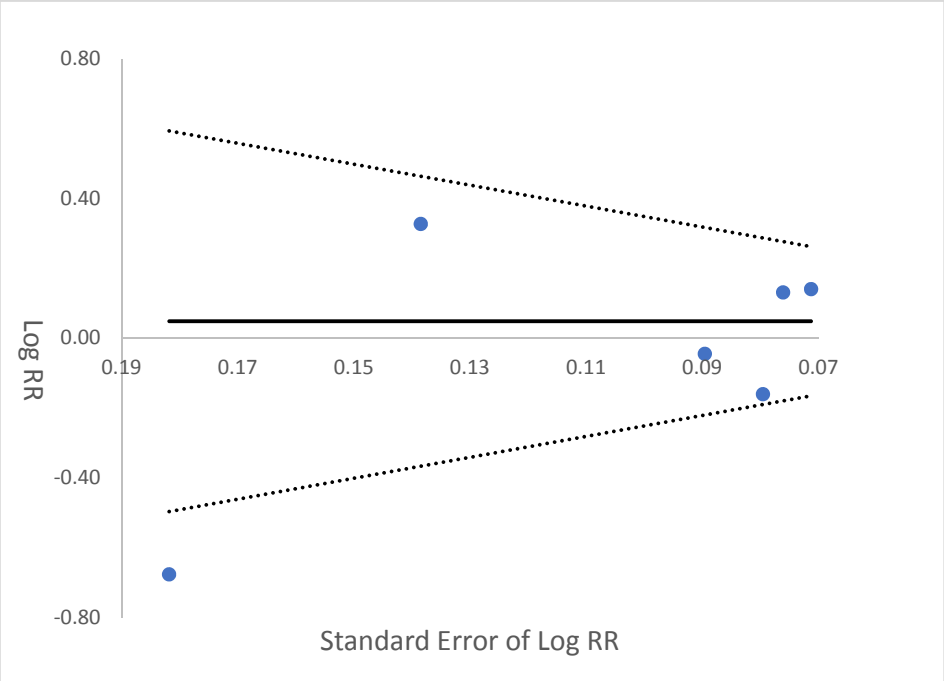


Figure 4.5: Funnel plot of studies included in the meta-analysis

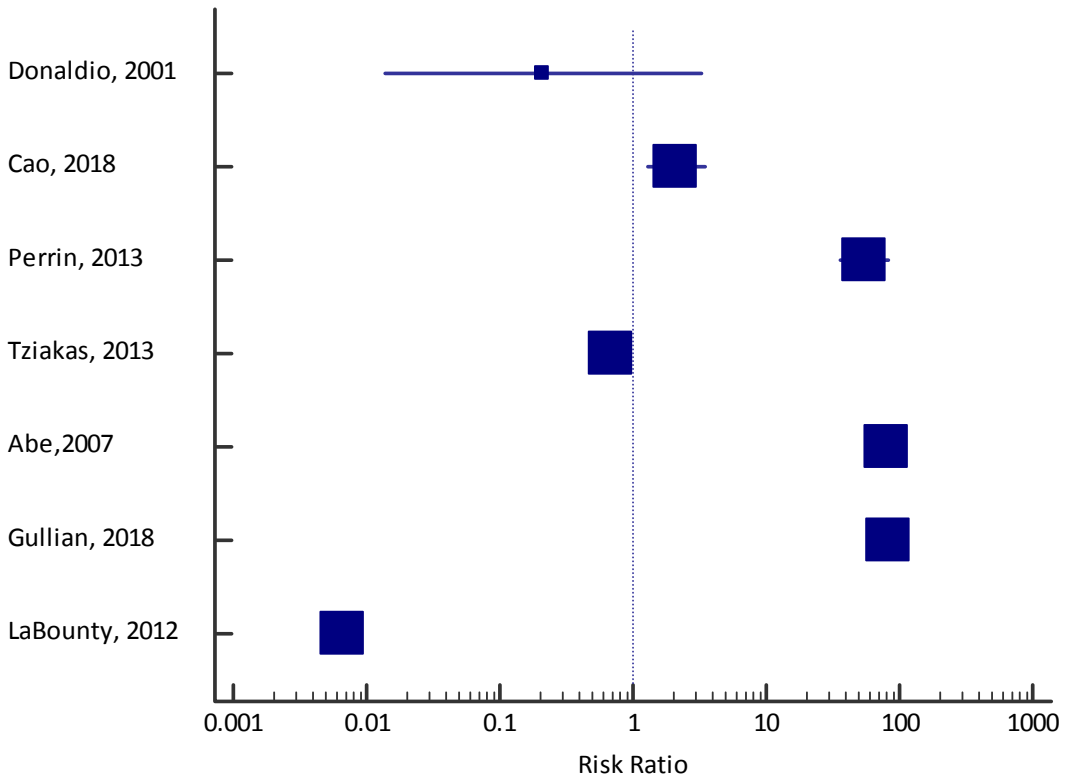
Formal tests commonly used to objectively verify the symmetry of funnel plots (such as Egger's test, or Harbord's modified test for small-study effects) were avoided because of their low power in detecting bias when there is a small number of trials available for meta-analysis. This practice is recommended by Debray, Moons and Riley (2018:47). The meta-analysis in this study contained six records, and tests for funnel plot asymmetry should only be used when a meta-analysis contains ten or more records (Sterne et al 2011:4).

