

# **Prescribing patterns of non-steroidal anti-inflammatory drugs in patients with chronic kidney disease**

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*Deuteronomy 33:25*

*“Thy shoes shall be iron and brass; and as thy days, so shall thy strength be”*

## LIST OF ACRONYMS AND ABBREVIATIONS

ACE	Angiotensin-converting enzymes
ACR	Albumin-to-creatinine ratio
AER	Albumin excretion rate
ANOVA	Analysis of variance
APD	Automated peritoneal dialysis
ARB	Angiotensin receptor blocker/antagonist
ASA	Acetylsalicylic acid
BUN	Blood urea nitrogen
CDL	Chronic disease list
CKD	Chronic kidney disease
COX	Cyclooxygenase
CRC	Colorectal cancer
CVD	Cardiovascular disease
DPP-4	Dipeptidyl peptidase-4
DUR	Drug utilisation review
eGFR	Estimated glomerular filtration rate
eGFRcystatinC	Cystatin C-based estimate of glomerular filtration rate
ESRD	End-stage renal disease
FDA	Food and Drug Administration
FSGS	Focal segmental glomerulosclerosis
GFR	Glomerular filtration rate
GI	Gastro-intestinal

GLP-1	Glucagon-like peptide-1
HREC	Health Research Ethics Committee
IASP	International Association for the Study of Pain
IL-1	Interleukin-1
ISN	International Society of Nephrology
MCD	Minimal changed disease
MDRD	Modification of Diet in Renal Disease Study
MGN	Membranous glomerulonephritis
MIMS	Monthly Index of Medical Specialities
MUSA	Medicine Usage in South Africa
NAPPI	National Pharmaceutical Product Interface
NSAIDs	Non-steroidal anti-inflammatory drugs
OTC	Over-the-counter
PBM	Pharmaceutical Benefit Management company
PCR	Protein-to-creatinine ratio
PER	Protein excretion rate
PDD	Prescribed daily dosage
PGE <sub>2</sub>	Prostaglandin E2
PGI <sub>2</sub>	Prostaglandin I2
SAMF	South African Medicines Formulary
SIGN	Scottish Intercollegiate Guidelines Network
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
TNF	Tumour necrosis factor

Tukey's HSD

Tukey's honestly significant difference

WHO

World Health Organization

## **PREFACE**

This study was presented in an article format, with Chapter 3 containing the results in the form of two manuscripts. The two manuscripts were submitted for publication to the following journals:

- *South African Family Practice*
- *International Journal of Clinical Pharmacy*

The study was divided into four chapters:

- Chapter 1 provides a brief background on the study, along with the objectives, the methodology and statistical methods used, as well as the ethical considerations applicable to this research.
- Chapter 2 offers a literature review that provides detailed information on non-steroidal anti-inflammatory drugs (mechanism of action, adverse effects, prescribing patterns, etc.) and chronic kidney disease (classification, treatment, prevalence, etc.), and concludes with the renal effects of NSAIDs and their use in CKD patients.
- The two manuscripts for this study are provided in Chapter 3, which includes the results and discussions of this study.
- This study is concluded with Chapter 4, which includes the conclusions, limitations, strengths and recommendations for further studies.
- The references and annexures for the study are found at the end.

The co-authors were the supervisor and co-supervisors and they approved this study as well as the two manuscripts. The contributions to the study of each of the authors are listed on the following pages.

## AUTHOR'S CONTRIBUTIONS (STUDY)

The contribution of each author of the study, entitled "Prescribing patterns of non-steroidal anti-inflammatory drugs in patients with chronic kidney disease" is stipulated below:

Author	Role in the study
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Dr JM du Plessis (Supervisor)	Guidance in selection of the research topic Supervision of concept and design of the study and manuscript Supervising the writing of the literature review and manuscript Cautious reviewing of the manuscript for intellectual content and eventual approval of version to be published
Dr JR Burger (Co-supervisor)	Co-supervision of the concept and design of the study and manuscript Guidance in the interpretation of the results Supervision in the writing of the manuscript Cautious reviewing of the manuscript for intellectual content and eventual approval of the version to be published
Prof MS Lubbe (Co-supervisor)	Co-supervision of the concept and design of the study and manuscript Acquisition of data Programming for statistical analysis of data Cautious reviewing of the manuscript for intellectual content and eventual approval of the version to be published
Ms M Cockeran	Verified all the results obtained from the statistical analyses

The co-authors confirm their different roles in this study, as well as their permission that the manuscript may form part of the dissertation:

*I declare that I have approved the above-mentioned manuscript and that my role in this study, as indicated above, is a representation of my actual contribution, and I hereby give my consent*

*that it may be published as part of the master's degree in Pharmacy Practice of Mr WP Meuwesen.*

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## AUTHOR'S CONTRIBUTIONS (MANUSCRIPT 1)

The contribution of each author to manuscript 1, entitled "Prevalence of chronic kidney disease (CKD) and co-occurring chronic conditions in the private health sector of South Africa" is stipulated below:

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Dr JR Burger (Co-supervisor)	Co-supervision of concept and design of the manuscript Guidance in the interpretation of the results Supervision in the writing of the manuscript Cautious reviewing of the manuscript for intellectual content and eventual approval of the version to be published
Prof MS Lubbe (Co-supervisor)	Co-supervision of concept and design of the manuscript Acquisition of data Programming for statistical analysis of data Cautious reviewing of the manuscript for intellectual content and eventual approval of the version to be published
Ms M Cockeran	Verified all the results obtained from the statistical analyses

The co-authors confirm their different roles in this study, as well as their permission that the manuscript may form part of the dissertation:

*I declare that I have approved the above-mentioned manuscript and that my role in this study, as indicated above, is a representation of my actual contribution, and I hereby give my consent that it may be published as part of the master's degree in Pharmacy Practice of Mr WP Meuwesen.*

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The contribution of each author for manuscript 2, entitled "Prescribing patterns of non-steroidal anti-inflammatory drugs in chronic kidney disease (CKD) patients in the private health care sector of South Africa" is stipulated below:

Author	Role in the study
Mr WP Meuwesen	Literature review for introduction Planning and designing the manuscript Interpretation of results Writing the final conclusions of the manuscript
Dr JM du Plessis (Supervisor)	Supervision of concept and design of manuscript Cautious reviewing of the manuscript for intellectual content and eventual approval of the version to be published
Dr JR Burger (Co-supervisor)	Co-supervision of concept and design of the manuscript Guidance in the interpretation of the results Supervision in the writing of the manuscript Cautious reviewing of the manuscript for intellectual content and eventual approval of version to be published
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Ms M Cockeran	Verified all the results obtained from the statistical analyses

The co-authors confirm their different roles in this study, as well as their permission that the manuscript may form part of the dissertation:

*I declare that I have approved the above-mentioned manuscript and that my role in this study, as indicated above, is a representation of my actual contribution, and I hereby give my consent that it may be published as part of the master's degree in Pharmacy Practice of Mr WP Meuwesen.*

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## ABSTRACT

Prescribing patterns of non-steroidal anti-inflammatory drugs in chronic kidney disease patients

The main aim of this study was to characterise the prescribing patterns of non-steroidal anti-inflammatory drugs (NSAIDs) in chronic kidney disease (CKD) patients in the private health sector of South Africa. This was done after determining the prevalence of the disease (CKD) in the private health sector. A quantitative, descriptive drug-utilisation review (DUR) was performed during the empirical investigation by using retrospective medicine claims data obtained from a pharmaceutical benefit management company (PBM). The study population consisted of all patients registered on the database with an ICD-10 code for CKD (N18) during the study period of 1 January 2009 to 31 December 2013.

The number of CKD patients identified over the study period ranged from 1 017 to 1 158 and represented 0.10 to 0.14% of the total number of registered beneficiaries included in the database. The patients were predominantly male (male-to-female ratio 1:0.8) ( $p=0.668$ ; Cramer's  $V=0.021$ ), whereas the 35–64-year age group indicated the highest CKD prevalence rates ( $p=0.014$ ; Cramer's  $V=0.039$ ) with a mean age ranging from  $59.7 \pm 16.8$  (95% CI 58.7;60.7) years in 2009 to  $57.8 \pm 16.1$  (95% CI 56.9;58.8) years in 2013. There were several chronic conditions that co-occurred with CKD, with hypertension being the most prevalent, occurring in more than half the CKD patients. Other prevalent chronic conditions co-occurring with CKD included hyperlipidaemia (36 to 43%) and diabetes mellitus type 2 (19 to 25%). No practically significant associations were found between CKD prevalence and the patient's age or gender.

Non-steroidal anti-inflammatory drugs were prescribed in 26% ( $n=309$ ) to 40% ( $n=492$ ) of the CKD patients from 2009 to 2013. The mean number of NSAID items per CKD patient ranged from  $2.4 \pm 2.67$  (95% CI 2.1;2.6) in 2009 to  $1.9 \pm 1.2$  (95% CI 1.7;1.9) in 2013. No association was found between gender and CKD patients who received NSAIDs vs. those who did not ( $p<0.05$ ; Cramer's  $V<0.01$ ). A weak association was found between CKD patients who used NSAIDs vs. those who did not and age groups ( $p<0.05$ ; Cramer's  $V\geq 0.1$ ). The NSAID that was prescribed the most was diclofenac (34.3%), followed by the COX-2 inhibitors celecoxib (18.8%), meloxicam (19.5%) and etoricoxib (9.5%). The NSAIDs were mostly prescribed in dosages similar to and even exceeding the recommended daily dosage for these NSAIDs in patients with normal kidney function. Non-steroidal anti-inflammatory drugs that were regularly prescribed in dosages greater than the recommended daily dosage were ibuprofen (44.9%), indomethacin (39.1%) and diclofenac (12.8%). The general medical practitioners were responsible for prescribing NSAIDs most frequently, with 61.6% of the NSAID items prescribed.

In conclusion this study determined that CKD has several chronic conditions co-occurring with it, which should be accounted for when treatment and management of disease is being considered. Secondly, nephrotoxic drugs (NSAIDs) are frequently prescribed to patients who have a reduced renal function. There is no difference between the dosages at which these drugs are prescribed to CKD patients and the recommended daily dosages of these drugs in patients with healthy kidneys. Further research should be conducted to improve pain management in CKD patients.

Keywords: prevalence, prescribing patterns, CKD, NSAIDs, chronic conditions, hypertension, private health sector, South Africa

## OPSOMMING

Voorskrifpatrone van nie-steroïed anti-inflammatoriese middels by pasiënte met kroniese niersiekte

Die hoofdoel van die studie was om die voorskrifpatrone van nie-steroïed anti-inflammatoriese middels (NSAIM's) by pasiënte met kroniese niersiekte (KNS) in die private gesondheidssektor van Suid-Afrika te ondersoek. 'n Kwantitatiewe, beskrywende medisyneverbruiksevaluering is gedurende die empiriese navorsing uitgevoer deur retrospektiewe medisyne-eisedata, verkry vanaf 'n nasionaal verteenwoordigende farmaseutiese voordelemaatskappy, te gebruik. Die studiepopulasie het bestaan uit alle pasiënte wat op die databasis geregistreer is met 'n ICD-10-kode vir KNS (N18) gedurende die studietydperk van 1 Januarie 2009 tot 31 Desember 2013.

Die getal KNS-pasiënte wat gedurende die studietydperk geïdentifiseer is, het tussen 1 017 en 1 158 gewissel, wat 0.10% tot 0.14% van die totale getal geregistreerde begunstigdes in die databasis verteenwoordig. Die pasiënte was oorwegend manlik (manlik-tot-vroulik-verhouding 1:0.8) ( $p=0.668$ ; Cramer's  $V=0.021$ ). Die ouderdomsgroep met die hoogste KNS-voorkoms was die 35–64-jaargroep ( $p=0.014$ ; Cramer's  $V=0.039$ ) met 'n gemiddelde ouderdom van die pasiënte wat wissel van  $59.7 \pm 16.8$  (95% CI 58.7;60.7) jaar in 2009 tot  $57.8 \pm 16.1$  (95% CI 56.9;58.8) jaar in 2013. Verskeie kroniese kondisies wat saam met KNS voorkom, is geïdentifiseer, waarvan hipertensie, die algemeenste, by meer as die helfte van die KNS-pasiënte voorgekom het. Ander algemene kondisies wat saam met KNS voorkom, het hiperlipidemie (36 tot 43%) en diabetes mellitus type 2 (19 tot 25%) ingesluit. Daar was geen prakties betekenisvolle assosiasie tussen KNS-voorkoms en die pasiënte se ouderdom of geslag nie.

Nie-steroïed anti-inflammatoriese middels is tussen 2009 en 2013 by 26% ( $n=309$ ) tot 40% ( $n=492$ ) van die KNS-pasiënte voorgeskryf. Die gemiddelde NSAİM-items per KNS-pasiënt het tussen  $2.4 \pm 2.67$  (95% CI: 2.1;2.6) in 2009 tot  $1.9 \pm 1.2$  (95% CI 1.7;1.9) in 2013 gewissel. Daar was geen assosiasie tussen geslag en KNS-pasiënte wat 'n voorskrif vir NSAİM's ontvang het teenoor dié wat dit nie ontvang het nie ( $p<0.05$ ; Cramer's  $V<0.01$ ). Daar bestaan 'n "swak" assosiasie tussen KNS-pasiënte wat 'n voorskrif vir NSAİM's ontvang het en dié wat dit nie ontvang het nie en ouderdomsgroep ( $p<0.05$ ; Cramer's  $V\geq 0.1$ ). Diklofenak is die NSAİM wat die algemeenste (34.3%) voorgeskryf is, gevolg deur die siklo-oksigenase-2- (COX-2-) remmers celekoksib (18.8%), meloksikam (19.5%) en etorikoksib (9.5%). Die dosisse waarin die NSAİM's vir KNS-pasiënte voorgeskryf is, was soortgelyk aan die aanbevole daaglikse dosis van dié NSAİM's vir pasiënte met 'n normale nierfunksie, en het selfs in sommige gevalle dié dosis oorskry. Die NSAİM's wat gereeld die aanbevole daaglikse dosis van die middels oorskry het,

was ibuprofeen (44.9%), indometasien (39.1%) en diklofenak (12.8%). Die algemene geneesher was die voorskrywers wat NSAIM's die meeste voorgeskryf het, met 61.6% van die voorskrifte.

Die studie het bepaal dat KNS saam met verskeie ander kroniese kondisies kan voorkom, wat in ag geneem moet word wanneer besluite rakende die behandeling en bestuur van die siekte geneem word. Tweedens, nefrotoksiese geneesmiddels (NSAIM's) word gereeld by pasiënte met verminderde nierfunksie voorgeskryf. Daar is egter geen verskil in die dosisse waarin hierdie geneesmiddels by KNS-pasiënte voorgeskryf word en die aanbevole daaglikse dosis van die middels by pasiënte met normale nierfunksie nie. Verdere navorsing moet uitgevoer word om die pynbeheer by KNS-pasiënte te bevorder.

Trefwoorde: voorkoms, voorskryfpatrone, KNS, NSAIM's, kroniese kondisies, hipertensie, private gesondheidssektor, Suid-Afrika

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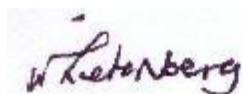
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## EDITING

### LANGUAGE EDITOR DECLARATION

I hereby declare that I completed the text editing on this dissertation, entitled *Prescribing patterns of non-steroidal anti-inflammatory drugs in patients with chronic kidney disease*, submitted in partial fulfilment of the requirements for the degree Magister Pharmaciae in Pharmacy Practice at the North-West University, Potchefstroom Campus, for Pieter Meuwesen, 22125515.



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# CHAPTER 1: INTRODUCTION

## 1.1 Introduction

Non-steroidal anti-inflammatory drugs (NSAIDs) are among the most commonly used pharmaceutical agents worldwide. According to Schnitzer (2006:S22-S23), NSAIDs are widely used in the treatment of inflammation and musculoskeletal pain. Pain, especially chronic pain, is an increasing medical concern because of the relatively high prevalence of the condition in South Africa and the world.

Non-steroidal anti-inflammatory drugs have several adverse effects, one of which is serious adverse effects on the kidneys. This means that NSAIDs, which are nephrotoxic drugs, should be used with caution or even avoided completely in high-risk patients such as patients with chronic kidney disease (CKD).

Levey *et al.* (2003:138) define CKD as either kidney damage or decreased kidney function (measured by a decrease in glomerular filtration rate (GFR)) for three months or more. In 2010, CKD was the 18th highest cause of death worldwide (Stanifer, 2014:e174), increasing in ranking from the 27th position in 1990 (Lozano *et al.*, 2012:2095). This change in ranking was related to an 82% increase in global deaths overall, which was the third highest increase of all diseases, after HIV/AIDS (396%) and diabetes (93%).

The prescribing patterns of NSAIDs in patients with CKD is therefore of great concern and was analysed in this research.

## 1.2 Background

Non-steroidal anti-inflammatory drugs, which include, *inter alia*, ibuprofen, celecoxib, diclofenac, and naproxen (Schnitzer, 2006:S22-S23), inhibit cyclooxygenase (COX) -enzymes, thereby inhibiting the release of prostaglandins and therefore exercising an anti-inflammatory, analgesic and antipyretic effect (Schnitzer, 2006:S23; Solomon, 2014).

Non-steroidal anti-inflammatory drugs are widely prescribed in patients with pain conditions. Prevalence rates of these drugs vary widely, ranging from 20% of prescriptions (n=3 796) in Abha City (Al-Homrany & Irshaid, 2007:372), to 35% in Italy (Motola *et al.*, 2004:734), up to nearly 60% in Denmark (Fosbøl *et al.*, 2008:824).

The high frequency of NSAID use is due to the high prevalence of pain in the global population. According to the American Academy of Pain Medicine (2011), approximately 100 million Americans suffer from chronic pain, which is almost double the number of patients with

diabetes, cancer and heart diseases combined. In a survey on the prevalence of pain conducted in the Netherlands, Picavet and Schouten (2003:169) reported that 74.5% of the Dutch population older than 25 years complained of musculoskeletal pain during the 12 months prior to the inception of the study. Of these patients, 53.9% reported pain during the survey, and 44% reported musculoskeletal pain during the three months prior to inception. They also found that 28% of the Dutch population consulted a healthcare professional on an annual basis because of musculoskeletal pain (Picavet & Schouten, 2003:176).

High prevalence rates of chronic pain have also been reported in the general population of other countries, e.g. Scotland (46.5%) (Elliot *et al.*, 1999:1248-1252) and the Northern Sydney area in Australia (22.1%) (Blyth *et al.*, 2003:43). According to Verhaak *et al.* (1998:232), between 25 and 30% of the populations in industrialised countries have chronic pain. In South Africa, studies done in a rural community in the Eastern Cape (Igumbor *et al.*, 2011:65) and Mthatha (Puone *et al.*, 2011:329) revealed that 42.9% and 38.5% of the study populations, respectively, reported having chronic pain.

Non-steroidal anti-inflammatory drugs, like any other drug, have several adverse effects and because NSAIDs can be obtained easily, these effects are often considered as not being that serious. The different NSAIDs all conform to a plateau of effectiveness, despite the maximum dosage (Schnitzer, 2006:S23). However, the risk of side effects increases with an increasing dosage (Gøtzche, 2010). General adverse effects of NSAIDs include nausea, vomiting, constipation and fluid retention, resulting in oedema. More serious side effects of NSAIDs include liver failure, ulcers of the stomach and prolonged bleeding after an injury or surgery (Sostres *et al.*, 2010:123).