4.9 ADDITIONAL ANALYSIS

Sensitivity analysis was performed in this study by including the research by LaBounty et al (2012:1594-1599) to observe the impact it would have on the overall result. RRs for each included study were calculated using MedCalc statistical software. Using the random effects model to pool all the studies together, unacceptable levels of heterogeneity were observed. The I^2 test yielded a result of 94.15%, which corresponds to a high level of heterogeneity. Figure 4.6 shows the forest plot which was obtained during the sensitivity analysis.

The inclusion of the study by LaBounty et al (2012:1594-1599) for sensitivity analysis brought the total number of studies to seven, which corresponds to six degrees of freedom. The critical value for this on the chi square distribution is 12.592. Therefore, the study's obtained Q value of 102.60, which was higher than the critical value was not acceptable.

According to Melsen et al (2014:128), meta-analyses with high levels of heterogeneity should not provide a pooled estimate as the level of accuracy of any findings concluded will always be low. Consequently, the data could not be meta-analysed with the inclusion of this study owing to high levels of heterogeneity.



0.21	**0.014 - 3.225**	**0.263**	**12.16**
2.12	1.283 - 3.495	0.003	14.59
53.94	35.795 - 81.276	0.060	14.62
0.69	0.520 - 0.917	0.011	14.65
80.55	62.66 - 103.54	0.778	14.66
82.49	65.83 - 103.34	0.590	14.67
0.52	0.389 - 0.705	<0.0001	14.65

(Random Effects)
I^2=94.15% Q=102.60

Figure 4.6 Sensitivity analysis: forest plot obtained after inclusion of the study by LaBounty et al (2012:1594-1599).

5.10 CONCLUSION

This chapter presented the results of the research and described how the included studies were selected and the properties of each study which were pertinent to this research. Each study was subjected to a thorough analysis concerning the quality of evidence supplied in respect to the aims of this research. The PIICCOTS format was used to extract relevant data and afterwards RRs of CIN development after exposure to either Ioversol or Iomeprol were calculated for each study. This was the primary measure of effect selected for this study. The obtained data was pooled together and meta-analysed using statistical methods and it was seen that there was no statistically significant difference in the safety profiles of the two contrast media under study. Additional analysis to check for risk of bias was performed, and no evidence of publication bias was identified with a forest plot. A sensitivity analysis confirmed that the exclusion of one of the studies in the meta-analysis was necessary for meaningful analysis of results to be performed. The following chapter will give a discussion of the obtained results and their relevance.

CHAPTER FIVE

DISCUSSION AND RECOMMENDATIONS

5.1 INTRODUCTION

The previous chapter presented the processes, which were used to extract data, its management, and the statistical analyses that led to eventually obtaining the main findings of the research. This chapter will discuss these findings and will draw upon existing knowledge to bring added meaning to the observations. The limitations will also be discussed, as well as recommendations for best clinical practice and conclusions. The next section will provide a summary of the knowledge contributed by this research study.

5.2 SUMMARY OF EVIDENCE

Section 1.2.2 outlined the research objectives that this study was designed to achieve. These were presented as follows:

- To determine the extent to which Ioversol and Iomeprol elicit CIN in randomly selected adult patients undergoing CA examinations.
- To determine if Iomeprol is safer than Ioversol in terms of lower observed incidences of CIN.
- To make recommendations for improved clinical practice based on the prevalence of side effects of the contrast media.

The evidence presented in this chapter will therefore be targeted at satisfying these stated objectives. Before the study objectives can be effectively addressed, it is important to evaluate the overall strength of evidence that this systematic review provides. This is explained below.

5.2.1 Accuracy of evidence provided by this study

The meta-analysis conducted included six studies, and of these, three were rated highly in the quality of evidence provided with respect to the aims of this study, and they had low overall risk of bias.

One study had a medium rating, and two studies had weak ratings. The scoring of studies is shown in Table 4.2. The overall risk of publication bias appeared low, as demonstrated by the symmetrical funnel plot in Figure 4.5. There was moderate heterogeneity noted across studies ($I^2 = 54.21$). Based on these different measures employed in this research to evaluate the accuracy of evidence supplied, it may be concluded that any conclusions drawn are of moderate strength, and as such may be subject to additional scrutiny.

5.2.2 Hypothesis testing

In Section 1.2.1 of this research study, the null and alternative hypotheses were presented. The null hypothesis is that there is no statistically significant difference in nephrotoxicity between Ioversol and Iomeprol when either contrast medium is used for CA in a randomly selected adult population, as shown by the following equation:

$$H_0 : \quad N_{IOV} = N_{IOM}$$

Where N_{IOV} and N_{IOM} denote the nephrotoxicity of Ioversol and Iomeprol respectively.

The alternative hypotheses were that

- there is a statistically significant difference in nephrotoxicity of the two contrast media; and
- Iomeprol is less nephrotoxic than Ioversol.

This was shown by the equations:

$$H_1 : \quad N_{IOM} \neq N_{IOV}$$

and

$$N_{IOM} < N_{IOV}$$

To test these hypotheses, in Section 4.7, the random effects model was used to combine data extracted from the included studies so that a pooled summary effect of RRs could be obtained. The obtained p-value of 0.466 was higher than the significance value of 0.05, meaning that the null hypothesis could not be rejected. The obtained p-value showed a lack of statistical significance in the data obtained, and so any variation between N_{IOM} and N_{IOV} could effectively be attributed to chance or sampling error.

Now the aims of the study referenced in section 5.2 shall be addressed, in light of the evidence obtained by this study.

5.2.3 Incidence of contrast-induced nephropathy

All of the included studies recognised CIN as an important side effect of CA, and its development was a primary measure of contrast medium safety within each study. Included studies noted the importance of the definition used for CIN because this directly affects the observed incidence of the condition.

The study by LaBounty et al (2012:1594-1599) recruited a large patient population of 66319 people who were exposed to Ioversol. However, the authors were unable to detect the true effect of contrast media nephrotoxicity owing to an inferior definition of CIN. The study authors defined patients as having developed CIN if they were re-admitted for the condition within a 30-day period post contrast exposure. Consequently, the incidence observed was uncharacteristically low for such a large population because the vast majority of patients who develop CIN are asymptomatic and do not require hospitalisation, and consequently they would have not been identified by LaBounty et al's (2012:1594-1599) definition (Andreucci et al 2014:3). For this reason, CIN incidence data from this study was not considered as accurate.

Patients in the remaining six included studies were exposed to both Ioversol and Iomeprol, and a total of 342 patients developed CIN, and the remaining 2089 did not. Therefore, the overall observed prevalence of the condition was 14.0%. However, as discussed in section 2.4.5, certain risk factors are known to increase the likelihood of CIN development, and these will now be discussed in relation to the included records, and the outcomes of this research. The first risk factor to be examined will be the comorbidities in the population under study.

5.2.3.1 Association of CIN risk ratio with patient comorbidities

Although the included studies provided data on the nature of comorbidities that were present in their patient populations, it was not possible to determine from the supplied information the total proportion of patients who had comorbidities that may have increased their risk of CIN and those who did not.

This data would have been useful in determining if included studies observed any association between the obtained RR, and the percentage population with comorbidities that are linked to an increased likelihood of CIN.

5.2.3.2 Association between CIN risk ratio and age

A positive association was observed between average patient age and RR. This is depicted in Figure 4.2. With the exception of the study by Cao et al (2018:369-375), all included studies observed a directly proportional relationship between increasing age and increase in RR. This is consistent with the information supplied by the KDIGO guidelines (2012:73).

The record by Cao et al (2018:369-375) had patients with the lowest average age of 59 years, but these authors obtained the highest RR relative to other studies. This study also administered the lowest average contrast medium dosage, and had the most stringent exclusion criteria to preclude patients with several different comorbidities from participating in the study. In light of these conditions, it is unclear why the study attained the highest RR. A speculative explanation may be that of ethnic origin. The study by Cao et al (2018:369-375) was performed in China. Therefore, it may be reasonably assumed that the majority of study participants were of Chinese origin. As discussed in Section 2.6, although primary studies investigating the prevalence of CIN on the African continent are few, the obtained incidence rates are higher than comparative studies performed in European countries. This may also be true for studies performed in Chinese populations, but the available data in this study is inconclusive, and further research is necessary to prove if indeed an association exists between ethnic origin and the likelihood of development of CIN in CA patients. Chawla, Turlington, Arora, and Jovin (2017:612) arrived at a similar conclusion in their publication, and underscored that the effect of race and ethnic origin on the development of CIN is poorly addressed in literature and warrants further investigation.