Non-steroidal anti-inflammatory drugs and COX inhibitors furthermore inhibit renal prostaglandin synthesis, which results in a decrease in blood flow as well as glomerular filtration rate (Murray & Brater, 1990:559-560), causing renal impairment. In healthy individuals, the effects on the kidneys cause little renal damage, but exceptions are seen in endurance athletes such as ultra-marathon runners. This effect of NSAIDs in athletes may be ascribed to volume depletion and the subsequent impaired urine-diluting capacity of the kidney, causing renal damage (Rosner & Kirven, 2007:152-153). The adverse effects of NSAIDs on the kidneys are also more pronounced in patients at risk, such as patients with chronic renal insufficiency (e.g. chronic kidney disease (CKD)) and other risk factors, including renal failure, systemic lupus erythematosus, congestive cardiac failure and hepatic cirrhosis (Unsworth *et al.*, 1987:233; 236).

According to Launay-Vacher *et al.* (2005:138-141), NSAIDs should not be used in patients with chronic renal failure – acetaminophen (650 mg every six hours) or a low-dose aspirin should be

used instead. If NSAIDs cannot be avoided, additional risk factors such as volume depletion, angiotensin receptor antagonist (ARB) intake, or potassium-sparing diuretics should be avoided (Launay-Vacher *et al.*, 2005:140).

The use of NSAIDs increases with age. For instance, in an epidemiological study done in the United Kingdom (UK), approximately one in five people between the ages of 65 and 74 years were using NSAIDs (Blower *et al.*, 1996:286). Based on a systematic review that included all potentially relevant publications before July 2006 done by Zhang and Rothenbacher (2008:1), the median prevalence of CKD was 7.2% in individuals aged 30 years and older, and 23.4 to 35.8% in individuals 64 years and older. Data that was retrieved during the period 2000 to 2003 by Nahas and Bello (2005:332) shows the European average for the prevalence of end-stage renal disease to be 700 per million, whereas in the United States the overall average is 1 403 per million.

The South African Council for Medical Schemes has constructed a chronic disease list (CDL) that specifies the registered 26 chronic conditions in South Africa. Chronic kidney disease is among the CDL conditions in South Africa (Council for Medical Schemes, 2010). A medical scheme has to cover medication, doctors' consultations and tests relating to the condition if the condition is one of the 26 listed chronic diseases.

Toto *et al.* (1986:760) state that renal function should be closely monitored, and dosages of NSAIDs adjusted for patients with renal insufficiency. In a study conducted in 2007 on 92 CKD patients, 69% of these patients experienced pain (Cohen *et al.*, 2007:921). According to a recent study conducted by Platinga *et al.* (2011:426) in an American population with CKD, the mean number of NSAID agents taken per day was 3.0 for normal kidney patients, 3.3 for mild CKD patients and 2.6 agents for moderate to severe CKD patients. This emphasises the importance that pain management in CKD patients is of concern to healthcare professionals.

On the basis of the above discussion it is evident that the risks of NSAID use in patients at risk, especially CKD patients, should be emphasised. Great caution should be exercised by prescribers when prescribing NSAIDs to these patients. It has, however, been shown that anti-inflammatory drugs are being prescribed to and used on a daily basis by CKD patients.

With this being the problem, the research questions formulated for this study were:

- How prevalent is impaired renal function in South Africa and other countries?
- How prevalent is the use of NSAIDs for the treatment of pain and inflammation in South Africa and other countries?
- What effect do NSAIDs have on renal function?

- How are NSAIDs prescribed to patients with CKD in the private health sector of South Africa?

### **1.3 Research aims and specific objectives**

The general aim of the study was to investigate the current prescribing patterns of NSAIDs in CKD patients in the private health sector of South Africa by using data from a medicine claims database for the period of 1 January 2009 to 31 December 2013.

This study consisted of a literature review and an empirical investigation.

The specific objectives for the literature review included the following:

- To investigate the prevalence of impaired renal function in South Africa and other countries.
- To investigate the prevalence of NSAID use in South Africa and other countries.
- To investigate the safety concerns regarding NSAID use, especially with respect to the effect on the kidneys.
- To investigate the prevalence of NSAID use in patients with impaired renal function in South Africa and other countries (All addressed in Chapter 2).

The specific objectives for the empirical investigation included the following:

- To determine the prevalence of CKD over the study period using the data from a medicine claims database, stratified by age, gender and co-occurring chronic conditions (Manuscript 1).
- To determine the proportion of CKD patients receiving NSAIDs using data from a medicine claims database (Manuscript 2).
- To characterise the prescribing patterns (age, gender, type of NSAID and dosage of NSAID) of NSAID-prescribed CKD patients using the medicine claims data (Manuscript 2).
- To characterise the prescribing patterns of NSAIDs in patients with CKD, stratified by prescriber specialty (Manuscript 2).

### **1.4 Research methodology**

The research for this study consisted of two phases, namely a literature review and an empirical investigation.

#### **1.4.1 Literature review**

The literature review was conducted by using books, articles, as well as internet sources. Keywords used in the search (as single entities and in combination) were: chronic kidney

disease, CKD, prevalence of chronic kidney disease, pain statistics, treatment of pain, analgesic use in renal insufficiency, NSAID use and NSAID use in chronic kidney disease patients.

## **1.4.2 Empirical investigation**

A quantitative, retrospective drug utilisation review was performed in this study. The method used in conducting the empirical investigation will be discussed further.

### **1.4.2.1 Study design**

Numerical information, e.g. the percentage of CKD patients using NSAIDs, was analysed and no interviews were conducted, thereby giving the study a quantitative research design. Further evidence to confirm this design is that information and data were collected under controlled conditions and the researcher did not participate in the collection; logical reasoning was used to analyse and interpret the data received, and structured procedures were used to collect the information (Brink *et al.*, 2012:10).

According to Hopkins (2008), the aim of quantitative research is to determine the relationship between two variables, called the dependent and independent variable, in a population. This study also compared several variables while the statistical analysis was done. Borland (2003) further states that the purpose of quantitative research is to describe, predict and control. This is done by isolating specific variables by controlling the environment, e.g. sampling techniques, and investigating the relationship between these variables while eliminating any confounding variables.

The prevalence of drug use was studied, making this a descriptive, quantitative study. Descriptive studies are also called observational studies because subjects are observed without the researcher intervening in the study (Hopkins, 2008). Brink *et al.* (2012:112) state that descriptive studies describe the variables in order to answer the research questions. Descriptive studies describe the existing distribution of variables without taking other hypotheses into account and are often used to monitor trends and search for clues to the cause of diseases (Grimes & Schultz, 2002:145-148). Grimes and Schultz (2002:145) simplify the use of descriptive studies by stating that a good descriptive study should be able to answer the five basic “W” questions, which are “who”, “what”, “why”, “when” and “where”.

### **1.4.2.2 Setting and data source**

The data used in this study was obtained from a medicine claims database of a Pharmaceutical Benefit Management company (PBM) (the identity of the database may not be disclosed due to a confidentiality agreement). Data from 1 January 2009 to 31 December 2013 was used.

Data fields on the database that was used included:

- Prescription number
- Date of birth of patient
- Gender of patient
- The date of dispensing of the prescription
- NAPPI codes
- NAPPI code description
- ICD-10 code (N18 for CKD)
- Quantity of medicine items prescribed
- Days' of medicine supplied
- Prescriber specialty
- Drug trade name
- Encrypted patient member number
- Encrypted dependant code

#### **1.4.2.3 Target population**

The target population for this study included all CKD patients in the South African private health sector who are beneficiaries of medical aid schemes with the same beneficiary profile as those contracted with the PBM.

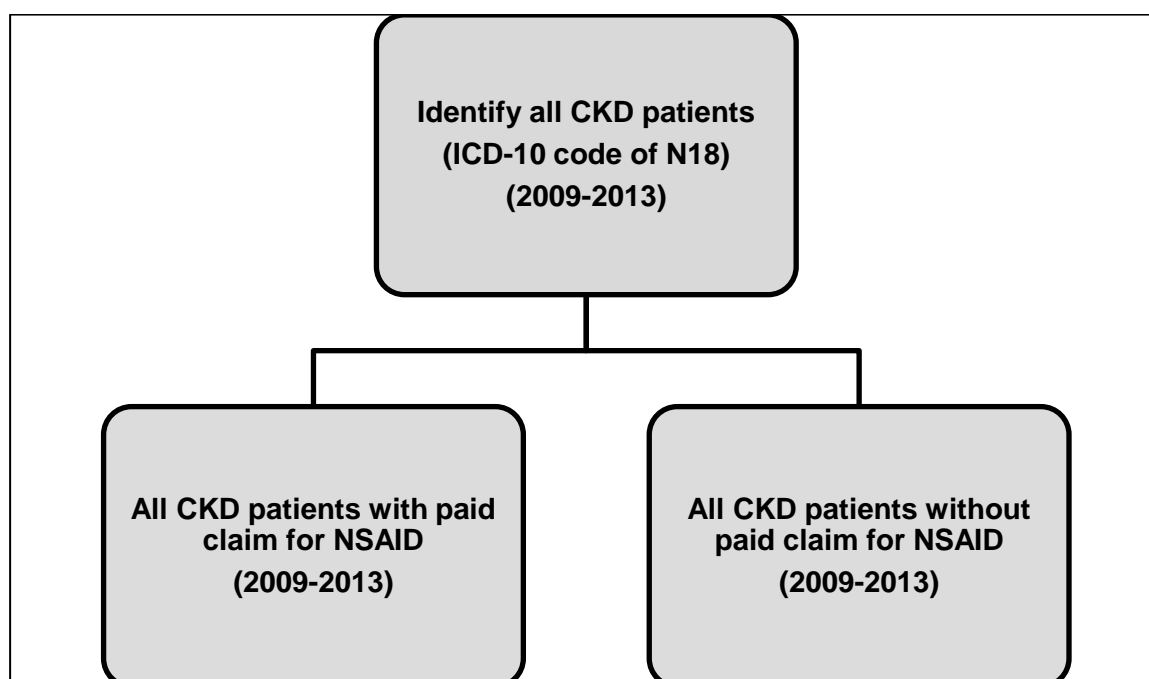
#### **1.4.2.4 Study population**

The study population consisted of all patients with an ICD-10 code for a CKD (N18) during the time period 1 January 2009 to 31 December 2013.

The following inclusion and exclusion criteria were applied in the study: Trade name of the drug, the National Pharmaceutical Product Interface (NAPPI) code, the date the prescription was filled and presence or absence of ICD-10 codes for a PMB chronic disease list condition. This process is explained by Table 1-1 and Figure 1-1.

**Table 1-1: Inclusion and exclusion criteria**

Inclusion criteria	Exclusion criteria
<p><b>Date the prescription was filled (study period):</b> Prescriptions for a five-year period (Jan 2009 to Dec 2013) were included in the analysis.</p> <p><b>Trade name of the drug:</b> The drugs that were identified and included in the analysis were the NSAIDs that are listed by Snyman (2012:78-89) in the Monthly Index of Medical Specialities (MIMS).</p> <p><b>NAPPI code:</b> The NAPPI code of the NSAIDs was used to identify the NSAIDs on the database and is discussed in paragraph 1.4.3.3.1.</p> <p><b>ICD-10 codes for PMB chronic disease list conditions:</b> All patients with an ICD-10 code of N18.</p>	<p><b>Date the prescription was filled (study period):</b> If the prescription was filled outside the study period (Jan. 2009-Dec 2013).</p> <p><b>Trade name of the drug:</b> If the drugs were not listed under NSAIDs by Snyman (2012:78-89) in the MIMS.</p> <p><b>NAPPI code:</b> All NAPPI codes that did not correspond with those of NSAIDs.</p> <p><b>ICD-10 codes for PMB chronic disease list conditions:</b> All patients with an ICD-10 code other than N18.</p>



**Figure 1-1: Steps in selection of study population**

### 1.4.3 Data analysis

A retrospective drug utilisation review (DUR) study was performed using medicine claims data from a South African PBM company. In the next section, the study variables, which are divided into dependent and independent variables, all aspects of a DUR as well as the classification systems used in the study will be discussed.

### 1.4.3.1 Study variables

It was important for the variables involved in this study to be identified, because, according to Leedy and Ormrod (2014:40), a variable is any quality or characteristic in a research investigation that has two or more possible values, while variables can also be defined as a condition or characteristic that can take on two different values or categories (Burke & Christensen, 2014:676).

One can differentiate between different variables, namely independent and dependent variables.

#### 1.4.3.1.1 Independent variables

The independent variable can be defined as the variable the researcher manipulates, or it is the variable that has a direct effect on the dependent variable (McLeod, 2008).

The independent variables that appeared in this study were age, gender, time periods (study period), presence of disease, prescriber specialty and name of the active ingredient.

- Age

Age is referred to as a period of time that has passed since the time of birth (Stedman's medical dictionary, 2000:34). The age of a patient was calculated on the date of treatment, using 1 January of the following year as reference (this age was calculated by using the date of birth of the patient and the date of the treatment).

The age of the patients in this study were categorised as follows:

- >0 years and  $\leq$ 18 years
- >18 years and  $\leq$ 34 years
- >34 years and  $\leq$ 65 years
- >65 years

This categorisation of age was based on two previous studies conducted by Otero *et al.* (2010:80) and Motola *et al.* (2004:733), who investigated previous NSAID use in CKD patients.

- Gender

In this study, only patients whose gender was known were included. The gender was used to indicate whether a prescription had been prescribed for either a male or female patient.

- Time periods (study period)

The study period indicates the most applicable time period that was used in the study to achieve the specific objective. The study period in this study was from 1 January 2009 to 31 December 2013.

- Presence of disease

The ICD-10 code for diagnosis in South Africa classifies the individual medical conditions in the database.

Chronic kidney disease was studied in this research and was therefore identified on the database by an ICD-10 code (N18).

- Prescriber specialty

The prescriber of the medication is the person responsible for writing/issuing the prescription. The prescribers were divided into four categories. These categories were general medical practitioners, pharmacotherapists, pharmacists and other. Table 1-2 discusses the different categories.

**Table 1-2: Prescriber specialty categories**

<b>Prescriber categories</b>	<b>Description</b>
General medical practitioners	This category featured all the medical providers who are registered with the HPCSA as a medical practitioner.
Pharmacotherapists	This category included all the pharmacotherapists who are registered with the SAPC as a qualified pharmacist, with an additional qualification that permits them to provide a primary health service.
Pharmacists	This category included all personnel who are registered with the SAPC and are legally capable of providing NSAIDs.
Other	This group included all prescribers who are valid and registered to legally prescribe NSAIDs, e.g. anaesthesiology practices, approved day clinics, cardiology practices, gastroenterology practices, general dental practices, group practices, neurology practices, gynaecology practices, oncology practices, ophthalmology practices, orthodontics practices, orthopaedics practices, urology practices, private hospitals, rheumatologists, nephrologists, endocrinologists, provincial hospitals, etc.

- Name of active ingredient of the NSAID

The name of the anti-inflammatory drugs (active ingredient) was used to identify the NSAIDs that were used in the study population and assisted in determining the prescribing patterns of the NSAIDs.

#### 1.4.3.1.2 Dependent variables

McLeod (2008) defines the dependent variable as the variable that is being measured or that is affected by the independent variable.

The dependent variables in this study were prevalence and the prescribed daily dosage (PDD).

- Prevalence

Prevalence is described in paragraph 1.5.1.1 and was used to identify the number of CKD patients, the number of medicine items per prescription and the number of CKD patients using NSAIDs.

- Prescribed daily dosage (PDD)

The prescribed daily dosage is defined by the World Health Organization (WHO) (2003:4) as the average daily dose prescribed, as obtained from a representative sample or prescription. An equation to determine the PDD is:

$$PDD = \frac{\text{strength} \times \text{quantity}}{\text{days' supply}}$$

Where:

Strength = strength per tablet, capsules in mg

Quantity = the number of tablets or capsules

Days' supply = the number of days' supply dispensed

#### 1.4.3.2 Drug utilisation review (DUR)

In this study, a retrospective DUR study was performed because the research investigated drug use over a period of time in the past or was conducted after the patient had received the medication.

Drug utilisation research was defined by the WHO in 1977 as the marketing, distribution, prescription, and use of drugs in a society, with special emphasis on the resulting medical, social and economic consequences (WHO, 2003). According to Radloff and Jones (2007:34), a retrospective DUR is a study of the drug usage in patients after the medication has been

dispensed to these patients. Drug utilisation review (DUR) studies aim to control the inappropriate prescription of drugs (Zimmerman *et al.*, 1994:89).

The essential steps in conducting a DUR study that most authorities agree with are (Academy of Managed Care Pharmacy, 2009):

- Identify optimal drug use: the purpose of the DUR is to compare optimal drug use with actual drug use. In this study, the optimal use of NSAIDs in CKD patients was identified during the literature phase of the study.
- Measure actual use: the data on the actual use of NSAIDs in CKD patients was determined from the database.
- Evaluate: the prescribing patterns of NSAIDs were evaluated during this step and the actual use was compared to the optimal use of these drugs in the study population.

### **1.4.3.3 Classification systems**

To assist in the development of evaluation criteria, the National Pharmaceutical Product Index (NAPPI codes) and the MIMS classification systems were used in this study.

#### **1.4.3.3.1 NAPPI code**

In the databases used in this study, medicine items were indicated using NAPPI codes. A NAPPI code is a unique identifier for a given ethical, surgical or consumable product that enables electronic transfer of information throughout the healthcare delivery chain (MediKredit, 2014). This helps to distinguish between different medicine items and also different dosage forms of the same active ingredient. The NAPPI code of NSAID items was used to identify the NSAIDs on the medicine claims database in this study.

#### **1.4.3.3.2 The MIMS classification system**

This classification system classifies medicine according to their pharmacological action.

The medicine items that were used in this study were the NSAIDs, and they are classified as follows by the MIMS (Snyman, 2012:78-89):

Section 4: Musculoskeletal agents

Section 4.1: Non-steroidal anti-inflammatory drugs

Section 4.1.1: COX-inhibitors

Section 4.1.2: Selective COX-2 inhibitors

Section 4.1.3: Specific COX-2 inhibitors (coxibs)

## **1.5 Statistical analysis**

### **1.5.1 Data analysis plan**

The data of this study was analysed by means of the Statistical Analysis System® SAS 9.3® programme. To assist with the general computations, Microsoft® Office Excel 2010 was used.

Statistics can be classified into two groups, namely descriptive and inferential. Descriptive statistics describe and summarise data (Brink *et al.*, 2012:179). In other words, it is a method of arranging, organising, summarising and presenting data. This data presentation can be in the form of tables, charts or statistical measures. Inferential statistics use sample data to draw an inference about the population of the study at hand from a smaller sample (Brink *et al.*, 2012:179).

#### **1.5.1.1 Description of data analysis plan**

To assist in describing the statistical data, frequency and prevalence, average and standard deviation were used in the study.

##### **1.5.1.1.1 Frequency and prevalence**

Rubin and Babbie (2014:330) define frequency as the number of times something occurs over a particular period of time. Prevalence is most meaningfully reported as the number of cases as a fraction of the total population at risk, and can be further categorised according to different subsets of the population. The prevalence is therefore the number of people with the condition divided by the number of people at risk (Diaz-Buxo & Himmele, 2014).