5.2.3.3 Association between CIN risk ratio and contrast media volume

Figure 4.3 shows the RR for each study and the average volume of contrast media that was administered. Within the included studies, there was no observed association between contrast medium volume and CIN incidence. This is at variance with the KDIGO (2012:79) guidelines that stipulate that risk of CIN development increases in tandem with higher contrast volumes. Solomon et al (2006:S40) report that the association between increased contrast medium volume and increased CIN incidence is controversial as it is not always demonstrated in research studies. However, the same authors do note that most studies that are able to prove this association are usually large, retrospective trials involving thousands of patients. Applying this logic, a larger number of patients may be required to prove this association, and it is possible that this study's patient population did not possess sufficient statistical power to establish the association between contrast medium volume and RR (Solomon et al 2006:S40).

5.2.4 Comparison of Ioversol and Iomeprol renal safety

LaBounty et al (2012:1599) note in their record that there is a paucity of literature with regards to large studies that directly compare renal safety between low-osmolar contrast media. In this systematic review, the researcher was unable to identify any peer-reviewed studies that directly compared the renal safety of Ioversol and Iomeprol in CA patients with CIN as a primary end-point. The null hypothesis in this study was that there is no statistical significance in CIN incidence when either Ioversol or Iomeprol is administered to CA patients. Pooling the RRs for included studies and performing a meta-analysis showed that the null hypothesis could not be rejected. This is consistent with what other authors have concluded, although they did not perform a head-to-head comparison for the two contrast media, as was done in this study (McCullough, Bertrand, Brinker & Stacul 2006:692).

5.3 IMPLICATIONS FOR CLINICAL PRACTICE

Section 5.2.3 discussed the incidence of CIN in adult CA patients when using Ioversol and Iomeprol, and this was found to be 14%. This is a high incidence, which warrants a recommendation that the use of these nephrotoxic radiological contrast media be minimised when possible, to avoid exposing patients to CIN. This recommendation is particularly important for patients of advanced age, due to the demonstrated association between increasing age and RR, as discussed in sub-section 5.2.3.2.

Despite the lack of statistical significance in CIN risk for the two contrast media under study, the records included in the review did show some considerable differences in the renal safety profiles. The three studies that looked at CIN development when Ioversol was used in CA patients obtained incidence percentages that ranged from 0 to 31.43%. However, in the Iomeprol group, there was a much narrower range of CIN incidence, which was 10.25 to 15.30%.

This sharp difference in the range of CIN incidence suggests that Ioversol and Iomeprol are tolerated very differently by the kidneys of CA patients. It is therefore strongly recommended that these contrast media be considered as having differing renal safety profiles, meaning clinicians should not use them interchangeably in clinical practice. Renal safety must always be taken into account when deciding which contrast medium to use. In clinical practice, this would make Iomeprol more desirable for use with regards to renal safety because the outcome is more predictable, as demonstrated by the observed narrower range of CIN incidence.

5.4 RECOMMENDATIONS FOR FUTURE RESEARCH

The hypothesis in this research was that Iomeprol results in a lower incidence of CIN compared to Ioversol for CA patients. This premise was based on the assumption that the addition of the nephrotoxic agent, edetate calcium disodium, during the commercial manufacture of Ioversol makes it more nephrotoxic. However, since Iomeprol does not contain any nephrotoxic additives, it may have a better renal safety profile. This systematic review and meta-analysis failed to validate this hypothesis, and found no statistically significant reduction in CIN rates when Iomeprol was used

for CA. Therefore, it can be inferred that edetate calcium disodium does not increase the overall nephrotoxicity of Ioversol.

Edetate calcium disodium is an example of a chelating agent, and these are usually added to contrast media during commercial manufacture to improve chemical stability and prolong shelf life (Mallinckrodt 2015:1-5). This research has shown no statistically significant difference in CIN incidence between a contrast medium that contains a chelating agent and one that does not when used for CA in a healthy adult population. This information may be of significance to manufacturers who are looking to develop new, safer types of contrast media, but are concerned about the usage of chelating salts as chemical stabilizers.

The association between ethnic origin and CIN remains unclear. While certain CIN risk factors such as diabetes are more prevalent in certain racial groups, it is yet to be investigated whether prevalence is higher in healthy populations of non-Caucasian individuals. Prospective studies and systematic reviews performed using primary data from African, Asian and mixed-race populations need to be carried out to establish this. The results of such research would assist clinicians dealing with such populations to make better informed decisions when recommending patients for CA examinations, particularly in situations where other non-contrast diagnostic examination options exist.