In this study, prevalence and frequency were used as synonyms to indicate the number of CKD patients on the database, number of chronic conditions co-occurring with CKD, the percentage of diagnosed CKD patients who were prescribed NSAIDs during their treatment, the type of NSAID items prescribed to CKD patients and the number of NSAID items prescribed by prescriber. The proportion of CKD patients who was prescribed a NSAID was calculated by dividing the number of CKD patients who claimed NSAIDs by the total number of CKD patients in the study population.

##### **1.5.1.1.2 Average (arithmetic mean)**

Thomas (2013:250) describes the average as the total number of characteristics that are being studied divided by the total number of observations. A mathematical equation for the calculation of the mean is (Dowdy *et al.*, 2004:130):

$$\bar{x} = \frac{\sum x_i}{n}$$

Where:

- $\bar{x}$  = mean
- $\sum x_i$  = sum of all given x values
- $n$  = number of observations in the population

For the purpose of the analysis of the data in this study, the average value (mean) was used to determine the following:

- The average age of CKD patients
- Average number of NSAID items per patient
- Average number of co-occurring chronic conditions per CKD patient.

#### 1.5.1.1.3 Standard deviation

Thomas (2013:136) defines the standard deviation as the average amount by which each characteristic differs from that of the mean of all the characteristics. The standard deviation can be calculated as follows (Dowdy *et al.*, 2004:136):

$$s = \sqrt{\frac{\sum(x_i - \bar{x})^2}{n - 1}}$$

Where:

- $s$  = standard deviation
- $\sum$  = sum
- $x_i$  = value of any variable in the dataset
- $\bar{x}$  = mean
- $n$  = the number of observations

For the purpose of the study, the standard deviation was used to determine the following:

- The variance around the mean age of the CKD patients who use NSAIDs
- The variance of the number of NSAID items per CKD patient during the study period
- The variance around the mean number of chronic conditions co-occurring with CKD

#### 1.5.1.2 Statistical and practical significance

All statistical significance was considered with a probability of  $p \leq 0.05$ . The practical significance of the statistical results was measured by certain tests/measures if the  $p$ -value was deemed to be statistically significant.

#### 1.5.1.2.1 Analysis of variance (ANOVA)

ANOVA is a statistical method used to test differences between two or more means (Lane, 2004). The one-way ANOVA was used to measure the differences in the means of NSAID prescriptions between different age groups.

#### 1.5.1.2.2 Chi-square test ( $\chi^2$ )

The chi-square is one of the most common non-parametric tests and is used to compare data that is in the form of frequencies (Brink *et al.*, 2012:191). The chi-square therefore determines whether the deviations between the observed and expected counts are too large to be attributed to chance.

#### 1.5.1.2.3 Cramer's $V$

Cramer's  $V$  measures the association between two nominal variables, usually after the chi-square test had been applied (Torres-Reyna, 2007). Its values range from zero to one, with  $\geq 0.1$  regarded as a weak association;  $\geq 0.3$  seen as a moderate association and  $\geq 0.5$  seen as a strong association (Nandy, 2012).

#### 1.5.1.2.4 Tukey's honestly significant difference (HSD) test

When a significant result is given by an analysis of variance (ANOVA), it is an indication that one variable/group differs from another variable/group, but gives no indication of the pattern of the difference. In order to analyse the pattern of the difference, a comparison between the two means of the groups can be made. This can be done by using Tukey's HSD test, which compares the honestly significant difference between the means by using the statistical distribution (Abdi & Williams, 2010).

#### 1.5.1.2.5 Effect size

The effect size is explained by Burke and Christensen (2014:661) as the measure of strength and magnitude of a relationship between the independent and dependent variables.

Effect size is calculated by the following formula (Cohen & Lea, 2004:60):

$$\text{Cohen's } d = \frac{\bar{x}_a - \bar{x}_b}{S_{max}}$$

Where:

- $d$  = Cohen's effect size
- $\bar{x}_a$  = average value of  $a$

- $\bar{x} b$  = average value of  $b$
- $S_{max}$  = the maximum standard deviation between variable  $a$  and  $b$

The following  $d$ -values are given by Becker (2000) as guidelines for practical significance:

- Where  $d = 0.2$ , it is considered to be a small effect with no significance.
- Where  $d \geq 0.5$ , the effect size is considered to be medium; in this case, the effect is observable and may have practical significance.
- Where  $d \geq 0.8$ , the effect is considered to be large and significant, and therefore of practical importance.

In this study, Cohen's  $d$ -value was used to determine the practical significance of the difference between averages.

## **1.6 Ethical considerations**

In order to conduct this study, permission was obtained through a formal contract between the PBM and Medicine Usage in South Africa (MUSA). Permission to conduct the study was obtained from the Health Research Ethics Committee (HREC) of the Faculty of Health Sciences of the North-West University (NWU-00179-14-S1). Goodwill permission was obtained from the Board of directors of the PBM. This was a low-risk study, since retrospective medicine claims data were analysed anonymously.

No individual patient, medical scheme or health plan can be identified, thereby ensuring confidentiality of the information and the maintenance thereof. The researcher only had access to the processed, depersonalised data. All the data was stored on a password-protected computer that is furthermore protected by firewall and anti-virus software.

All data will be kept by MUSA until the agreement with PBM expires in 2019 and will then be destroyed. Once the study has been completed, all the files will be deleted from personal computers.

## **1.7 Chapter summary**

This chapter illustrates the methods that were used and ethical considerations followed to eventually achieve the different objectives of the study. A literature review on non-steroidal anti-inflammatory drugs and chronic kidney disease is given in Chapter 2.

## **CHAPTER 2: LITERATURE REVIEW**

### **2.1 Introduction**

The aim of this chapter is to discuss non-steroidal anti-inflammatory drugs (NSAIDs) and chronic kidney disease (CKD), both as single entities but with the focus on the use of NSAIDs in patients with CKD. It will therefore provide greater insight into the use of NSAIDs in both patients with and without CKD. A broad outline of NSAIDs will also cover a very important aspect of NSAID use, such as pain treatment.

### **2.2 Non-steroidal anti-inflammatory drugs**

An overview of NSAIDs will be given in this section, thus giving a greater understanding of all aspects of NSAID use, which includes its definition, classification, mechanism of action, indications, prescribing patterns, safety and adverse effects as well as any drug-drug interactions regarding NSAID usage.

#### **2.2.1 Definition and history of non-steroidal anti-inflammatory drugs**

Dellwo (2013) defines NSAIDs as drugs that are inflammation-fighting, that do not contain steroids, are non-narcotics and reduce pain and fever, and are blood thinners. Non-steroidal anti-inflammatory drugs are among the most commonly used and prescribed drugs in the modern world of medicine (Meek *et al.*, 2010:2146). These drugs have been used very effectively for pain, fever and inflammation and have been used by millions of patients worldwide since salicin was derived from willow bark in 1874 (Dugowson & Gnanashanmugam, 2006:347). There are, however, suggestions that Hippocrates of Cos (460–377 BC) chewed on the leaves of the willow bark tree and found that it reduced pain (Vonkeman & Van de Laar, 2010:295). The more acceptable form of salicylic acid, acetylsalicylic acid (aspirin), was introduced on the market by Bayer™ in 1899 (Rao & Knaus, 2008:81s), after chemist Felix Hoffman perfected the formula for acetylating salicylic acid and convinced the head of Bayer's pharmacological division to conduct experiments with this formula (Vonkeman & Van de Laar, 2010:295). In 1971, Sir John Vane discovered that aspirin and indomethacin also inhibit the production of prostaglandins, which gives them anti-inflammatory properties (Green, 2001:50).

#### **2.2.2 Classification of non-steroidal anti-inflammatory drugs**

Non-steroidal anti-inflammatory drugs can be classified by their chemical structure (Table 2-1) or action (Table 2-2) into salicylates, propionates, fenamates, oxicams, pyrazolones, cyclo-oxygenase-2 (COX-2) inhibitors, etc. (Dyall-Smith, 2010). There are more than 30 NSAID compounds available on the market in the USA alone (Green, 2001:50). In South Africa there

are 14 active substances, with 68 brand names available on the market (Koch, 2012:96). The Monthly Index of Medical Specialities (MIMS) lists 58 brand names in the March 2015 edition (Snyman, 2015:89-98). These NSAIDs are clinically relatively equal in potency (Koch, 2012:96). This is attributed to the “ceiling effect” that NSAIDs exhibit when, once the recommended maximum dose has been reached, further dose increases do not bring about an increase in clinical effects (Poveda-Roda *et al.*, 2007:E13). The selection of specific NSAIDs for certain patients and conditions is influenced by subtle differences in the NSAIDs, which are usually determined by the side effect profile, rather than efficacy of the NSAIDs (Green, 2001:50). Although NSAIDs share many common properties, there are differences in their chemical character and they show clear differences in biochemical structure and origin (Poveda-Roda *et al.*, 2007:E11). Table 2-1 lists the various types of NSAIDs according to their chemical class (Green, 2001:51).

**Table 2-1: Common non-steroidal anti-inflammatory drugs**

<b>Class</b>	<b>Active ingredient/substance</b>
Salicylates	Acetylsalicylic acid (aspirin) Salsalate Diflunisal
Non-acetylated salicylates	Magnesium salicylate Choline magnesium trisalicylate
Propionic acid derivatives	Fenoprofen calcium Flurbiprofen Ibuprofen Ketoprofen Naproxen Naproxen sodium Oxaprozin
Fenamates	Mefenamic acid Meclofenamate sodium
Naphthylalkanone	Nabumetone
Indoles	Indomethacin Sulindac Tolmetin sodium

**Table 2-1: Common non-steroidal anti-inflammatory drugs**

Class	Active ingredient/substance
Oxicams	Piroxicam
Phenylacetic acids	Diclofenac sodium Diclofenac potassium Diclofenac sodium plus misoprostol
Pyrazole derivatives	Phenylbutazone
Pyrrolo-pyrrole	Ketorolac tromethamine
Pyranocarboxylic acid	Etodolac
Selective COX-2 inhibitors	Celecoxib Rofecoxib
Semi-selective COX-2 inhibitors	Meloxicam

Snyman (2012:78-89) classifies NSAIDs according to their mechanism of action (COX-inhibition), which will be discussed in paragraph 2.2.3. According to this classification system, NSAIDs are classified into three groups. In Table 2-2 the classification system by Snyman, (2012:78-89) is combined with additional information gathered from Rao and Knaus (2008:90s), and Süleyman *et al.* (2007:249).

**Table 2-2: Classification of non-steroidal anti-inflammatory drugs by their cyclooxygenase inhibition activity**

Class	Properties	Example
COX inhibitors	NSAIDs that inhibit both COX-1 and COX-2 with little selectivity	Aspirin Ibuprofen Diclofenac
Selective COX-2 inhibitors	NSAIDs that inhibit COX-2 with little selectivity	Meloxicam
Specific COX-2 inhibitors (coxibs)	NSAIDs that inhibit COX-2 with strong selectivity	Rofecoxib Celecoxib
Specific COX-1 inhibitors		S-Indobufen Valeryl salicylate Aspirin

Non-steroidal anti-inflammatory drugs can thus be classified according to their chemical character as well as their relative COX activity. The efficacy of these NSAIDs does not vary much within the different groups; their use is therefore mostly determined by their strength and safety profile.

### 2.2.3 Mechanism of action of non-steroidal anti-inflammatory drugs

The clinical effects of NSAIDs are attributed to their inhibition of the cyclo-oxygenase (COX) enzymes, which are the enzymes responsible for the transformation of arachidonic acid into prostaglandins and thromboxane after receiving a stimulus (Poveda-Roda *et al.*, 2007:E13) (refer to Figure 2-1). Prostaglandins result in several physiological and pathological processes, which include vasodilatation, vasoconstriction, contraction and relaxation of bronchial or uterine muscles, increase in renal blood flow (which results in diuresis, and stimulation of renin secretion) and an increase in body temperature at the hypothalamus through cytokine stimulation (Hilário *et al.*, 2006:207). This increase in prostaglandin production causes an increase in sensitivity to pain and fever, which then increases the inflammatory response. This is a result of the suppression of interleukin-1 (IL-1) and tumour necrosis factor (TNF) synthesis (Hilário *et al.*, 2006:207). The inhibition of COX enzymes will inhibit prostaglandin synthesis, thus resulting in analgesia and reduction in inflammation (Green, 2001:52).

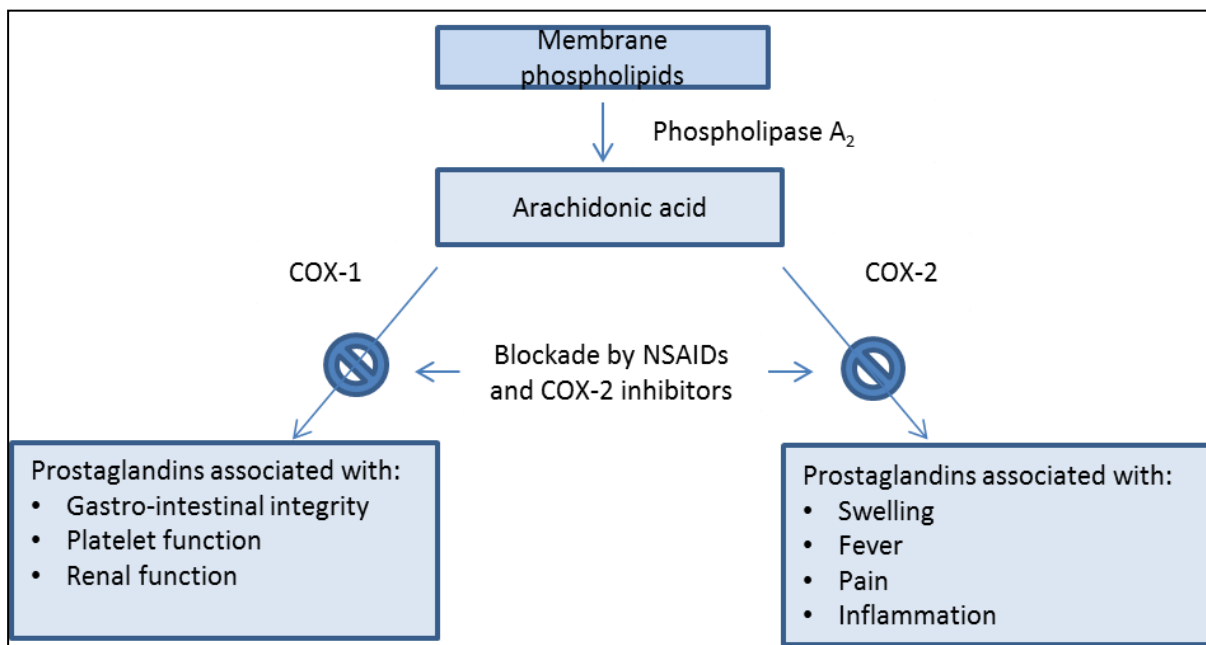
Non-steroidal anti-inflammatory drugs have the ability to inhibit both COX-1 and COX-2 enzymes. The inhibition of COX-1 reduces gastro-intestinal integrity, which according to Brunton *et al.* (2011:963) complicates therapy and provides further motivation for the development of specific COX-2 selective NSAIDs. The inhibition of COX-1 further reduces platelet aggregation and renal function. By inhibiting COX-2, NSAIDs reduces inflammation, however also bone formation and renal function (Green, 2001:52). The COX-2-inhibiting NSAIDs thus have a better safety profile than the COX-1 inhibitors (Brunton *et al.*, 2011:963). The inhibition of the COX enzymes not only accounts for the clinical effects of NSAIDs, but also for their adverse effects. The location and function of COX enzymes in the human body are described in Table 2-3 (Schellack, 2012:14).

**Table 2-3 Location and function of the cyclooxygenase isoforms**

	COX-1	COX-2
<b>Location (where COX enzymes are normally located in the body)</b>	Body tissue, which includes the stomach, kidneys and platelets	Is particularly expressed in inflammatory conditions, but not so much during normal physiological conditions
<b>Function</b>	Regulates normal physiological processes by producing protective prostaglandins that restores gastrointestinal mucosal integrity, platelet homeostasis and renal function	Is responsible for the production of prostaglandins caused by inflammatory stimuli, which then results in pain and fever

It is evident that COX-1 inhibition is mainly responsible for NSAIDs' adverse effects, whereas the inhibition of COX-2 provide the anti-inflammatory properties of NSAIDs.

As indicated in Figure 2-1 (Chhabra, 2012), NSAIDs inhibits COX enzymes, which further inhibits prostaglandin production and produces an anti-inflammatory effect.



**Figure 2-1: Mechanism of action of non-steroidal anti-inflammatory drugs**

According to Dugowson and Gnanashanmugam (2006:348), the mechanism of action of NSAIDs can also be divided into their effects on inflammation, pain and fever. Hilário *et al.*

(2006:206) describe NSAIDs as a heterogeneous group of drugs with anti-inflammatory, analgesic and antipyretic effects. These effects will be discussed in subsequent paragraphs.

### **2.2.3.1 Anti-inflammatory effect**

The NSAIDs exert an anti-inflammatory effect by inhibiting prostaglandin through the inhibition of COX enzymes (Dugowson & Gnanashanmugam, 2006:348). The anti-inflammatory effect of NSAIDs can be largely attributed to NSAIDs' ability to inhibit the COX-2 isoform (Schellack, 2012:14) (Table 2-3). According to DeRuiter (2002), the anti-inflammatory effect of NSAIDs can also be attributed to other mechanisms. These mechanisms include the induction of apoptosis, reduction of superoxide radicals, inhibition of adhesion molecule expression, a decrease in the synthesis of nitric acid and the pro-inflammatory cytokine levels, as well as the modification of lymphocyte activity (DeRuiter, 2002). Non-steroidal anti-inflammatory drugs thus exert an anti-inflammatory effect by reducing pain, fever, redness and swelling caused by inflammatory stimuli (Solomon *et al.*, 2015).

### **2.2.3.2 Analgesic effect**

Non-steroidal anti-inflammatory drugs are in fact classified as mild analgesics, because they exert analgesic effects on pain that results from an increased peripheral sensitisation that occurs during inflammation (Dugowson & Gnanashanmugam, 2006:348). The analgesic effect of NSAIDs can thus be attributed to the reduction of inflammation, which is a result of the action of NSAIDs on the central nervous system (Poveda-Roda *et al.*, 2007:E11) or because of the interference of prostaglandin-mediated pain formation in the nociceptive system (DeRuiter, 2002). By inhibiting COX in the central nervous system, the NSAIDs thus reduce concentrations of prostaglandin E<sub>2</sub> that lead to the activation of the descending inhibitory serotonergic pathways, which then produces analgesia (Buck, 2011).

### **2.2.3.3 Antipyretic effect**

The antipyretic effects of NSAIDs can be attributed to the inhibition of PGE<sub>2</sub> synthesis. The hypothalamus is triggered by PGE<sub>2</sub>, which leads to an increase in body temperature during the inflammation process (Dugowson & Gnanashanmugam, 2006:348).

The NSAIDs' mechanism of action therefore consists of the suppression of COX enzymes, which results in the reduction of prostaglandin production, thus controlling inflammation, pain and fever (Hilário *et al.*, 2006:207).