This research made use of CIN incidence data which was obtained from different countries, but it was noted that there is a paucity of primary studies carried out on the African continent. In South Africa, only a single primary study pertaining to CIN incidence was identified (Banda et al 2016). It is highly recommended that more research into CIN incidence be carried out within South African healthcare institutions, to avoid reliance on data sourced from foreign institutions, which may not necessarily be applicable within the local setting.

5.5 LIMITATIONS

Only peer-reviewed articles that were written in English were considered in this systematic review and meta-analysis. So, it is possible that a wealth of valuable data

in other languages was omitted. Additionally, no primary studies performed in Africa were included. It is unclear if ethnic origin plays a role in the observed incidences of CIN, but ideally the populations within included studies should have been more representative, with the inclusion of studies performed in Africa. This is particularly pertinent since this study was performed on the continent and is intended to be of relevance to African clinicians, in addition to the international community.
When considering study types, systematic reviews are considered to possess the strongest level of evidence. However, none were included in the selected articles limiting strength of evidence supplied.

The statistical analysis performed showed there was moderate heterogeneity of studies. This means any conclusions that are made are subject to further scrutiny, as ideally meta-analyses should possess no, or very low levels of heterogeneity for strong scientific conclusions to be derived (Haidich 2010:32).

The researcher executed data extraction in this study with no collaboration or assistance. This may have been a source of bias because ideally, two or more reviewers should be involved in the data extraction process to ensure robustness of a systematic review.

5.6 CHAPTER CONCLUSION

This chapter discussed the study's findings in relation to the aims and objectives outlined in Chapter 1. An assessment of the accuracy of the evidence was done, and the researcher concluded that this study offers moderate evidence that may be subject to further scrutiny. The null hypothesis in this study could not be rejected based on the evidence that was attained, and it was concluded that there is no statistically significant difference in nephrotoxicity between Ioversol and Iomeprol for randomly selected adult CA patients. The association between certain risk factors and CIN were discussed, and it was noted that although a positive correlation between advanced age and increased CIN risk could be established, increasing contrast medium volume did not have a bearing on the RR for CIN in this study, in variance with KDIGO guidelines. Iomeprol was deemed the better contrast agent for use in practice, because of a more predictable safety profile. It was also noted that there is a gap in literature with regards

to the effect of race and ethnic origin on the development of CIN, and this may help explain some incongruent findings in CIN incidence data, particularly when observing non-Caucasian populations. The chapter ends with the limitations of this study, and potential biases.

5.7 STUDY CONCLUSION

Chapter 1 gives an overview of the entire study, putting the research problem of CIN incidence when either Ioversol or Iomeprol are administered into context. The aims, objectives, and hypotheses are discussed, as well as the systematic review methodology. Chapter 2 provides greater depth and background to the research problem, with detailed explanations of CIN, CA, and the contrast media under study. In Chapter 3, the methodology used in this research is discussed, with an emphasis on adherence to the PRISMA statement to ensure that the systematic review is trustworthy, reliable, and compatible with internationally acceptable standards. Chapter 4 presents the results of the study, and analyses the data extracted. These results are both discussed and presented visually by means of graphs to illustrate the findings. Based on the obtained results, Chapter 5 draws conclusions, and addresses the aims, objectives, and hypotheses detailed in Chapter 1.

In summary, this systematic review has analysed and dissected literature relating to the renal safety associated with Ioversol and Iomeprol use for CA patients. The conclusion arrived at was that both contrast media have similar renal safety profiles. However, Iomeprol does appear to be more consistent in the obtained results with regards to renal safety, because the included studies showed it had a smaller range of CIN incidence, compared to Ioversol which had erratic results and a much wider range of incidences observed across different studies. In the absence of conflicting evidence, it may be preferable for clinicians to administer Iomeprol in preference to Ioversol when performing CA because of a higher level of predictability in CIN incidence when using this contrast medium.

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APPENDIX 1: Approval from university

UNISA university of south africa

RESEARCH ETHICS COMMITTEE: DEPARTMENT OF HEALTH STUDIES
REC-012714-039 (NHERC)

11 October 2017

Dear Mr Tawanda Gilbert Chipere

Decision: Ethics Approval

HSHDC/717/2017
Mr Tawanda Gilbert Chipere
Student No 6196-198-1
Supervisor: -Dr DD Mphuthi
Qualification: PhD
Joint Supervisor: -

Name: Mr Tawanda Gilbert Chipere

Proposal Contrast induced Nephropathy in Coronary angiography patients when using Loversol or Lomeprol

Qualification: **MPCHS94**

Thank you for the application for research ethics approval from the Research Ethics Committee: Department of Health Studies, for the above mentioned research. Final approval is granted from 11October 2017 to 11 October 2019.