## 2.2.4 Indications of non-steroidal anti-inflammatory drugs

Non-steroidal anti-inflammatory drugs were initially used as antipyretic agents (Green, 2001:53), but have come a long way in being both anti-inflammatory and analgesic agents (Dugowson & Gnanashanmugam, 2006:349) and are now widely used in controlling fever, acute and chronic pains and inflammation (Hilário *et al.*, 2006:208). The NSAIDs thus have a wide range of indications where pain and inflammation are present (Pountos *et al.*, 2011:21). The primary indication for NSAIDs is therefore pain that is mediated by inflammation such as rheumatologic arthritis (Dugowson & Gnanashanmugam, 2006:349) or mild to moderate painful conditions (Pountos *et al.*, 2011:21). Non-steroidal anti-inflammatory drugs provide rapid relief, and are therefore widely used in the treatment of acute gout, dysmenorrhoea, osteoarthritis and lower back pain (Day & Graham, 2013:34). Non-steroidal anti-inflammatory drugs can also be used to treat sinusitis to relieve pain and reduce inflammation, since this pain is a result of inflammation in the sinus cavity (DeSerio, 2013). According to Sinha (2014), the use of NSAIDs to relieve pain in acute sinusitis in particular is a vital part in the treatment algorithm of sinusitis.

According to Green (2001:53), a diagnosis of osteoarthritis accounts for almost half the prescriptions written for NSAIDs because of the analgesic effects of the NSAIDs in this condition. Another key indication for NSAIDs is the treatment of the inflammatory arthropathies, where indomethacin, for example, is used in the treatment of ankylosing spondylitis. Celecoxib is widely used with great success for the treatment of rheumatoid arthritis (Green, 2001:53).

The over-the-counter (OTC) NSAIDs (e.g. ibuprofen) are commonly used for the treatment of acute and chronic pain, whereas for severe pain, a codeine component can be added to the NSAID to achieve greater pain control (Green, 2001:53). Non-steroidal inflammatory drugs are also widely used in sports injuries, where pain and inflammation are caused by physical activity. In these circumstances the analgesic effects of the NSAIDs lead to early mobilisation of joints and ligaments, this enhances the healing process (Green, 2001:54).

A very intriguing use of NSAIDs is their potential to reduce the risk of colon cancer, as well as some studies that suggest a role in the treatment or prevention of bladder cancer and osteoporosis (Green, 2001:53). This is attributed to the effect of the aspirin and NSAIDs on the gene transcriptions and protein synthesis of several molecules involved in inflammatory and neoplastic pathways (Stolfi *et al.*, 2013:17973). These effects are a result of the ability of the NSAIDs and aspirin to suppress COX expression/activity, and downstream the signals that are crucial for colorectal cancer (CRC) cell growth, survival and diffusion (Stolfi *et al.*, 2013:17973). These anticancer effects of NSAIDs often require higher concentrations than those needed to inhibit COX, which increases the risk of gastro-intestinal and other side effects (Stolfi *et al.*, 2013:17979).

The most common indications for NSAIDs as listed by Pountos *et al.* (2011:22) include:

- Mild to moderate pain caused by inflammation
- Sprains, strains and rheumatism
- Back pain and sciatica
- Osteoarthritis and rheumatoid arthritis
- Acute gout
- Inflammatory arthropathies (ankylosing spondylitis, psoriatic arthritis, Reiter's syndrome)
- Dysmenorrhea, headache and migraine
- Postoperative pain
- Renal and biliary colic
- Fever
- Other inflammatory conditions

Non-steroidal anti-inflammatory drugs are therefore a popular choice of treatment in conditions relating to pain and inflammation among the general population. These will be discussed further in subsequent paragraphs.

#### **2.2.4.1 Pain**

Since pain management is among the main indications for NSAIDs, this section will briefly discuss certain aspects of pain; including its definition, classification, prevalence and treatment. The importance of pain management in CKD patients will be discussed in paragraph 2.4.

##### 2.2.4.1.1 Definition of pain

The International Association for the Study of Pain (IASP) provided the most common and well-known definition for pain in which they define pain as “*an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage*” (IASP, 2012). According to Chen (2011:348), pain serves as a sensory detection and alarm system for escape when the body is hurt/in pain. Pain can facilitate in the healing process of injuries, but can also be harmful when it becomes persistent or chronic (Chen, 2011:348). Pain is therefore a multidimensional, unpleasant sensory experience that is associated with hurt and soreness (Woolf, 2004:441).

##### 2.2.4.1.2 Classification of pain

The classification of pain can be very complicated and a great source of confusion for many healthcare practitioners. Many different classification systems for pain therefore exist (Cole, 2002:23). Pain is generally classified according to its location, duration, underlying cause and

intensity (Cole, 2002:23). Woolf (2004:441) also classifies pain on the basis of pathophysiology (Table 2-5).

- Location of pain

The pain is classified according to the sites of pain on the body (e.g. lower back pain, headache, pelvic pain, etc.). Another classification that can be used focuses on the body system (e.g. musculoskeletal, neurological, vascular, etc.). This classification system therefore only identifies the site of pain (Cole, 2002:23).

- Duration of pain

The duration of pain is probably the most common classification system used that distinguishes between acute and chronic pain. Table 2-4 (Cole, 2002:24) provides a comparison between acute and chronic pain.

**Table 2-4: Acute vs. chronic pain**

Acute pain	Chronic pain
Pain that generally lasts less than 30 days	Pain persists for more than 6 months
Serves as a warning; it limits the use of any injured body parts and is an indication of the healing of any limiting condition.	Has little/no protective significance, does not clear when injury or disability resolves and reduces productivity/activity.
Sub-acute pain: Illustrates the interval from the end of the first month to the beginning of the seventh month of continued pain.	Non-cancer related pain: Benign or non-malignant pain
Recurrent acute pain: Is isolated episodes of pain that occurs over an extended period of time.	Cancer-related pain: Malignant pain

- Underlying causes of pain

According to Cole (2002:24-25), it is important to identify the aetiology of pain in order to treat the underlying cause and determine with which treatment to persist. In the underlying cause, pain can be divided into somatic pain, visceral pain (bowel obstruction, constipation, etc.) and neuropathic pain. Jacques (2014) describes somatic pain as a type of nociceptive pain, which is felt on the skin and the deep tissue. Somatic pain is thus experienced with a cut to the skin, stretching of a muscle, fractures or traumatic injury. Visceral pain is caused by a direct stimulation of the afferent nerves, is usually poorly localised and ill-defined and can be a deep, aching or colicky pain such as bowel obstruction and constipation (Perron & Schonwetter, 2001). According to Markman and Narasimhan (2014), neuropathic pain is caused by damage to, or dysfunction of the peripheral and central nervous system and not by stimulation of pain

receptors. Causes of neuropathic pain include alcoholic and nutritional neuropathy, diabetic mono- and polyneuropathy, etc. (Cole, 2002:25).

- Intensity of pain

This is the classification of pain that is probably the least used and the least accurate, because different patients experience pain differently (Cole, 2002:25). A patient rates their experience of pain on some type of scale, e.g. 0–10, with 10 being the worst pain (Cole, 2002:26).

- Pathophysiology of pain

Woolf (2004:441) classifies pain on the basis of pathophysiology. This classification system is depicted in Table 2-5. This classification system is second to the classification system based on acute and chronic pain classification – the most common system used for pain.

**Table 2-5: Classification of pain on the basis of pathophysiology**

Nociceptive pain	Inflammatory pain	Neuropathic pain	Functional pain
Transient pain as a response to a noxious stimulus, which arises from pain outside the nervous system. This pain occurs when nociceptors are activated as a result of tissue injury (WHO, 2012). Nociceptors thus respond to heat, cold, vibration, chemical substances, etc. and can be divided into somatic and visceral pain (WHO, 2012).	Spontaneous pain and hypersensitivity to pain initiated by tissue damage and inflammation (WHO, 2012).	Pain or hypersensitivity to pain initiated by damage to or lesion of the nervous system. Neuropathic pain can be caused by any injury to the nerves, which could include any metabolic-, infectious-, traumatic or immune-mediated conditions (WHO, 2012).	Pain resulting from an abnormal central processing of normal output (WHO, 2012).

To summarise, the classification of pain can be very complex, but still remains vital in the diagnosis and eventual successful treatment of pain.

#### 2.2.4.1.3 Epidemiology of pain

Pain is seen as a major global health problem and it is estimated that globally one in five adults suffers from acute pain, with a further one in ten adults being diagnosed with chronic pain (Goldberg & McGee, 2011). Table 2-6 summarises studies conducted to determine the prevalence of pain during the past ten years.

**Table 2-6: Summary of studies conducted on the prevalence of pain**

Reference	Study period	Study participants (N)	Setting	Units of measurement	Main/Key findings
Kennedy <i>et al.</i> (2014:981)	2010	89 976	USA	Proportion of the US adult population with persistent pain.	19% of adults in the US reported persistent pain (sample group).
Wong and Fielding (2011:239)	Mar. 2007- May 2007	5001	Hong Kong	Prevalence of chronic pain.	35% of study participants reported chronic pain.
Johannes <i>et al.</i> (2010:132)	Dec. 2008- Feb. 2009	27 035	USA	Number of participants who reported chronic, recurrent, or long-lasting pain.	41% of respondents reported chronic, recurrent, or long-lasting pain.
Igumbor <i>et al.</i> (2011:65)	May 2006- Jun. 2006	394	South Africa	Participants who reported chronic pain	42,9% reported chronic pain.
Muthunarayanan <i>et al.</i> (2015:37)	Aug. 2013- Oct. 2013	1264	Tamil Nadu	Participants who reported some form of pain.	51.1% reported some form of pain.
Gunnarsdottir <i>et al.</i> (2010:154)	December 2002	575	Iceland	Participants who experienced pain in a specific week	232 participants (40.3%) experienced pain during a specific week.
Landmark <i>et al.</i> (2013:184)	2006-2008	3 421	Norway	Prevalence of chronic pain among men and women.	36% among women and 25% among men.
Azevedo <i>et al.</i> (2012:775)	Jan. 2007- Mar. 2008	5094	Portugal	Prevalence of chronic pain.	36.7% of participants reported chronic pain.
Chung and Wong (2007:240)	Mar. 2003- May 2003	1853	Hong Kong	Prevalence of pain in a community population.	45.9% of the population reported pain.

From Table 2-6 it can be concluded that pain is a global health problem and is clearly among the most common conditions worldwide, with prevalences ranging from 19% to 51% between developing and developed countries. The high global prevalence of pain thus accounts for NSAIDs being among the most commonly used drugs worldwide.

#### 2.2.4.1.4 Treatment of pain

Pain is among the most common conditions worldwide (refer to paragraph 2.2.4.1.3), but also among the most under-treated (O'Sullivan, 2008). As was previously discussed (refer to paragraph 2.2.4.1.2), different types of pain require different treatments. In this section the difference in the treatment of acute and chronic pain will be discussed.

In the treatment of acute pain, O'Sullivan (2008) distinguishes between three different levels of pain, such as mild, moderate and severe pain. In treating mild pain an oral analgesic can be administered (e.g. paracetamol or ibuprofen); with moderate pain a codeine compound can be added to the oral analgesic (e.g. diclofenac or ibuprofen); and for severe pain, an intravenous analgesic (e.g. morphine) should be administered (O'Sullivan, 2008).

According to Zeller *et al.* (2008:128), acute pain can be treated during the initial stages, followed then by a secondary tier of treatments. During the initial treatment the patient should rest the affected body part, while applying heat or ice. Non-steroidal anti-inflammatory drugs such as aspirin, ibuprofen or naproxen can be given along with physical therapy, exercise and bio-electric therapy. Further drug treatment can include an opioid (codeine or morphine) and muscle relaxant medications such as orphenadrine (Norflex) (Truven Health Analytics, 2015).

According to the Department of Health of South Africa (2012:12.1), patients with chronic pain require a physical assessment and other psychological disorders such as depression should be taken into account. This assessment includes a full medical and physical examination, the establishment of a working diagnosis of the chronic pain, treatments for specific diseases where appropriate, and an overall pain management plan (Park & Moon, 2010:104). In treating chronic pain, the least invasive route of medication administration should be used, preferably the oral route (Department of Health, 2012:12.2). In treating chronic pain, different types of analgesics can be used, and if necessary adjuvant therapy can be administered (Department of Health, 2012:12.2). Table 2-7 (Department of Health, 2012:12.2) describes the different types of drugs that can be used to treat chronic pain.

**Table 2-7: Drugs used to treat chronic pain**

Analgesics	Adjuvant therapy
Paracetamol, 1 000 mg every 6 hours	These agents enhance the pain control by targeting specific pain mechanisms and should be used in addition to analgesia.
Non-opioid drugs such as NSAIDs (ibuprofen, 400–800 mg every 8 hours)	Amitriptyline, 10 mg, titrate up to 75 mg.
Opioid drugs such as tramadol, 50 mg every 6 hours as starting dose, which may increase to 400 mg daily	Carbamazepine, 100 mg every 12 hours for 2 weeks, then 200 mg every 12 hours.
Morphine oral solution 30 mg–60 mg 12 hourly, then titrate to desired effect.	

### 2.2.5 Prescribing patterns of non-steroidal anti-inflammatory drugs

Non-steroidal anti-inflammatory drugs are among the most widely prescribed drugs worldwide, and constitute the largest single group of drugs used in developed countries (Paul & Chauhan, 2005:889). According to Conaghan (2012:1493), NSAIDs are used by more than 30 million people every day and more than 111 million NSAID prescriptions are written in the United States annually. These drugs are used as prescription drugs, but also as OTC medicine, thus resulting in an increase in overall use of these drugs. Clinard *et al.* (2001:329) state that NSAIDs represent about 8% of all prescriptions issued by French practitioners, thus constituting around 30 million NSAID prescriptions per year. According to Paul and Chauhan (2005:890), all 1 916 practitioners studied in India admitted to frequently prescribing NSAIDs, with the number of prescriptions ranging from one to fifteen per day. In a questionnaire-based survey conducted in Italy, 35% (n=2 738) of the study population reported NSAID use during the study period (Motola *et al.*, 2004:731), and results collected in a private hospital in Dubai showed that NSAIDs were the most commonly prescribed drug class with 23.4% (n=2 659) of the prescriptions (Sharif *et al.*, 2008:11). In the Texas prison system, Williams *et al.* (2010:758) found that 65% (n=13 117) of all the prescriptions for patients 55 years and older, were for NSAIDs. In a nationwide study done in Denmark, 57.8% (n=4 614 807) of the population claimed at least one NSAID prescription during 1997 and 2005 (Fosbøl *et al.*, 2008:824).

The prescribing patterns of NSAIDs cannot be determined only in terms of the number of NSAID prescriptions, but also the type of NSAID prescribed. In the study done in Denmark (Fosbøl *et*

*al.*, 2008:828), ibuprofen (38.9%), diclofenac (20.6%) and the COX-2 inhibitors (9.3%) were the three most frequently used NSAIDs during the study period. Al-Homrany and Irshaid (2007:370) found that ibuprofen (14.9%) and diclofenac (9%) again were among the most frequently prescribed drugs in the Aseer Central Hospital in Abha City, but they also identified aspirin (6.7%) as the third most commonly prescribed NSAID in the study (n=3 796). In the study done by Clinard *et al.* (2001:332), who compared the prescribing patterns of NSAIDs reported by general practitioners (GP-based survey) and from a pharmacy-based survey, it was found that piroxicam (22.3%, n=770) was the most commonly used NSAID in the GP-based survey and 26% (n=1 050) in the pharmacy-based survey, with diclofenac (19.4% and 15.7%, respectively) again being the second most commonly used NSAID. Motola *et al.* (2004:735) report that nimesulide was the most frequently prescribed drug in their Italian-based study with 35.1% of the prescriptions, followed by aspirin (14.1%) and ibuprofen (11.4%).

Prescribing of NSAIDs may differ on the basis of prescriber and provider categories. Siddiqi *et al.* (2002:30) found that private practitioners prescribed at least one NSAID in 30.2% (n=988) of the prescriptions, compared to 25.2% (n=925) for public healthcare providers in Pakistan. Siddiqi and co-workers also showed that instances where two or more NSAIDs were prescribed happened more frequently in the private sector (7.8%) than the public sector (1.4%). Paul and Chauhan (2005:890) revealed that aspirin was prescribed by 71% of all general practitioners (n=731), 52% of gynaecologists (n=302), 60% of orthopaedic surgeons (n=289), 99% of paediatricians (n=297) and 98% of all physicians. The results of this study for all NSAIDs prescribed are given in Table 2-8 (Paul & Chauhan, 2005:890).

**Table 2-8: Prescribing of non-steroidal anti-inflammatory drugs**

Drugs	Percentage of prescribers				
	General practitioner (n=731)	Gynaecologist (n=302)	Orthopaedic surgeon (n=289)	Paediatrician (n=297)	Physicians (n=297)
Aspirin	71	52	60	99	98
Diclofenac	31	47	65		61
Ibuprofen	38	51	19	59	39
Piroxicam	17	10	66		14
Indometacin	3	58		60	2
Mefenamic acid	1	9			
Nimesulide	2		1		
Ibuprofen + paracetamol	37	41	59	45	54
Diclofenac + paracetamol	2	20	17		14

NSAIDs are commonly used among all age intervals, but an increase in age was associated with more frequent NSAID use (Fosbøl *et al.*, 2008:824). Fosbøl *et al.* (2008:824) state that patients between the ages of 51 and 70 years have higher odds of claiming more than three NSAIDs prescriptions during the study period of 1997 to 2007. Table 2-9 summarises previous studies conducted on the prescribing patterns of NSAIDs.

Minimal data remains regarding the prescribing of NSAIDs in South Africa, which is a cause for concern in the healthcare system. Beeka (2008) investigated the use of COX-2-selective inhibitors and NSAIDs in patients with rheumatoid arthritis (n=2 818) in the managed healthcare environment in South Africa over a six-month period in 2003. According to the findings, 48.7% of patients used COX-2 inhibitors, with 29.4% using NSAIDs (Beeka, 2008). Kapp *et al.* (2013:80) investigated drug interactions in a primary healthcare facility in George, South Africa and studied 400 prescriptions. They found that aspirin (second) and ibuprofen (eighth) were among the most-prescribed drugs, accounting for 32.8% and 17.8% of the total drugs prescribed respectively (Kapp *et al.*, 2013:80).

**Table 2-9: Summary of studies on the prescribing patterns of non-steroidal anti-inflammatory drugs**

Source	Study period	Study participants (n)	Setting	Units of measurement	Main/key findings
Paul and Chauhan (2005)	Jan. 1996 – Feb. 1997	1 916	Mumbai, India	Average NSAID prescriptions per day	1–15 NSAID prescriptions per day.
Motola <i>et al.</i> (2004)	Mar. 2002 – Sep. 2002	3 250	Italy	Prevalence based on drug use in population	35% of the study population used NSAIDs.
Sharif <i>et al.</i> (2008)	Dec. 2005	1 190	Dubai	Prevalence based on drug prescribed in population	23.4% of prescriptions were NSAIDs.
Williams <i>et al.</i> (2010)	Sep. 2006 – Aug. 2007	13 117	Texas, USA	Prevalence based on drug prescribed in population	65% of all prescriptions were NSAIDs.
Fosbøl <i>et al.</i> (2008)	1997 – 2005	4 614 807	Denmark	Prevalence based on drug prescribed in population	57.8% of population claimed at least one prescription for a NSAID.
Albarrán and Zapata (2008:866)	Apr. 2007 – Aug. 2007	909	Chile	Prevalence of self-medicated drugs used in three pharmacies	33.2% of population requested NSAIDs.

**Table 2-9: Summary of studies on the prescribing patterns of non-steroidal anti-inflammatory drugs**

Source	Study period	Study participants (n)	Setting	Units of measurement	Main/key findings
Kitchen and Kane (2010:358)	Jul. 2008	388	Ireland	Prevalence of hospital patients using NSAIDs at time of study	14.7% of hospital patients using NSAIDs.
Shankar <i>et al.</i> (2007:17)	Sep. 2002 – Dec. 2002	186 patients and 352 drugs	Nepal	Proportion of drugs prescribed at hospital that were NSAIDs	59.9% of drugs prescribed were NSAIDs.