The application was reviewed in compliance with the Unisa Policy on Research Ethics by the Research Ethics Committee: Department of Health Studies on 2 August 2017.

The proposed research may now commence with the proviso that:

1) *The researcher/s will ensure that the research project adheres to the values and principles expressed in the UNISA Policy on Research Ethics.*

2) *Any adverse circumstance arising in the undertaking of the research project that is relevant to the ethicality of the study, as well as changes in the methodology, should be communicated in writing to the Research Ethics Review Committee, Department of Health Studies. An amended application could be requested if there are substantial changes from the existing proposal, especially if those changes affect any of the study-related risks for the research participants.*

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3) *The researcher will ensure that the research project adheres to any applicable national legislation, professional codes of conduct, institutional guidelines and scientific standards relevant to the specific field of study.*

4) *[Stipulate any reporting requirements if applicable].*

Note:
The reference numbers [top middle and right corner of this communiqué] should be clearly indicated on all forms of communication [e.g. Webmail, E-mail messages, letters] with the intended research participants, as well as with the Research Ethics Committee: Department of Health Studies.

Kind regards,

Prof JE Maritz
CHAIRPERSON
maritje@unisa.ac.za

Prof MM Moleki
ACADEMIC CHAIRPERSON
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APPENDIX 2: Data collection form

Data collection form

Adapted from Cochrane Training Learning Resources: Data Collection for intervention reviews, 2014.

Title of Article	
Surname of First Author and Year	

Study eligibility

Study Characteristics	Eligibility criteria	Eligibility criteria met? Yes	No	Unclear	Location in text
Type of study		☐	☐	☐	
POPULATION: Age ≥ 18yrs		☐	☐	☐	
INTERVENTION: CA/PCI/both		☐	☐	☐	
OUTCOME: CIN		☐	☐	☐	
TIME: When were biomarkers measured?		☐	☐	☐	
INCLUDE ☐		EXCLUDE ☐			
Reason for exclusion					

DO NOT PROCEED IF STUDY EXCLUDED FROM REVIEW

Characteristics of included studies

Participants

	Description *Include comparative information for each intervention or comparison group if available*	Location in text or source
Population description *(from which study participants are drawn)*		
Setting *(including location and social context)*		
Inclusion criteria		

1

Inclusion criteria		
Exclusion criteria		
Total no. randomised		
Age		
Co-morbidities		

Other

Possible conflicts of interest *(for study authors)*		

Data and analysis

Dichotomous outcome

	Description as stated in report/paper				Location in source
Comparison					
Outcome					
Results	Ioversol		Iomeprol		
	No. of CIN cases	Total no. of patients	No. of CIN cases	Total no. of patients	
Any other relevant results reported					