From Table 2-9, it can be deduced that there is great variation in global NSAID use, but it is clear that NSAIDs are indeed among the most commonly used drugs worldwide. This high frequency NSAID use results in the prevalent occurrence of their adverse effects (refer to paragraph 2.2.6).

### **2.2.6 Safety and adverse effects of non-steroidal anti-inflammatory drugs**

Non-steroidal anti-inflammatory drugs are clinically very efficient drugs and evidently widely used as well (refer to paragraph 2.2.5). Extreme caution should, however, be exercised while prescribing these drugs, because there is a fine balance between the therapeutic efficacy and toxicity of NSAIDs. When considering which treatment options to follow, the risk/benefit ratio of treatment should be balanced, especially when considering NSAIDs (Park & Moon, 2010:104).

Several risk factors for increased toxicity have been identified (Pountos *et al.*, 2011:23) and the risk for adverse effects increases in patients over 70 years and with duration of use and the size of the dose (Day & Graham, 2013:35). According to the Beers criteria expert panel of the American Geriatrics Society (2012:622) older individuals are indeed a high-risk group of patients when using NSAIDs due to an increased risk of gastro-intestinal bleeding and several other resulting effects. Individual risk factors increase the toxicity of NSAIDs, especially for cardiovascular and gastro-intestinal harm. Some of the most important risk factors associated with NSAID use include a history of pre-existing gastro-intestinal complications, age, anti-coagulation therapy and high-dose or multiple NSAIDs (Pountos *et al.*, 2011:23). While identifying adverse effects of different NSAIDs, it might be helpful to distinguish between aspirin, non-selective NSAIDs and selective COX-2 inhibitors, because these different classes might differ slightly in the risks that they pose (Dugowson & Gnanashanmugam, 2006:350).

The NSAIDs have several adverse effects on and risk factors with respect to different systems in the human body. These adverse effects on different systems include gastro-intestinal toxicity, cardiovascular adverse effects, aspirin-induced asthma, renal effects and hypertension, effects on platelets and liver toxicity, and will be addressed from paragraph 2.2.6.1 to 2.2.6.6.

#### **2.2.6.1 Gastro-intestinal toxicity**

The most common and major adverse effects of NSAIDs are associated with the upper gastro-intestinal (GI) tract and this is also the primary limiting factor for their use. Non-selective NSAIDs are the most common cause for these effects, whereas the COX-2 selective inhibitors present fewer adverse effects on the GI tract (Day & Graham, 2013:35). Non-steroidal anti-inflammatory drugs damage the GI tract through both local and systemic effects by acting as a weak acid at mucosal level, which reduces the protective effects of the gastric mucosa and thus results in epithelial damage (Day & Graham, 2013:35). Epithelial damage may vary from hidden blood loss to ulcer perforations (Süleyman *et al.*, 2007:251.)

According to Pountos *et al.* (2011:23), the gastro-intestinal toxicity of NSAIDs can be characterised into three groups. The first group of side effects occurs in about 20–40% of NSAID users and include mild GI disturbances such as nausea, dyspepsia, heartburn and abdominal pain and cramps. The second group represents more serious side effects, which include GI mucosal erosions and asymptomatic ulcers. The third group includes symptomatic ulcers, which can be life-threatening and occur in about 1% to 2% of NSAID users (which relates to an annual occurrence of about 140 000 NSAID-related complications in the US), with a mortality rate of about 10% (Pountos *et al.*, 2011:23). According to Green (2001:54), there are about 16 000 NSAID-related deaths annually secondary to GI complications in the USA, thus making it the 15th most common cause of death in the country.

There are existing methods available to avoid ulcer development and additional NSAID-induced GI complications. These methods include combination therapy with a daily proton pump inhibitor or prescribing a selective COX-2 inhibitor instead (Dugowson & Gnanashanmugam, 2006:351). If the patient is at high risk of developing GI-adverse effects, the patient's haemoglobin levels should be monitored regularly in order to identify any signs of bleeding. It is therefore important to emphasise the importance of taking NSAIDs with food (Day & Graham, 2013:36).

#### **2.2.6.2 Cardiovascular effects**

There seems to be increasing evidence that the use of COX-2 inhibitors is associated with cardiovascular adverse events (Pountos *et al.*, 2011:24), because this group of NSAIDs does not inhibit platelet thromboxane A<sub>2</sub>, which alters the balance in antithrombotic and prothrombotic pathways and promotes thrombogenesis (Dugowson & Gnanashanmugam, 2006:352). The

U.S. Food and Drug Administration (FDA) (2004) reported that Merck and Co. Inc. announced the withdrawal of Vioxx (rofecoxib) from the market on 30 September 2004 in the United States. The reason for the withdrawal of the product was that Vioxx showed an increased risk of cardiovascular events, which included heart attack and stroke, in patients using this product (FDA, 2004). Although some uncertainties remain, there is still enough evidence to suggest that COX-2 inhibitors increase the likelihood of a cardiovascular event, especially in patients at increased risk such as older patients, individuals with hypertension and electrolyte disturbances or deteriorating kidney function (Dugowson & Gnanashanmugam, 2006:352). Consultation with a cardiologist with regard to risk management of cardiovascular issues is strongly advised before COX-2 inhibitors are prescribed to risk patients.

### **2.2.6.3 Aspirin-induced asthma**

It has been reported that aspirin and other NSAIDs can initiate or aggravate asthma, which can result in violent and even fatal attacks (Pountos *et al.*, 2011:24). This is a result of the NSAID's ability to inhibit COX-1, which then causes a change in the metabolism of arachidonic acid and results in an overproduction of leukotrienes (Pountos *et al.*, 2011:24) (refer to Figure 2-1).

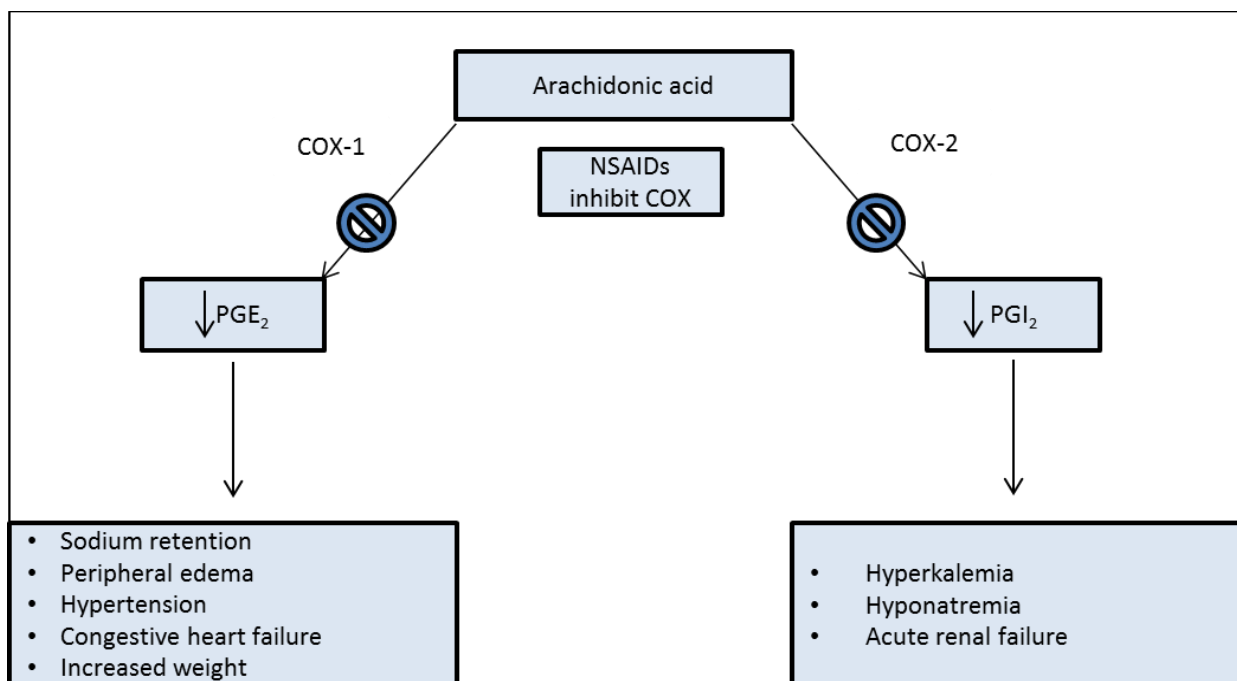
According to Day and Graham (2013:35), aspirin reduces forced expiratory volume in one second in about 20% of adults and 5% of children with asthma. As suggested, the use of aspirin in asthmatic patients can be fatal and should be avoided at all times. Recent data, however, suggests that selective COX-2 inhibitors do not result in bronchospasm and could be a safer option in asthmatic patients (Pountos *et al.*, 2011:24). Koschel *et al.* (2013:275) conducted a study in Germany in which they reviewed the tolerability of the COX-2 inhibitor etoricoxib in patients with aspirin-exacerbated respiratory disease. In this study, etoricoxib was tested in 104 aspirin-sensitive patients and etoricoxib was tolerated in all but three of these patients. This shows that etoricoxib, which is a COX-2 inhibitor, is tolerated in most but not all patients with aspirin-exacerbated respiratory disease (Koschel *et al.*, 2013:278).

### **2.2.6.4 Renal effects and hypertension**

According to Green (2001:56), renal effects are the second most serious side effects of the non-steroidal anti-inflammatory agents. Renal disease is a result of a decrease in renal prostaglandin, which maintains the renal flow. Thus further inhibition of prostaglandin by NSAIDs can cause further renal dysfunction, ranging from reversible impairment of glomerular filtration rate to irreversible renal damage (Pountos *et al.*, 2011:23). The renal effects of NSAIDs will be discussed thoroughly in paragraph 2.4.

In newly initiated NSAID therapy renal impairment is higher within the first 4–6 weeks, when it is estimated that approximately one in every 200 patients over the age of 65 years develops acute

renal injury (Pountos *et al.*, 2011:24). In patients with impaired renal function, NSAID use can lead to increased plasma potassium concentration and further loss in kidney function (Day & Graham, 2013:35). The use of NSAIDs has also been associated with acute interstitial nephritis, membranous nephropathy and nephritic syndrome (which will be discussed in paragraph 2.4.3) (Pountos *et al.*, 2011:23). More renal adverse effects of NSAIDs include salt retention, acute reversible renal insufficiency and tubulo-interstitial nephritis (Hilário *et al.*, 2006:210). However, the most frequent renal effects related to NSAID use include hypertension, salt and water retention, oedema and hyperkalaemia (Weir, 2002:S1-53). As shown in Figure 2-2, the renal effects of NSAIDs can be grouped according to their effects through the inhibition of prostaglandin synthesis and thus inhibiting PGE<sub>2</sub> and PGI<sub>2</sub> (Bathon *et al.*, 2007; Weir, 2002:S1-54).



**Figure 2-2: Renal syndromes caused by non-steroidal anti-inflammatory drugs' effect on prostaglandin**

As can be seen in Figure 2-2, the renal effects of NSAIDs are a direct result of their mechanism of action. The NSAIDs inhibit COX, which leads to reduction in prostaglandin synthesis, thus causing the renal effects.

These renal effects could also result in a rise in the patient's blood pressure and the patient should therefore be regularly monitored for any increase in blood pressure if starting long-term treatment with NSAIDs (Day & Graham, 2013:35). It is therefore important that patients on long-term NSAID use must discontinue the use of NSAIDs at the first sign of any loss of renal function and that the patient's renal function should be closely monitored.

### **2.2.6.5 Effects on platelets**

The inhibition of COX in thrombocytes leads to a decreased production of thromboxane A<sub>2</sub> and thus prolongs the bleeding time (Süleyman *et al.*, 2007:251). A low-dose aspirin causes an irreversible effect on platelet function through its inhibition of COX-1, which can last for up to 7 to 10 days. Non-selective NSAIDs, on the other hand, inhibit COX-1 reversibly, which results in the effect on platelet function lasting only about two to twelve hours (Dugowson & Gnanashanmugam, 2006:348). The degree to which platelet aggregation is blocked is clinically important in patients with underlying bleeding diathesis.

Although the antiplatelet effect of a low-dose aspirin can be fatal in patients with underlying bleeding diathesis, it is used for patients at high risk of myocardial infarction (Day & Graham, 2013:35).

### **2.2.6.6 Liver toxicity**

Non-aspirin NSAIDs are metabolised in the liver and this can result in an increase in transaminases (Pountos *et al.*, 2011:24). An increase in these enzymes can result in a variety of conditions, which includes agranulocytosis, aplastic anaemia, toxic epidermal necrosis, and cartilage metabolism dysfunction, and is also responsible for Reye's syndrome in children (Süleyman *et al.*, 2007:251). These increases are usually mild and very rarely necessitate the discontinuation of the drug in healthy patients (Green, 2001:56). The use of NSAIDs in patients with cirrhotic liver disease should therefore be avoided, as it can lead to varietal bleeding, a decrease in hepatic function and kidney failure (Pountos *et al.*, 2011:24). Fortunately, NSAIDs rarely cause hepatic damage and the hepatic effects are usually reversible (Pountos *et al.*, 2011:24).

### **2.2.6.7 Safety and monitoring of non-steroidal anti-inflammatory drugs**

On the basis of the foregoing discussion it is evident that although NSAIDs act as effective analgesic and anti-inflammatory agents, there are an abundance of safety precautions to be considered when starting any treatment with NSAIDs.

Non-aspirin NSAIDs are among the most commonly and controversially used drugs during pregnancy, with a prevalence of 17% (Nakhai-Pour *et al.*, 2011:1713). Nakhai-Pour *et al.* (2011:1713) conducted a study in which they evaluated the use of non-aspirin NSAIDs and their association with spontaneous abortions, and found that the use of the NSAIDs significantly increased the risk of having a spontaneous abortion. In the study, 7.5% of woman who had a spontaneous abortion had filled at least one prescription for an NSAID during pregnancy (n=4 705) (Nakhai-Pour *et al.*, 2011:1718). This is a result of the premature closure of the

ductus arteriosus when NSAIDs are consumed in the third trimester of pregnancy (Poveda-Roda *et al.*, 2007:E16). Non-steroidal anti-inflammatory drugs should be avoided, especially during the third trimester of pregnancy. Paracetamol is a safer alternative analgesic drug to use during pregnancy.

It is clear that the selections of NSAIDs in different patients are very important, for instance paracetamol or topical NSAIDs can be preferred over oral NSAIDs in prolonged treatment, for elderly patients (over 75 years), pregnancy and lactation (Day & Graham, 2013:36).

From a healthcare practitioner's perspective, it is therefore important to discuss any successes and adverse effects the patient might have from previous NSAID treatments to decide on which treatment will be the most effective, but also the safest for the patient.

### **2.2.7 Drug-drug interactions of non-steroidal anti-inflammatory drugs**

As was described in paragraph 2.2.3, NSAIDs work by inhibiting COX-1 and COX-2 enzymes. The inhibition of the COX enzymes, however, not only results in its therapeutic effects (refer to paragraph 2.2.4), but also its adverse effects (refer to paragraph 2.2.6). Furthermore, NSAIDs might also interact with other drugs because of their strong binding to plasma proteins and subsequent displacement of other drugs from binding sites (Hilário *et al.*, 2006:211).

According to Trevor *et al.* (2010:532), some of the most important drug-drug interactions regarding NSAIDs are the interaction of NSAIDs with anticoagulants (e.g. heparin and warfarin), its interaction with angiotensin-converting enzyme (ACE) inhibitors (e.g. captopril and enalapril), and the interaction of NSAIDs with diuretics (loop diuretics such as furosemide and thiazides such as hydrochlorothiazide). If an NSAID is used with an anticoagulant, it could result in an increased bleeding tendency because of reduced platelet aggregation (Trevor *et al.*, 2010:532). Non-steroidal anti-inflammatory drugs could cause a decrease in the antihypertensive efficacy of the ACE inhibitors and can also result in a decrease in the efficacy of diuretics (Trevor *et al.*, 2010:532).

The additive use of aspirin and other NSAIDs should be avoided, as this can cause several GI adverse events, leading to admission of the patient to a hospital (Brewer & Williams, 2012).

It is well known that NSAIDs are nephrotoxic drugs, and when these NSAIDs are administered in combination with cyclosporine, the incidence of renal damage might increase, more so than when these drugs are used separately (Bauer, 2008:656). Another drug that interacts with NSAIDs is lithium, which is used for the treatment of bipolar disease. An increase in lithium concentration is a result of an NSAID-induced decrease in renal blood flow and thus a decrease in lithium clearance (Bauer, 2008:716). Aspirin and some highly protein-bound NSAIDs can

displace phenytoin from its plasma binding sites and thus result in unsuccessful treatment of seizures (Bauer, 2008:499). Through the same mechanism that NSAIDs displace phenytoin, NSAIDs effect treatment with valproic acid as well (Bauer, 2008:566).

Non-steroidal anti-inflammatory drugs can impair the antihypertensive effect of beta blockers (e.g. atenolol, acebutolol) through the inhibition of renal prostaglandin synthesis (Tatro, 2004:259). By reducing renal clearance, NSAIDs can increase the toxicity of methotrexate (Tatro, 2004:930). This interaction can occur regularly because NSAIDs in combination with methotrexate can be used to treat rheumatoid arthritis and other inflammatory diseases. However, toxicity is less likely to occur with weekly low-dose methotrexate regimens (Tatro, 2004:930).

From the above discussion it is evident that NSAIDs should be used with caution and that there are several risk factors to consider before prescribing and providing NSAIDs to patients. Table 2-10 summarises some of the different drugs that interact with NSAIDs, with their classification and effect (Tatro, 2004:6-1435).

**Table 2-10: Summary of drugs that interact with non-steroidal anti-inflammatory drugs**

Drugs that interact with NSAIDs	Classification	Effect of interaction
Lisinopril	ACE inhibitor	Hypotensive effect of lisinopril may be reduced.
Warfarin	Anticoagulants	Anticoagulant activity may be increased by NSAIDs, increasing the risk of bleeding.
Aspirin	Salicylate	Pharmacological effects of certain NSAIDs may be decreased. Increase in possible gastric effects .
Atenolol, acebutolol, bisoprolol, metoprolol, propranolol, etc.	Beta blockers	Impaired antihypertensive effect of beta blockers.
Furosemide	Loop diuretics	Effects of furosemide may be decreased.
Cimetidine, ranitidine, etc.	Histamine H <sub>2</sub> antagonists	Therapeutic actions of NSAIDs may be altered.
Chlorothiazide, hydrochlorothiazide, etc.	Thiazide-type diuretics	Decrease in antihypertensive and possible diuretic effects of the thiazide diuretics.
Methotrexate	Cytostatics	Increased methotrexate toxicity.
Desipramine	Tricyclic antidepressants	Increase in serum concentration of desipramine, resulting in higher risk of adverse effects.
Alendronate, etidronate, etc.	Bisphosphonates	Increase in risk of gastric ulcers.
Lithium		Increase in lithium toxicity
Streptomycin, gentamicin, amikacin, etc.	Aminoglycosides	Plasma aminoglycoside concentration may increase.

## 2.3 Chronic kidney disease

In this section, chronic kidney disease (CKD), also known as renal insufficiency will be discussed and an overview will be given of certain aspects of this disease. These aspects include its definition, classification, clinical diagnosis, its diagnostic challenges, monitoring of CKD, the treatment and its prevalence.