APPENDIX 3: PRISMA checklist

PRISMA 2009 Checklist

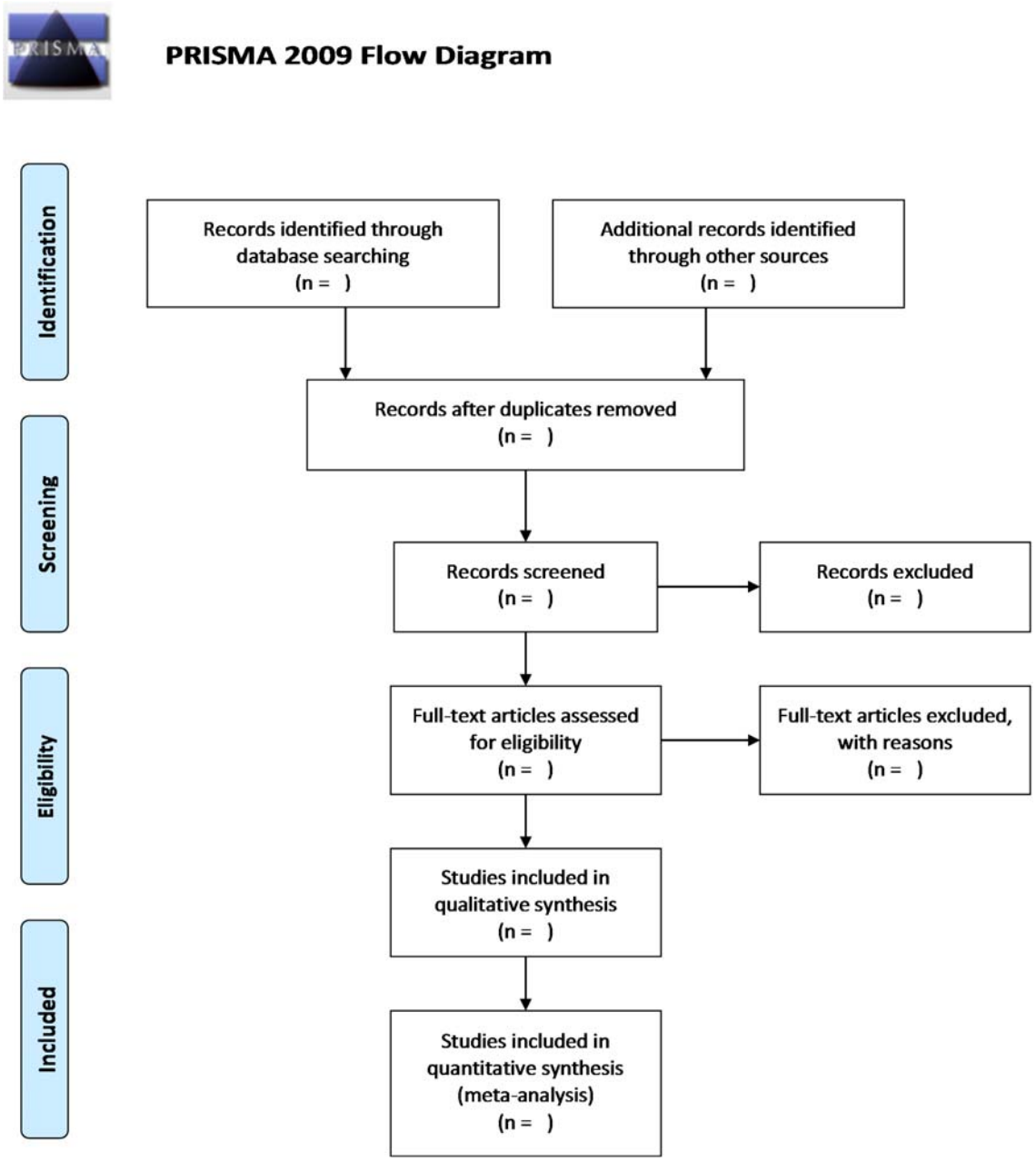
Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	Title Page
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	ii
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	6
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	41
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	46
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	49
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	49
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	49
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	50
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	51
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	52

Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	55
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	56

Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	57
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	58
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	63
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	65
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	71
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	78
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	81
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	83
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	84
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	87
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	93
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	95
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	95

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement.

APPENDIX 4: PRISMA flow diagram



From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

APPENDIX 5: CASP checklist for systematic reviews

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CASP Checklist: 10 questions to help you make sense of a Systematic Review

How to use this appraisal tool: Three broad issues need to be considered when appraising a systematic review study:

- Are the results of the study valid? (Section A)
- What are the results? (Section B)
- Will the results help locally? (Section C)

The 10 questions on the following pages are designed to help you think about these issues systematically. The first two questions are screening questions and can be answered quickly. If the answer to both is "yes", it is worth proceeding with the remaining questions. There is some degree of overlap between the questions, you are asked to record a "yes", "no" or "can't tell" to most of the questions. A number of italicised prompts are given after each question. These are designed to remind you why the question is important. Record your reasons for your answers in the spaces provided.

About: These checklists were designed to be used as educational pedagogic tools, as part of a workshop setting, therefore we do not suggest a scoring system. The core CASP checklists (randomised controlled trial & systematic review) were based on JAMA 'Users' guides to the medical literature 1994 (adapted from Guyatt GH, Sackett DL, and Cook DJ), and piloted with health care practitioners.

For each new checklist, a group of experts were assembled to develop and pilot the checklist and the workshop format with which it would be used. Over the years overall adjustments have been made to the format, but a recent survey of checklist users reiterated that the basic format continues to be useful and appropriate.

Referencing: we recommend using the Harvard style citation, i.e.: *Critical Appraisal Skills Programme (2018). CASP (insert name of checklist i.e. Systematic Review) Checklist. [online] Available at: URL. Accessed: Date Accessed.*

CASP
Critical Appraisal Skills Programme

Section A: Are the results of the review valid?

1. Did the review address a clearly focused question?

Yes ☑
Can't Tell ☐
No ☐

HINT: An issue can be 'focused' In terms of
- the population studied
- the intervention given
- the outcome considered

Comments: The population studied was randomly-selected adults undergoing coronary angiography examinations, where either Iomeprol or Ioversol were used. The outcome considered was contrast-induced nephropathy. Two interventions were considered, namely coronary angiography and percutaneous coronary intervention as these two examinations are freuquently combined.