### 2.3.1 Definition of chronic kidney disease

Chronic kidney disease is a global health problem and the magnitude of this problem will be discussed in section 2.3.3. According to Levey and Coresh (2012:165), CKD is a term used to describe all disorders that affect the structure and function of the kidneys. Chronic kidney disease is defined by Levey *et al.* (2003:138) as kidney damage or decreased kidney function for three months or more, where kidney function is measured in terms of glomerular filtration rate (GFR). This decrease in GFR is where GFR is less than 60 ml/minute/1.73 m<sup>2</sup>. According to Bailie *et al.* (2005:493), CKD can also be defined by kidney abnormalities, with or without a decreased GFR. The abnormalities of the kidneys can be structural or functional and include abnormalities in the composition of the blood or the urine or in imaging testing.

### 2.3.2 Classification of chronic kidney disease

The classification of CKD is essential during the diagnosis of the disease as well as the treatment of CKD. According to Haynes and Winearls (2010:525), CKD can be classified according to five stages on basis of the GFR of the patient. Table 2-11 classifies the stages of CKD (Levin *et al.*, 2008:1155; National Institute for Health and Clinical Excellence, 2014:5).

**Table 2-11: Classification of chronic kidney disease by stage**

Stage	Description	Glomerular filtration rate (ml/min/1.73m <sup>2</sup> )
1	Kidney damage (includes proteinuria, abnormalities in urine sediment, etc.) with normal or increased GFR	≥90
2	Kidney damage with mild decrease in GFR	60-89
3A	Moderate decrease in GFR	45-59
3B	Moderate decrease in GFR	30-44
4	Severe decrease in GFR	15-29
5	Kidney failure	<15 (or dialysis)

The categorisation (Table 2-12) gives an indication on the severity of the kidney disease. The International Society of Nephrology (ISN) (2013:31) classifies CKD on the basis of their

albuminuria and proteinuria categories by measuring their excretion rates in timed urine collections, ratio of concentrations to creatinine concentration in spot urine samples and using reagent strips in urine samples. In Table 2-12, the measures used to categorise CKD are shown along with the severity of increase in the measures (International Society of Nephrology, 2013:31).

**Table 2-12: Relationship for categories among albuminuria and proteinuria**

Measure	Categories		
	Normal to mildly increased	Moderately increased	Severely increased
AER (albumin excretion rate) (mg/24hours)	30	30-300	4300
PER (protein-to-creatinine ratio) (mg/24hours)	150	150-500	4500
ACR (albumin-to-creatinine ratio) (mg/mmol) (mg/g)	3 30	3-30 30-300	430 4300
PCR (protein excretion rate) (mg/mmol) (mg/g)	15 150	15-50 150-500	450 4500
Protein reagent strip	Negative to trace	Trace to positive (+)	Positive (+) or greater

It is important to note that the relationship between these categories varies within age, gender, race and diet, therefore these relationships are approximate only.

Bailie *et al.* (2005:494) provides a simplified classification of CKD, where the types of CKD is provided and are classified as diabetic kidney disease, non-diabetic kidney disease and kidney disease in kidney transplant recipients. Table 2-13 illustrates the category of CKD along with examples of the major types CKD (Bailie *et al.*, 2005:495).

**Table 2-13: Types of chronic kidney disease**

Category of kidney disease	Examples of major types
Diabetic	Type 1 and type 2 diabetes
Non-diabetic	Glomerular disease (which includes systemic infections, autoimmune diseases, neoplasia and drugs) Vascular disease (hypertension, micro-angiopathy, etc.) Tubulo-interstitial disease (urinary tract infections, kidney stones, etc.) Cystic kidneys (polycystic kidney disease)
In the kidney transplant recipient	Chronic rejection Drug toxicity (cyclosporine or tacrolimus) Recurrent diseases (glomerular diseases) Transplant glomerulopathy

The classification of CKD, whether it is in terms of severity or the types of CKD, is therefore very important during the diagnosis of the disease, because it not only determines the prognosis of the disease, but also the path of treatment that should be embarked on.

### 2.3.3 Epidemiology of chronic kidney disease

Chronic kidney disease is undoubtedly a public health problem globally, with an estimated prevalence of 8–16% worldwide (Jah *et al.*, 2013:260). According to Levey and Coresh (2012:166), the incidence in many countries is as high as 200 cases per million per year, and nearing 400 cases per million per year in countries such as the USA and Taiwan. In 2010, CKD was the 18th highest cause of death worldwide (Stanifer, 2014:e174), increasing in rank from the 27th position in 1990 (Lozano *et al.*, 2012:2095). There is an increased risk of renal impairment with increasing age (SIGN, 2008:4) because, according to Graves (2008:1064), GFR declines by 1% per year for every year of life after 30 years, resulting in a decrease in kidney function with age. A study conducted in Germany (n=9 806) found that the CKD prevalence peaked at 26.9% in participants aged between 70 and 74 years, thus indicating that renal function decreases with age (Zhang *et al.*, 2009:122). Another risk factor associated with CKD is gender, where a study done in Iran (n=10 063) found that the overall prevalence of CKD in females is 23%, compared to 13.1% in their male counterparts (Hosseinpanah *et al.*, 2009:47).

Chronic kidney disease has become a global health problem (Platinga *et al.*, 2010:225). As was previously stated, the global prevalence of CKD is estimated to be in the range of 8 to 16% (Jah *et al.*, 2013:260), but this prevalence varies within different demographic regions. In South Africa there has been a 67% increase in deaths due to CKD between 1999 and 2006 (Moosa *et*

*al.*, 2015:320). From the summary of studies conducted on overall prevalence (Annexure A), the global prevalence of CKD is great cause for concern. Very high prevalence rates of CKD are observed in developed countries such as the United States (16%) (Warnock *et al.*, 2005:1428), and even higher prevalence rates are seen in developing countries such as the Democratic Republic of Congo (36%) (Sumaili *et al.*, 2009:18). South Africa also indicated high prevalence rates of CKD (14.3%) (Stanifer *et al.*, 2014:e177).

According to Zhang and Rothenbacher (2008:124), the prevalence of CKD can vary strongly within different age groups. An increase in age correlates to a higher risk of developing CKD (refer to paragraph 2.3.4.1). Trifiró *et al.* (2014:3) found that CKD prevalence increased from 0.2% in patients <45 years to 9.2% in patients 80 years and older (n=158 510). A study done in Spain (n=2 746) proved that age is indeed a risk factor for CKD when they found that patients older than 64 years had a CKD prevalence of 21.4%, compared to subjects aged 40 to 64 years, where the CKD prevalence was 3.3% (Otero *et al.*, 2010:80). An increase in CKD prevalence with an increase in age was found by Zhang *et al.* (2009:125), with CKD prevalent in 24%, 18.8%, 16.2%, 15.4% and 13.2% in the age groups 70–74, 65–69, 60–64, 55–59 and 50–54 years, respectively (n=9 806). Imai *et al.* drew the same conclusion with a CKD prevalence of 59.1% in patients 80–89 years of age, compared to 44% and 31.8% in subjects aged 70–79 and 60–69 years respectively (n=527 594).

There is some controversy over the influence of gender as a risk factor of CKD, with inconsistent findings from various studies. For example, Tohidi *et al.* (2012) showed that females tend to be associated with a slightly higher risk of CKD, whereas Trifiró *et al.* (2014:3) found that the CKD prevalence was slightly higher in male subjects, with a ratio of 1:1. Chronic kidney disease was prevalent in 9.1% of female subjects, as opposed to 4.4% in the male subjects in a study (n=743 935) conducted by Kearns *et al.* (2013:52). Stevens *et al.* (2007:94) found that the CKD prevalence was 10.6% among females and 5.8% among their male counterparts (n=130 226). Further evidence that female gender could be a risk factor for CKD is a study performed in Mexico, where CKD was prevalent in 16% of the female subjects and in only 4% of the male subjects (Amato *et al.*, 2005:s14). Prevalence of CKD thus ranges between two to four times higher in females.

By increasing our knowledge and understanding regarding the epidemiology of CKD, we might be able to assess the level of its underdiagnosis (refer to 2.3.5) and estimate the impact of potential screening policies (Otero *et al.*, 2010:79) (refer to paragraph 2.3.4).

### **2.3.4 Clinical diagnosis of chronic kidney disease**

In the management of CKD, early diagnosis and intervention of the disease could reduce the risk of cardiovascular events, kidney failure and death that are associated with CKD (James *et al.*, 2010:1296). Chronic kidney disease is, however, difficult to diagnose as it can be seen as quite a silent condition, since it has few symptoms (Zhang *et al.*, 2007:1093) and is nearly always asymptomatic during the early stages of the disease (Qaseem *et al.*, 2013:835).

The Scottish Intercollegiate Guidelines Network (SIGN) (2008:14) has developed a preliminary algorithm that provides a guideline that can be used to evaluate patients and assist in the identification of CKD. This algorithm divides the guidelines into the identification of risk patients, initial abnormality detection, clinical evaluation and the characteristics of a confirmed CKD patient. In this section, clinical diagnosis will be discussed on the basis of this algorithm, which is found in Annexure B (SIGN, 2008:14).

#### **2.3.4.1 Identification of higher-risk chronic kidney disease patients**

There are several clinical conditions that are seen as risk factors and patients with these conditions should be closely monitored when CKD is suspected. Some conditions should be monitored very closely, e.g. diabetes mellitus, while other conditions such as hypertension and cardiovascular diseases should be taken note of. Other risk factors that might increase the risk of CKD include smoking, obesity, age, and chronic use of NSAIDs (SIGN, 2008:14).

According to a fact sheet of the US Centers for Disease Control (2014), approximately one in three adults with diabetes and one in five adults with hypertension has CKD. Diabetes seems to be the leading cause of kidney disease in Canada, with an incidence of 34% in 2009 (Canadian Institute for Health Information, 2011:12). Diabetic nephropathy is a form of kidney disease in patients with diabetes, which is caused by an increase in proteinuria in patients with diabetes, which eventually leads to a decline in renal function (McFarlane *et al.*, 2013:S129). Other forms of kidney disease, such as ischaemic damage related to vascular disease and hypertension, can also be seen in diabetic patients (McFarlane *et al.*, 2013:S129). Cardiovascular disease is another risk factor for CKD (National Centre for Chronic Disease Prevention (US Centers for Disease Control, 2014), and according to Weiner *et al.* (2004:1307), the mortality rate of cardiovascular disease in dialysis patients is ten to thirty times higher than in the general population. Cardiovascular disease and hypertension decrease the GFR, which further increases the risk of CKD (Tomson & Bailey, 2011:409). It is therefore important to understand the relationship between diabetes, cardiovascular disease and hypertension and the role these factors play in the decrease in kidney function.

Ejerblad *et al.* (2004:2184) found that smoking is a significant risk factor for CKD, and 8.9% of all the CKD cases in the Swedish population can be attributed to smoking. Age is an important risk factor for CKD, because the kidneys experience an age-associated decline in function (Tomson & Bailey, 2011:408). The risk of chronic NSAID use and its relationship with CKD will be discussed in paragraph 2.4.

#### **2.3.4.2 Initial abnormality detection**

It is important to understand the difference between direct and indirect detection of kidney damage. Direct screening includes a renal tract ultrasound, which will be discussed in paragraph 2.3.4.2.3, while indirect screening to detect kidney abnormalities includes urinalysis to check proteinuria, albuminuria and GFR (SIGN, 2008:5). This section discusses these different screening methods used to detect abnormalities in kidney function.

##### **2.3.4.2.1 Urine dipstick abnormality**

According to SIGN (2008:5) proteinuria, along with albuminuria, is associated with cardiovascular and renal disease and is therefore an important test of kidney function. Proteinuria is when the kidneys allow more protein to be filtered through the glomerular capillaries (usually 150 mg/day) than is usually filtered in healthy kidneys (Roberts, 2007). According to James *et al.* (2010:1299), screening for proteinuria is a popular detection method, since it is easy to undertake and predicts cardiovascular morbidity and mortality and might even be a better predictor of further GFR decline than estimated GFR (eGFR) (refer to paragraph 2.3.4.2.2).

Urine dipstick analysis is one of three components of a complete urinalysis, which also includes a physical examination and a microscopic examination of the urine sediment (Arici, 2014). According to Griffith (2010:83), proteinuria should be quantified by using albumin-creatinine ratio (ACR) (refer to Table 2-12) and where a dipstick is positive for proteinuria, the protein-creatinine ratio (PCR) should be used. The ACR is an important test, especially in diabetic patients, where it indicates the earliest stages of diabetic nephropathy, since it is sensitive where small amounts of protein are leaked (micro-albuminuria) (Griffith, 2010:83). In cases of albuminuria, it is usually a reflection of a damaged glomerulus (US Department of Health and Human Services, 2014), and albumin excretion of 30–300 mg/day usually reflects high albuminuria (Arici, 2014).

##### **2.3.4.2.2 Measurement of abnormal renal function**

In diagnosing CKD, eGFR is commonly used. The GFR can be defined as the volume of plasma that is filtered by the glomeruli per unit, and is usually measured by estimating the rate of

clearance of a substance from the plasma (SIGN, 2008:8). Estimated glomerular filtration rate is an estimate based on equations, with the most popular equations being the Cockcroft-Gault (CG) equation and the Modification of Diet in Renal Disease Study (MDRD) equation (Zhang & Rothenbacher, 2008:118). As was discussed in paragraph 2.3.1, a safe diagnosis of CKD can be assumed when the eGFR decreases below 60 ml/min/1.73 m<sup>2</sup>, even when there is no clear evidence of kidney damage (Arici, 2014). According to Griffith (2010:82), eGFR should not be used to predict kidney function in children under the age of 18 years, in pregnant women or in patients with extreme muscle mass. The classification of CKD (refer to paragraph 2.3.2) can be utilised effectively in the diagnosis of the disease, especially when GFR is used to determine kidney damage in patients.

Another estimate of kidney function can be the cystatin C-based estimate of GFR, as cystatin C correlates inversely with GFR (SIGN, 2008:9). The cystatin C-based estimate of GFR (eGFR<sub>cystatinC</sub>) should be used in people with an eGFR of 45-59 ml/min/1.73 m<sup>2</sup> for at least 90 days, or in patients where there is no indication of proteinuria (ACR ratio less than 3 mg/mmol) or any other markers of kidney disease (NICE, 2014:18).

#### 2.3.4.2.3 Abnormality in kidney function

When CKD is suspected, it is often useful to evaluate if there is structural damage to the kidney through imaging (SIGN, 2008:8). This can be done by using renal tract ultrasound and can detect obstructive uropathy, renal size and symmetry, scarring and polycystic disease (SIGN, 2008:8). Ultrasound uses a Doppler component to evaluate patients with a raised creatinine level or any other indication of CKD (Graves, 2008:1067). Renal tract ultrasound is the most important test of kidney damage as it provides information on the size of the kidneys. If small kidneys (7–8 cm) are observed, then the chance of renal failure is very rare. If large kidneys (12–13 cm) are seen, the differential diagnosis can include glomerulonephritis, diabetic nephropathy and polycystic kidney disease (Graves, 2008:1067).

Screening and abnormality detection are a crucial part of the diagnosis of CKD, but unfortunately they are usually executed much later than they should be. These tests usually occur after signs and symptoms have been recognised. Table 2-14 provides some of the important signs and symptoms that occur during the early and latter stages of CKD (American Nephrology Nurses' Association, 2009; Arici, 2014:15; Tomson & Bailey, 2011:408).

**Table 2-14: Signs and symptoms of early and later stages of chronic kidney disease**

Signs and symptoms of early stages of chronic kidney disease	Signs and symptoms of later stages of chronic kidney disease
Weakness Loss of appetite Nausea Nocturia, polyuria Loin pain Oedema High blood pressure Blood in urine or dark-coloured urine Pale skin	Fatigue Volume overload Memory loss Intractable hiccups Pruritus Congestive heart failure Anorexia Nausea and vomiting Muscular twitches and cramps Restless legs Anaemia

Johnson (2012:2) indicates the diagnostic testing that should always be performed when CKD is suspected includes:

- A full blood count of patient
- Repeat the serum urea/electrolytes/creatinine/eGFR/albumin tests within a week
- Urine ACR
- Fasting lipids and glucose
- Urine microscopy and culture
- Renal ultrasound

These signs and symptoms act as an early identification of CKD and can improve the prognosis and prevention of complications of the disease.

### **2.3.5 Diagnostic challenges of chronic kidney disease**

Chronic kidney disease poses a global health problem and the key to its prevention is early detection and diagnosis. Unfortunately early detection of the disease might prove problematic, since it is asymptomatic in its early stages (Chen *et al.*, 2010:31). According to Dasari *et al.* (2014:363), the loss in kidney function usually takes months or years to occur, but on some occasions symptoms can appear only once the kidney function is less than one-tenth of its normal function. To identify CKD, individual risk factors as well as the appropriate laboratory test (as discussed in 2.3.4) should be considered (Plantinga *et al.*, 2010). According to James *et al.* (2010:1298), early recognition and identification are therefore the biggest challenge in treating and preventing CKD-associated complications. Unfortunately it is not that simple, because of several factors that complicate the diagnosis. Factors that complicate the diagnosis of CKD

include the absence of symptoms in the early stages of disease, the accessibility of laboratory tests and the availability of treatments that prevent complications (James *et al.*, 2010:1299).

Chronic kidney disease has several comorbidities that can lead to complications of the disease, but these comorbidities can provide challenges in the diagnostic process as well (Dasari *et al.*, 2014:363). These comorbidities include diabetes, hypertension, atherosclerotic vascular disease and several other cardiovascular conditions (Graves, 2008:1064). Chronic kidney disease can thus present differently, depending on the stage and cause of the disease, as well as individual factors such as age (Arora, 2015). This can result in differential diagnosis for CKD, which can include systemic lupus erythematosus, renal artery stenosis, urinary obstruction and Wegener granulomatosis (Arora, 2015).

According to Hwang *et al.* (2010:7), an incorrect diagnosis of CKD could be caused by an over- or underestimation of GFR when using the modification of diet in renal disease (MDRD) equation. The early identification of CKD is therefore an important factor in the prognosis of the disease, as it can prevent drastic loss in kidney function, as well as reduce the risk of further complications and loss of kidney function.

### **2.3.6 Monitoring of chronic kidney disease**

Monitoring of CKD should include the evaluation of high-risk patients and the implementation of lifestyle changes that will eventually slow the progression of CKD. The management and prevention as well as prescribing factors of CKD will be discussed in this section.

#### **2.3.6.1 Management and prevention of chronic kidney disease**

Early diagnosis and management are a vital part of the management of CKD and prevent further complications from occurring. All CKD management programmes should include symptom management, psychological care and spiritual care (Levin *et al.*, 2008:1154). The role of the healthcare practitioner in the prevention of CKD includes the mandatory measuring of blood pressure, routine screening for evidence of CKD (includes urine dipstick etc.) and control of comorbidities such as type 2 diabetes mellitus and hypertension (Moosa *et al.*, 2015).

Lifestyle management/intervention that is needed to improve the outcome of CKD includes:

- Smoke cessation (in smokers)
- Following a balanced diet that is low in salt, saturated fats and sugars
- Limiting alcohol intake
- Managing blood pressure and type 2 diabetes mellitus (Moosa *et al.*, 2015)
- An increase in physical activity (30 minutes per day) (Australian Kidney Foundation, 2015:53).