2. Did the authors look for the right type of papers?

Yes ☑
Can't Tell ☐
No ☐

HINT: 'The best sort of studies' would
- address the review's question
- have an appropriate study design (usually RCTs for papers evaluating interventions)

Comments: The search strategy is detailed in Section 3.4.1 (page 49). Key terms relating to the research title, such as 'contrast-induced nephropathy', and 'coronary angiography' were used in the search strategy. Synonyms and Boolean operators were used to increase the number of results obtained. Due to the paucity of information, no search restrictions were placed regarding the study type so that as many relevant articles as possible were retrieved.

Is it worth continuing?

3. Do you think all the important, relevant studies were included?

Yes ☑
Can't Tell ☐
No ☐

HINT: Look for
- which bibliographic databases were used
- follow up from reference lists
- personal contact with experts
- unpublished as well as published studies
- non-English language studies

Comments: 5 databases were used in the information search, namely Medline, Scopus, Pubmed Clinical Queries, CINHAL, and Science Direct. These are databses which contain millions of peer-reveiwed articles which cover numerous topics within the medical field. Reference lists were also used to find relevant articles. No unpublished articles were included in the review, and only English titles were considered. These have been discussed as limitations to the study in Section 5.5.

CASP
Critical Appraisal Skills Programme

4. Did the review's authors do enough to assess quality of the included studies?

Yes ☑
Can't Tell ☐
No ☐

HINT: The authors need to consider the rigour of the studies they have identified. Lack of rigour may affect the studies' results ("All that glisters is not gold" Merchant of Venice – Act II Scene 7)

Comments: Bias and quality scoring for each of the included studies was performed to assess the strength of evidence. This was done from section 4.4 to section 4.5.5. Table 4.2 is a graphic representation of the quality and bias scoring. Part of the scoring was based on an international standard- the Cochrane Risk of Bias tool. Statistical methods were also used to assess quality - Figure 4.5 shows a funnel plot which was used to check for publication bias and its potential effect on included studies.

5. If the results of the review have been combined, was it reasonable to do so?

Yes ☑
Can't Tell ☐
No ☐

HINT: Consider whether
- results were similar from study to study
- results of all the included studies are clearly displayed
- results of different studies are similar
- reasons for any variations in results are discussed

Comments: All studies included used contrast-induced nephropathy as an end-point with which to assess renal safety of the contrast media. Risk ratios were computed from the supplied data in each study so that a comparable platform of comparison could be established. All studies had clearly available risk ratio data which was used for pooling during the meta-analysis. One study showed variation from the other studies (LaBounty et al 2012:1594-1599) and this was discussed in section 4.6.1.

Section B: What are the results?

6. What are the overall results of the review?

HINT: Consider
- If you are clear about the review's 'bottom line' results
- what these are (numerically if appropriate)
- how were the results expressed (NNT, odds ratio etc.)

Comments: There was no statistically significant difference in the risk of contrast-induced nephropathy development when either loversol or lomeprol was used for coronary angiography adult patients. The pooled summary effect of all the included studies using the random effects model showed that p=0.466, so the null hypothesis could not be rejected (section 5.2.2). Results were expressed as risk ratios.

CASP
Critical Appraisal Skills Programme

7. How precise are the results?

HINT: Look at the confidence intervals, if given

Comments: A 95% confidence interval was used in this study (Figure 4.4 and section 1.2.1).

Section C: Will the results help locally?

8. Can the results be applied to the local population?

Yes ☑
Can't Tell ☐
No ☐

HINT: Consider whether
- the patients covered by the review could be sufficiently different to your population to cause concern
- your local setting is likely to differ much from that of the review

Comments: Included studies were performed on patient populations from 6 different countries. However, the study does note that no included studies were undertaken in Africa so this may be a limitation when applying the results to an African population. With the limited number of primary studies on the topic undertaken in Africa, it is reasonable to use data from studies undertaken in other parts of the world until local data becomes available.

9. Were all important outcomes considered?

Yes ☑
Can't Tell ☐
No ☐

HINT: Consider whether
- there is other information you would like to have seen

Comments: Association of contrast-induced nephropathy with age, as well as contrast media volume was discussed. Association of the condition with certain comorbidities was considered, but the information from the included studies could not be used for analysis due to the way data was presented in the studies.

10. Are the benefits worth the harms and costs?

Yes ☑
Can't Tell ☐
No ☐

HINT: Consider
- even if this is not addressed by the review, what do you think?

Comments: The systematic review did not address this question of harms and costs as it was not the primary focus of the study. However, the overall incidence of contrast-induced nephropathy in coronary angiography when using Iomeprol and Ioversol was shown to be 14% (section 5.2.3). The benefits of coronary angiography and percutaneous coronary intervention may potentially save a life, and so the risk of contrast-induced nephropathy and its associated costs may be worth enduring, given the benefits of the interventions.