According to Haynes and Winearls (2010:527), the management of a CKD patient should therefore include the treatment of the underlying cause, slowing the natural progression of the disease, treating the complications and counselling the patient to prepare them for renal replacement therapy or palliative care. The treatment and management of comorbidities of CKD are thus vital in the management of the disease. The more important risk factors or comorbidities of CKD include older age, diabetes, dyslipidaemia and hypertension (Levey *et al.*, 2003:139). These high-risk CKD patients should be identified early and monitored very closely to prevent the progression of the disease to later stages of CKD and eventually kidney failure (James *et al.*, 2010:1296).

### **2.3.6.2 Triggers and prescribing factors regarding chronic kidney disease**

In the management of CKD it is important for prescribers to review the prescription of renal excreted medications and avoid the use of nephrotoxic drugs. The Australian Kidney Foundation (2015:21) lists commonly prescribed drugs that should be avoided in CKD patients, namely:

- Aminoglycosides
- Calcineurin inhibitors
- Gadolinium
- Lithium
- NSAIDs and COX-2 inhibitors

According to Kalyesubula and Perazella (2011), some of the most commonly used HIV drugs, such as zidovudine, lamivudine, stavudine and tenofovir, are also nephrotoxic. If treatment with these drugs cannot be avoided, dosage adjustments are required.

### **2.3.7 Treatment of chronic kidney disease**

According to Johnson *et al.* (2004:869) the treatment of CKD consists of:

- Evaluation and management of underlying disorders and comorbidities
- Measures to slow the loss of kidney function
- Measures to effectively reduce and treat cardiovascular risk (James *et al.*, 2010:1296)
- Preparation of kidney failure and kidney replacement therapy
- Dialysis or transplantation

Underlying disorders of CKD that need to be controlled (refer to paragraph 2.3.5.) include hypertension, cardiovascular disease, diabetes, dyslipidaemias, and anaemia (Indian Society of Nephrology, 2013).

The controlling of hyperglycaemia and blood pressure in particular in kidney disease patients is vital in slowing the progression of kidney disease (McMillan, 2015). The target blood pressure should be about 110 to 130/<80 mmHg and the drugs most commonly used to treat hypertension and slow the progression of GFR are angiotensin-converting-enzyme inhibitor (ACE inhibitors) and angiotensin-2-receptor blockers (McMillan, 2015). According to James *et al.* (2010:1302), ACE inhibitors are the preferred choice of drugs in patients with proteinuric CKD. High blood pressure is the most prevalent risk factor in CKD patients (Zamboli *et al.*, 2006:497) and treatment goals in only a few patients are achieved, despite this high prevalence (Tedla *et al.*, 2011). Zamboli *et al.* (2006:497) also suggest the use of a diuretic (e.g. thiazide diuretic) to help lower blood pressure and prevent the development of cardiovascular complications.

According to the National Kidney Foundation (2010), medications that could be used in treating hypertension in CKD patients include ACE inhibitors, angiotensin-receptor blockers, diuretics, beta blockers and calcium-channel blockers (refer to Annexure C for full list of drugs). The nature of the underlying kidney disease should be taken into consideration when treating hypertension in CKD patients. Patients should benefit from the treatment of ACE inhibitors and angiotensin-2-receptor blockers to reach the target blood pressure (Tedla *et al.*, 2011).

According to Vladu *et al.* (2014:203), diabetes mellitus is the most frequent cause of CKD and is prevalent in about 50% of the end-stage CKD cases worldwide. Reversible kidney damage is prevalent in about one-third of type 2 diabetes mellitus patients and is the leading cause of cardiovascular morbidity and mortality in these patients (Shahady, 2014:21). It is therefore clear that the glycaemic control of CKD patients is an important part of CKD treatment and will help improve the prognosis of the disease.

To maintain glycaemic control of CKD patients, target treatment goals should be set, and according to Cavanaugh (2007:91), the haemoglobin A<sub>1c</sub> (HbA<sub>1c</sub>) target should be <7.0%, and for the fasting plasma glucose of the patients between 4–7 mmol/L (James *et al.*, 2010:1304). The diabetic medications to be used in CKD patients include oral agents and insulin. Oral agents that can be used in CKD patients include sulfonylureas, metformin, alpha-glucosidase inhibitors, repaglinide, thiazolidinediones, dipeptidyl peptidase-4 inhibitors (DPP-4 inhibitors) and glucagon-like peptide-1 (GLP-1) receptor agonists (Indian Society of Nephrology, 2013). Ahmed *et al.* (2009:55) provide a list of oral agents, as well as insulin (Indian Society of Nephrology, 2013), that can be used in the treatment of diabetes in CKD patients. This list is summarised in Table 2-15 (refer to Annexure C for another summary of medications used to treat CKD).

**Table 2-15: Anti-hyperglycaemic agents used to treat chronic kidney disease**

Oral agents		Insulin	
Class	Drug name	Class	Drug name
Sulfonylureas	Glipizide Gliclazide	Short acting	Humulin®R
Meglitinides	Repaglinide	Intermediate acting	Neutral Protamine Hagedorn Humulin®N
Thiazolidinediones	Rosiglitazone	Prolonged action	Humulin®U Glargine (Lantus®) Detemir (Levemir®)
GLP-1 receptor agonist	Exenatide		
Amylin analogue	Pramlintide		
DPP-4 inhibitor	Sitagliptin		
Alpha-glucosidase inhibitors	Acarbose		
Biguanide	Metformin		

Glycaemic control in CKD patients is needed, as it can improve the prognosis and prevent complications of the disease (Levin et al., 2008:1155).

Cardiovascular disease is very common in CKD patients and has major implications for the outcome of the disease (Wright & Hutchison, 2009:713). Cardiovascular disease is often the leading cause of death in CKD patients (Calabrese, 2011:s412). According to Herzog *et al.* (2011:572) cardiovascular cases can be divided into coronary artery disease, myocardial infarction, congestive heart failure, cerebrovascular disease, stroke, atrial fibrillation, peripheral arterial disease and sudden cardiac death.

Drug therapies that have been used to improve the cardiovascular outcome in renal disease patients include beta-blockers, renin-angiotensin-aldosterone system blockers and statins (Ardhanari *et al.*, 2014). According to Tan and Johnson (2008:156), cardiac failure and ischaemic heart disease can be treated with diuretics (furosemide, 120 mg twice daily) that will control fluid retention in CKD, whereas ACE inhibitors and beta blockers such as bisoprolol and carvedilol improve the prognosis. The cardiovascular risk in CKD patients can be prevented with lifestyle changes such as regular exercise and a healthy diet (Wright & Hutchison, 2009:719). Table 2-16, adapted from Herzog *et al.* (2011:572-582), provides a summary of the treatment of different cardiovascular cases in patients with CKD.

**Table 2-16: Treatment of cardiovascular diseases in chronic kidney disease patients**

Cardiovascular disease	Treatment
Coronary artery disease Myocardial infarction	Aspirin Clopidogrel Beta-blockers ACE inhibitors*
Congestive heart failure	Dietary salt restriction ACE inhibitors* Angiotensin-receptor blockers Mineralocorticoid receptor blocker
Cerebrovascular disease Stroke Atrial fibrillation Peripheral arterial disease	Statins ACE inhibitors* Thiazide diuretics Phosphodiesterase inhibitor (cilostazol)
Sudden cardiac death	Dialysis for volume removal

\*ACE inhibitors= angiotensin-converting-enzyme inhibitor

Urgent and focused attention should therefore be shifted to break the synergy between kidney and cardiovascular disease (Wright & Hutchison, 2009:720) that will eventually improve the prognosis of CKD.

Chronic kidney disease is often associated with hyperlipidaemia (Tan & Johnson, 2008:154). Dyslipidaemia is a risk factor for cardiovascular disease in CKD patients (Weiner & Sarnak, 2004:1045). The target goal for dyslipidaemia should be to achieve a serum total cholesterol of less than 4 mmol/L and a low density lipoprotein of below 2.5 mmol/L (Tan & Johnson, 2008:154). According to Bloch and Kuritzky (2012:s6), HMG-CoA reductase (statin) therapy is safe and effective and remains the first-line treatment in lowering the cholesterol of CKD patients. Further treatment options include fibrates that can be used when hypertriglyceridemia is the primary lipid abnormality, nicotinic acid (niacin), bile acid sequestrants and fatty acids (Omran *et al.*, 2013:169). Weiner and Sarnak (2004:1050) summarise the important treatment options that are available to treat dyslipidaemia in Table 2-17 (Also refer to Annexure C for a list of cholesterol-lowering medication).

**Table 2-17: Dyslipidaemia treatment in chronic kidney disease**

Class of drug	Active ingredient
Statins	Atorvastatin Simvastatin
Nicotinic acid	Niacin
Bile acid sequestrant	Cholestyramine Cholestipol
Fibrates	Clofibrate Fenofibrate

As CKD is exacerbated, Stage 5 of the disease occurs and eventually leads to kidney failure. The New Zealand Ministry of Health (2014) indicates that the treatment options for kidney failure can include dialysis or a kidney transplant. According to McMillan (2015), dialysis is initiated at the earliest sign of any uremic symptoms such as anorexia, nausea, pericarditis and pleuritic, or in severe cases that include hyperkalaemia and acidosis. These complications typically occur when the eGFR is less than 10 mL/min (McMillan, 2015). Two types of dialysis exist, namely haemodialysis and peritoneal dialysis (Foote & Manley, 2008). With haemodialysis the filtering of the blood takes place outside the patients' body in a filter that is connected to the dialysis machine, while peritoneal dialysis takes place inside the body, with the exchange of fluids using a catheter (New Zealand Ministry of Health, 2014).

An early kidney transplant could lead to better long-term outcomes for the patient if a living kidney donor is available (McMillan, 2015). The Australian Kidney Foundation (2015:24) provides a brief comparison between the different dialysis as well as kidney transplant treatments (see Table 2-18).

**Table 2-18: Kidney transplant and dialysis in chronic kidney disease**

Treatment	Types	Involves
Kidney transplant	Living or deceased donor	Surgery Lifetime immunosuppressants Waiting time for donor
Peritoneal dialysis	Continuous Ambulatory Peritoneal Dialysis (CAPD)	Four daytime bags changed manually
	Automated Peritoneal Dialysis (APD)	Overnight exchanges managed by machines
Haemodialysis	Daytime, 3–5 treatments weekly, 4–6 hours duration	Blood cleansed by filter
	Nighttime, 3–5 nights per week, 8 hours duration	

James *et al.* (2010:1304) summarise the important underlying diseases that need to be treated with their treatment goals and pharmacotherapy (refer to Annexure C). Pharmacotherapy is indicated as the class of drugs used, along with their active ingredient and commonly used trade name as given by the MIMS classification system for drugs (Snyman, 2012:107-157). (Refer to Annexure C for a table of drugs used to treat the underlying causes in CKD).

**2.4 Chronic kidney disease and non-steroidal anti-inflammatory drugs**

Non-steroidal anti-inflammatory drugs inhibit the COX function, reduce prostaglandin production and change the haemodynamics in the kidney, thus leading to renal failure (Tsai *et al.*, 2015: 382). These drugs are therefore regarded as a risk factor that can influence the progression of CKD (Nderitu *et al.*, 2013:247). In this section, the use of NSAIDs in patients with CKD, with

specific reference to the prevalence and prescribing patterns of NSAIDs in CKD patients, the effects of NSAIDs on renal function, greater-risk patients and the overall management and control of NSAID use in these patients will be discussed.

**2.4.1 Factors that contribute to non-steroidal anti-inflammatory drug use in chronic kidney disease patients**

To investigate the use of NSAIDs in CKD patients, it might be useful to identify the reason NSAIDs are used in these patients. The main reason NSAIDs are used in CKD patients is to relieve the pain they experience during the disease (McMillan, 2015). According to Santoro *et al.* (2012:S2) pain is a major health problem in CKD and end-stage renal disease patients, with almost half these patients experiencing pain. Pain during CKD can result from a variety of factors. According to Cohen *et al.* (2007:920), 69% (n=92) of the patients with CKD experience pain.

Kafkia *et al.* (2011:115) state that pain is the most common symptom experienced by CKD patients and could be caused by their primary disease (e.g. polycystic kidneys), renal failure, renal replacement therapy, peritoneal dialysis or a co-morbid illness (e.g. peripheral vascular disease, cardiovascular disease or diabetic neuropathy). Since CKD has many co-morbid conditions, these patients have to undergo surgical procedures frequently and therefore require pain management (Parmar & Parmar, 2013). According to Krishnan *et al.* (2009:267), a common complication in CKD patients is the occurrence of neuromuscular disease. Neuromuscular disease can manifest and cause pain in five different clinical features that include uremic neuropathy, mononeuropathy (e.g. carpal tunnel syndrome, ulnar neuropathy and femoral neuropathy), ischemic neuropathy, autonomic neuropathy and uremic myopathy (Krishnan *et al.*, 2009:267). Santoro *et al.* (2012:S4) listed the most important causes of pain in CKD patients and therefore also the main reasons these patients have a need to use NSAIDs. These causes are summarised in Table 2-19.

**Table 2-19: Important causes of pain in chronic kidney disease patients**

Peripheral polyneuropathy: Uremia, diabetes, vasculitis, Fabry disease	Renal bone disease: Ostetis fibrosa cystia, osteomalacia, low bone turnover osteopathy
Mononeuropathy: Carpal tunnel syndrome, ulnar or femoral neuropathy	Osteoarthritis
Ischemic monomelic neuropathy	Calciophylaxis (Calcific uremic arteriolopathy)
Critical lower limb ischemia	Headaches
Chronic infections: Osteomyelitis, discitis, shunt infection	Primary kidney disease: Renal stones, pyelonephritis, polycystic kidney disease
Nephrogenic systemic fibrosis	Gastro-intestinal complaints

**Table 2-19: Important causes of pain in chronic kidney disease patients**

Haemodialysis: Needle insertion, muscle cramps, headaches, abdominal/cardiac pain caused by volume contraction	Peritoneal dialysis: Installation of dialysate, abdominal distension and peritonitis
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#### **2.4.2 Epidemiology and prescribing patterns of non-steroidal anti-inflammatory drugs in chronic kidney disease patients**

According to Platinga *et al.* (2011:424) there is not enough information available regarding the patterns of NSAID use in the CKD population, but some prevalence studies have been conducted to create more awareness regarding the use of these drugs by CKD patients.

NSAIDs are prescribed to more than 50% of elderly patients with CKD (Nderitu *et al.*, 2013:247). A study on associated risk factors of CKD done in El Salvador (n=775) indicated that the total prevalence of NSAID use by CKD patients was 74.8% (Orantes *et al.*, 2011:18). A review done by Davison *et al.* (2013) reported the use of any NSAID in patients with CKD was 4.9% (n=25 725), while the use of NSAIDs in CKD patients with pain proved to be 19% (n=775). Platinga *et al.* (2011:426) found that 10.2% of CKD patients in the United States were currently using NSAIDs, while another 66.1% had used NSAIDs for one year or longer (n=12 065). In West Yorkshire, 55.5% of CKD patients were prescribed NSAIDs (n=1 427), with a concerning statistic that revealed that 20.2% of these patients had no record of CKD monitoring in the preceding year (Bhopal *et al.*, 2010:283).

Doubova *et al.* (2007:151) studied the potential drug-disease interactions and identified 18 cases (2.4%) (n=624) where NSAIDs had been used in patients with chronic renal insufficiency. In a study conducted in Italy (n=1 989), 56.3% of the study population reported the use of at least one NSAID, while 35.6% of CKD patients were treated with a NSAID for periods exceeding 90 days (Ingrasciotta *et al.*, 2014:1). Platinga *et al.* (2011:426) reported that the mean number of NSAID doses per day in patients with mild and severe CKD was 3.3 and 3 respectively.

Wei *et al.* (2013:174) reported the prescribing rate of NSAIDs in different CKD stages. They found that NSAIDs were prescribed to 24.5%, 18.3% and 7.7% of CKD patients with Stages 3, 4 and 5 respectively. Diclofenac was the most frequently prescribed NSAID during CKD Stages 3 (35.2%), 4 (32.1%) and 5 (35%), with ibuprofen the second most frequently prescribed NSAID (28.9% in Stage 3, 24.1% during Stage 4 and 15% during Stage 5) (Wei *et al.*, 2013:174).

Davidson and colleagues (2013) conducted a study evaluating CKD patients that were divided into CKD patients with pain and all CKD patients and were analysed by the use of analgesics and acetaminophen. Analgesics (excluding NSAIDs) were used in 27% and 65.8% of all CKD

patients and CKD patients with pain respectively. In all CKD patients acetaminophen was used in 8.9% of the patients, while it was used in 18.2% of the CKD patients with pain (Davison *et al.*, 2013). Kuo *et al.* (2010:747) identified 18 486 CKD patients without end-stage renal disease (ESRD) and a further 677 CKD patients with end-stage renal disease. The use of NSAIDs in CKD patients with ESRD was much higher than the use of NSAIDs in CKD patients without ESRD. Acetaminophen (52.9% in CKD patients with ESRD and 18.2% in CKD without ESRD) was the most frequently used NSAID, followed by aspirin, used by 27.5% and 7.2% of CKD patients with and without ESRD respectively (Kuo *et al.*, 2010:747).

The most frequently used NSAIDs one year prior to CKD diagnosis and one year after CKD diagnosis were found by Ingrasciotta *et al.* (2014:6) to be nimesulide, ibuprofen and diclofenac, as well as acetylsalicylic acid. Table 2-20 provides a list of drugs used in CKD patients one year prior to and one year after being diagnosed with CKD (Ingrasciotta *et al.*, 2014:6).

**Table 2-20: Non-steroidal anti-inflammatory drug use in chronic kidney disease patients**

Type of NSAID	Proportion of CKD patients receiving more than one NSAID	
	One year prior to CKD diagnosis	One year after CKD diagnosis
Low-dose acetylsalicylic acid	41.4%	43.5%
Nimesulide	20.2%	16.6%
Diclofenac	14.1%	11%
Ketoprofen	12.2%	10.6%
Coxib	6.3%	6.5%
Piroxicam	5.3%	4.5%
Ketorolac	5.1%	6.2%
Others (ibuprofen, tenoxicam, meloxicam, aceclofenac, etc.)	12.5%	9.9%

From the above discussion it is evident that there is a gap in information regarding the use of NSAIDs in CKD patients. The lack of information goes deeper than just at patient level, but is also prevalent in healthcare providers, thus resulting in poor prognosis in diseases. More research and information are required regarding this aspect of CKD and NSAID.

**2.4.3 Effect of non-steroidal anti-inflammatory drugs on renal function**

Non-steroidal anti-inflammatory drugs are nephrotoxic, with both acute and chronic effects (such as glomerular and tubulo-interstitial injuries) on kidney function (Gooch *et al.*, 2007:280.e1; Loh & Cohen, 2009:240).

The renal side effects of NSAIDs are a result of the NSAID's ability to inhibit the isoenzymes (COX-1 and COX-2) of COX (Hörl, 2010:2291). The mechanism of the nephrotoxicity of NSAIDs seems to be related to the vasodilatory effects of prostaglandins on renal arterioles, especially in patients with low intravascular volume, depleted kidney function or high levels of angiotensin, where the nephrotoxic effects of NSAIDs are likely to occur (Hunter *et al.*, 2011:41). The NSAIDs thus cause alterations in renal blood flow (Howse & Bell, 2007:399). Cyclo-oxygenase is the enzyme that converts arachidonic acid in prostaglandins, prostacyclin and thromboxane (Markowitz & Perazella, 2005:34). When NSAIDs thus inhibit COX production, the secretion of prostaglandins, prostacyclin and thromboxane is decreased as well (Markowitz & Perazella, 2005:34). The inhibition of these enzymes has different effects on renal function, resulting in salt depletion, hypovolemia, liver cirrhosis, congestive heart failure, nephrotic syndrome and CKD (Hörl, 2010:2291) (refer to paragraph 2.2.6.4).

Non-steroidal anti-inflammatory drugs can cause several clinical renal syndromes that will worsen the prognosis of CKD if NSAIDs are used by CKD patients (Perazella, 2009:1281). These clinical syndromes include nephrotic syndrome/proteinuria, glomerulonephritis, glomerulopathy, tubulo-interstitial nephritis, chronic interstitial fibrosis, hyponatremia, hyperkalemia and podocyte injury (Choudhury & Ahmed, 2006:83; Loh & Cohen, 2009:241; Perazella, 2009:1281). Most of these clinical syndromes can progress to CKD, especially in higher-risk patients (refer to paragraph 2.3.4.1) (Perazella, 2009:1281).

Nephrotic syndrome is considered to be the abnormal permeability of the glomerular capillary wall to protein, leading to proteinuria, and is commonly caused by a chronic renal insufficiency or a decreased GFR (The University of Tennessee Health Science Center, 2014). According to Keddiss and Karnath (2007:25), characteristics of nephrotic syndrome include proteinuria greater than 3.5 g/24 hr, hyperlipidemia, lipiduria, edema, hypoalbuminemia and hypercoagulability. According to Fitzclarence (2009), glomerulonephritis is the inflammation of the glomeruli, which results in impairment of the selective filtering properties of the kidney that leads to a decreased GFR and has similar clinical manifestations as nephrotic syndrome. Glomerulonephritis can be classified as minimal changed disease (MCD), focal segmental glomerulosclerosis (FSGS) and membranous glomerulonephritis (MGN), all three of which can result from NSAID use (Decloedt & Maartens, 2011:254).

Interstitial nephritis is another inflammatory kidney disease that occurs when drugs or their metabolites bind to the interstitial matrix of the kidney and form antigens (Decloedt & Maartens, 2011:253). Acute interstitial nephritis is usually an allergic reaction to certain medications, such as NSAIDs, that induces an immune reaction, while chronic interstitial nephritis can be caused by chronic, high-dose NSAID use, especially in kidney disease patients (Naughton, 2008:745).

Hyponatremia is when the body contains too little sodium for the amount of fluid it contains (< 136 mEq/L) (Lewis, 2013). The antidiuretic hormone (ADH) controls the water load in the body and thus prevents hyponatremia, but the effect of ADH is potentiated by the use of NSAIDs and thus decreases water excretion in the body (Liamis *et al.*, 2008:148). This effect is attributed to the fact that prostaglandin is usually an inhibitor of ADH, but since NSAIDs inhibit prostaglandins, the effect of ADH is potentiated. With the same mechanism that results in hyponatremia, NSAIDs can cause hyperkalaemia, which occurs when the patient's potassium level is higher than the normal range (>5 mmol/L) (National Kidney Foundation, 2014). Hyperkalaemia occurs regularly in CKD patients due to their declining renal function, with the simultaneous use of NSAIDs potentiating this effect.

The renal effects of NSAIDs are thus attributed to NSAIDs' ability to inhibit COX, which reduces prostaglandin synthesis. This affects renal homeostasis and the result is several renal adverse effects, especially in patients with an impaired renal function, such as CKD patients (Hörl, 2010:2305).

#### **2.4.4 Greater-risk patients**

As was seen in paragraph 2.4.3, NSAID use is an associated risk in CKD, but certain conditions exist that put patients at a higher risk for developing renal complications when using NSAIDs. According to Moon *et al.* (2011:2278), NSAID use can cause kidney damage in the presence of several pre-existing disease states such as congestive heart failure, liver cirrhosis, pre-existing renal disease, the adjuvant use of nephrotoxic drugs and advanced age. Kim and Joo (2007:123) further state that NSAIDs should be avoided in patients with an already decreasing renal function, severe heart disease, patients with volume depletion and/or hepatic failure. Yamagata *et al.* (2007:159) also indicate that hypertension and diabetes, along with several other metabolic abnormalities, are independent risk factors for developing CKD and will therefore be greater risk factors with a decline in renal function such as with adjuvant NSAID use.

Perazella (2009:1277) compiled a list of risk factors that increase the renal vulnerability of patients to nephrotoxins such as NSAIDs. Some of these factors include female gender, old age (>65 years), nephrotic syndrome, cirrhosis, immune response genes and pharmacogenetics that favour drug toxicity such as gene mutations in the hepatic and renal P450 system. Table 2-24 lists factors that could be predisposing to NSAID-induced renal failure and can therefore be seen as greater-risk patients (Rifkin & Parazella, 2005:16).

**Table 2-21: Factors contributing to non-steroidal anti-inflammatory drug-induced kidney failure**

<b>Predisposing factors for NSAID-induced kidney failure</b>
Decreased effective blood volume (from congestive heart failure, cirrhosis, nephrotic syndrome, anesthesia, shock)
Decreased absolute volume (from haemorrhage, sodium and water depletion)
Acute renal failure
Medications (ACE- inhibitor, angiotensin receptor blocker, aldosterone receptor antagonist, diuretics and cyclosporine)
Renal transplant patients
Advanced age (>65 years)

#### **2.4.5 Management, advice or dose adjustments**

The use of NSAIDs is a cause for concern in CKD patients, but their use seems to be inevitable at times, especially when the CKD patient experiences pain. According to Kirby (2009:30), NSAIDs present a three-fold increased risk of developing acute renal failure, which raises concern about the use of these drugs in CKD patients. The management of pain in CKD patients therefore presents certain challenges, which includes the prevention of further renal damage and the necessary dosage adjustments that need to be made (Tawfic & Bellingham, 2015:7).

According to Rifkin and Parazella (2005:16), aspirin and NSAIDs do not impair renal function in patients with normal renal function, but in CKD patients an aspirin dosage of more than 325 mg/day might decrease renal function. Non-steroidal anti-inflammatory drugs should preferably be used in CKD patients only in specific conditions, for a limited time period and with timely monitoring of renal function (Nayak-Rao, 2011:37). Munar and Singh (2007:1495) state that NSAIDs can be used if patients are well hydrated and have good renal function without heart failure, diabetes or hypertension. The monitoring of CKD patients receiving NSAIDs consists of serum creatinine measurements every two to four weeks after the start of the treatment (Munar & Singh, 2007:1495).

Dosing adjustments in CKD patients can be very complex, but are necessary for certain medications that are renally excreted and include ACE inhibitors, angiotensin-receptor blockers, bisphosphonates, furosemide, NSAIDs, histamin-2 antagonists, penicillamine and proton pump inhibitors (Bell *et al.*, 2013:27). Hassan *et al.* (2009:1099) provide a stepwise approach that can be followed when dosage adjustments are done in renal impairment patients. A summary of this approach from Hassan *et al.* (2009:1099) is provided in Annexure D.

There are several algorithms available for the treatment of pain in CKD that will reduce the risk of renal effects. According to Rifkin and Perazella (2005:13), non-pharmacological methods of treating pain should be used, including massage, exercise, mechanical vibration, heat or ice, and even surgery should be attempted before drug therapy is initiated. If drug treatment is unavoidable, pain in CKD patients can be treated with NSAIDs or other analgesics. Pham *et al.* (2009:115) recommend treatment for pain in non-CKD patients compared to CKD patients. This is depicted in Table 2-22.

**Table 2-22: Treatment of pain in chronic kidney disease patients**

<b>Pain severity (scored out of 10)</b>	<b>Treatment options for non-CKD patients</b>	<b>Considerations for CKD patients</b>
Mild pain (1–3/10)	Non-opioids (acetylsalicylic acid (ASA)) NSAIDs (acetaminophen)	Acetaminophen is required at greater intervals (650 mg every 6 hours instead of every 4 hours). ASA 650 mg every 4–6 hourly Short-acting NSAIDs (ibuprofen, diclofenac, etc.). Consider sulindac or salsalate (might have lower prostaglandin inhibitory effect). Avoid simultaneous use of other haemodynamic drugs.
Moderate pain (4–6/10)	Non-opioids Opioids (Codeine, Dihydrocodeine, Tramadol, Hydrocodone)	Tramadol might be used since it is not known to be nephrotoxic. Consider dose adjustments in opioid treatment.
Severe pain (7–10/10)	Non-opioids Opioids (Fentanyl, Morphine, Hydro-morphone, Methadone, Levorphanol, Oxycodone)	Fentanyl and methadone may be acceptable with dosage and frequency adjustments.

Tawfic and Bellingham (2015:8-12) provide guidelines for the management of pain in different CKD stages. Table 2-23 is a summary of these guidelines to treat pain in the different stages of CKD.

**Table 2-23: Treatment of pain during different stages of chronic kidney disease**

CKD stage	Treatment of pain
Stage 1	Neuraxial and peripheral nerve blocking where possible. Mild pain: acetaminophen + NSAID + tramadol. Moderate to severe pain: acetaminophen + NSAIDs or opioids. Gabapentin or pregabalin as adjuvants in trauma and neuropathic pain.
Stage 2	Same as for CKD Stage 1, but NSAIDs should only be used in selected patients for the shortest duration possible and renal function should be closely monitored. Avoid NSAIDs in advanced age, diabetes, with the use of ACE inhibitors, dehydration and hypotension.
Stage 3 and 4	Neuraxial and peripheral nerve blockage where possible. Avoid NSAIDs. Mild pain: acetaminophen and tramadol (dosage adjustment required) Moderate to severe pain: acetaminophen + opioids (fentanyl or hydromorphone) + tramadol (dose adjustment) + ketamine Avoid morphine and codeine as their metabolites are renally excreted and could cause hyperalgesia and neurotoxicity. Anti-epileptics in neuropathic pain only (adjusted dosages).
Stage 5	Same as for Stage 4, with further dosage adjustments required in patients undergoing dialysis.

Further complications of NSAIDs in CKD treatment are the occurrence of drug-drug interactions, with the most notable one being the interactions between ACE inhibitors, angiotensin-receptor blockers and NSAIDs, referred to as the “triple whammy” (Bell *et al.*, 2013:26). According to Loboz and Shenfield (2005:239), the triple whammy can be caused by a number of mechanisms, including the inhibition of the prostaglandin-mediated control of the glomerular afferent arteriole, the inhibition of angiotensin control of the efferent arteriole or the fact that diuretics reduce renal flow by decreasing plasma volume.

It can be clearly seen that the use of NSAIDs is associated with a rapid decline in renal function and should be used with extreme caution or avoided completely in patients with impaired renal function such as CKD patients (Gooch, 2007:280.e1).

## 2.5 Chapter summary

It is evident that NSAIDs are among the most widely used drugs worldwide, because of the high prevalence of pain and inflammation. Although these NSAIDs are highly effective in the treatment of their different indications, they also possess a variety of adverse effects, one of which is the impairment of renal function. Chronic kidney disease is growing in global prevalence, but remains undertreated and underdiagnosed. The use of NSAIDs in these CKD patients is a concern and worsens the prognosis of the disease, with NSAIDs still being used in

these patients on a regular basis. Further information and more education must be given to prescribers, providers and patients regarding the use of NSAIDs in CKD patients.

## CHAPTER 3: RESULTS AND DISCUSSION

### 3.1 Introduction

The findings of this study will be discussed in this chapter and is presented in the form of two manuscripts, which will be submitted for consideration of publication in their respective journals.

Manuscript one is entitled “Prevalence of chronic kidney disease (CKD) and co-occurring chronic conditions in the private health sector of South Africa” will be submitted to the journal “*South African Family Practice*”. The author’s guidelines for this journal are indicated in Annexure E, with proof of submission to the journal given in Annexure F. Instructions to the author can be viewed online with the following link:

<http://www.safpj.co.za/index.php/safpj/about/submissions#authorGuidelines>. Date of access: 14 Jun. 2015.

Manuscript two, entitled “Prescribing patterns of non-steroidal anti-inflammatory drugs in chronic kidney disease patients” will be submitted to “*International Journal of Clinical Pharmacy*”. Their author’s guidelines are indicated in Annexure G and proof of submission given in Annexure H. Instructions to the author can be viewed online with the following link:

<http://www.springer.com/medicine/internal/journal/11096>. Date of access: 30 Jun. 2015.

### 3.2 Manuscript 1

#### **Prevalence of chronic kidney disease (CKD) and co-occurring chronic conditions in the private health sector of South Africa**

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#### **Conflict of interest:**

The authors declare that we have no financial or personal relationship(s) that may have inappropriately influenced us in writing this paper.

**Keywords:** prevalence, chronic kidney disease, risk factors, comorbid chronic conditions, South Africa

## Abstract

**Background:** Chronic kidney disease (CKD) is a public health problem, with increasing global prevalence. Several factors could influence the prognosis of CKD, including, *inter alia*, age, gender and the prevalence of co-occurring chronic conditions. This study determined the prevalence of CKD in the private health sector of South Africa and the co-occurring chronic conditions.

**Methods:** Retrospective medicine claims data from a pharmaceutical benefit management (PBM) company was used to perform this descriptive, quantitative study. The study population consisted of all patients identified with an ICD-10 code for CKD (N18) during the study period of 1 January 2009 to 31 December 2013.

**Results:** CKD patients represented 0.10% to 0.14% of the total patients on the database from 2009 to 2013. The mean age of the CKD patients over the study period varied between 58 and 61 years. Prevalence was higher in males (male-to-female ratio 1:0.8) and in patients aged 35-64 years ( $p=0.014$ ; Cramer's  $V=0.039$ ). Patients with CKD and one other chronic condition boasted prevalence rates between 24% and 28% over the study period, whereas CKD patients with two other chronic conditions had a prevalence ranging from of 24% to 27% ( $p=0.263$ ; Cramer's  $V=0.039$ ). The occurrence of chronic conditions in the CKD population was prevalent with hypertension occurring in more than half the CKD patients. Other prevalent chronic conditions occurring over the study period included hyperlipidaemia (36% to 43%) and diabetes mellitus type 2 (19% to 25%).

**Conclusion:** It was evident that several chronic conditions, especially those with regard to atherosclerotic risk factors frequently co-occurred with CKD. Lifestyle management and frequent screening tests of these patients are of the utmost importance to improve the outcome of CKD patients.

**Keywords:** prevalence, chronic kidney disease, comorbid chronic conditions, hypertension, South Africa

## Introduction

Chronic kidney disease (CKD) is a global public health problem, with an estimate prevalence of 8%-16% worldwide.<sup>1</sup> Prevalence rates of CKD seems to be high in both developing and developed countries,<sup>2-3</sup> with an estimated prevalence of 14.3%<sup>4</sup> in South Africa.

Early diagnosis of and intervention in CKD can reduce the risk of cardiovascular events, kidney failure and deaths that are associated with CKD.<sup>5</sup> After CKD had been ranked in the 27th position in 1990, global CKD mortality rates increased to being the 18th biggest cause of death in 2010.<sup>6</sup> In South Africa, deaths caused by CKD increased by 67% from 1999 to 2006.<sup>7</sup>

Chronic kidney disease can be seen as a silent condition, thus complicating the diagnosis of the disease. Less than 10% of people with CKD are aware that they have the condition.<sup>8</sup> It has few symptoms<sup>9</sup> and is nearly always asymptomatic during the early stages of the disease.<sup>10</sup> In addition, several clinical conditions such as diabetes mellitus, hypertension and cardiovascular disease (CVD) are seen as risk factors, and patients with these conditions should be closely monitored when CKD is suspected.<sup>9-11</sup> These conditions could mask the diagnosis of CKD, thus resulting in patients with an insufficient renal function not being diagnosed as such. Other risk factors that might increase the risk of CKD include gender, smoking, obesity, age, genetics, metabolic disturbances and chronic use of NSAIDs.<sup>5,12</sup>

There is a lack of data regarding the prevalence of CKD in the private health sector of South Africa, especially data surrounding the occurrence of comorbid conditions. Chronic renal disease is regarded as one of the chronic conditions on the prescribed minimum benefit (PMB) chronic disease list (CDL) in the private health sector of South Africa. The PMB CDL is a feature of the Medical Schemes Act (Act 131 of 1998) and consists of 26 common conditions that requires treatment for more than 12 months and are considered to be life-threatening.<sup>13</sup> If provided for by way of a therapeutic algorithm for the condition, all costs relating to the diagnosis, medication, doctor consultations and tests must therefore be covered by medical schemes.<sup>14,15</sup> The chronic conditions co-occurring with CKD that forms part of the PMB CDL conditions, include diabetes mellitus, hypertension, hyperlipidaemia, cardiac failure, etc.

This study investigated the prevalence of CKD in the private health sector of South Africa, along with any comorbid conditions or CKD-related complications, in order to create awareness of and improve the clinical outcome and prognosis of the disease. By increasing our knowledge and understanding regarding the epidemiology of CKD in terms of risk factors and co-occurring chronic diseases, we might be able to assess the level of its underdiagnosis<sup>16,8</sup> and estimate the impact of potential early screening policies.

## Method

## Study design

A descriptive, quantitative study was performed using retrospective medicine claims data obtained from a national representative pharmaceutical benefit management company (PBM). Data from 1 January 2009 to 31 December 2013 was used. The database contained information on 1 033 057 (2009), 968 158 (2010), 864 977 (2011), 815 810 (2012) and 809 857 (2013) patients over the five year study period. The database represented 9% to 13% of the total medical schemes industry in South Africa.<sup>17</sup> Data fields that were used in the study included patients' member number and dependent code, date of birth, gender, date of treatment and ICD-10 codes of medicine claims.

## Study population

The study population included all patients with an ICD-10 (the International Statistical Classification of Disease and related problems, 10th edition)<sup>18</sup> code for CKD (N18) during the study period of 1 January 2009 to 31 December 2013.

## Data analysis

Variables included age, gender and the different comorbid chronic conditions co-occurring with CKD as the independent variables, and the prevalence of CKD as the dependent variable. The age of the patients was calculated using the date of birth of the patient and the date of the first prescription or treatment per year and was categorised as follows:

- >0 years and ≤18 years
- >18 years and ≤34 years
- >34 years and ≤65 years
- >65 years

The co-occurring chronic conditions were analysed according to the number of conditions, as well as the type or combination of conditions that occurred with CKD.

The comorbid CDL conditions were identified by using the different ICD-10 codes. These conditions with their ICD-10 codes are: Addison's disease (E27.1), asthma (J45, J45.8, J45.1), bronchiectasis (J47, Q33.4), cardiac failure (I27.9, I50.0, I50.1), cardiomyopathy (I42, I42.0, I42.2), chronic obstructive pulmonary disease (J43, J44), coronary artery disease (I20.0, I25.0), Chron's disease (K50.0, K50.8), diabetes insipidus (E23.2), diabetes mellitus type 2 (E10, E11, E12, O24.0), diabetes mellitus type 1 (E10, E12, O24.0), dysrhythmias (I47.2, I48), epilepsy (G40, G41), glaucoma (H40, Q15.0), haemophilia (D66, D67), hyperlipidaemia (G45, I20, I21, I22, I24, I25, I63, I65, I66, I70), hypertension (I10, I12, I13, I15, O12), hypothyroidism (E01.8, E02, E03), multiple sclerosis (G35), Parkinson's disease (G20, G21), rheumatoid arthritis (M05,

M06, M08), schizophrenia (F20), systemic lupus erythematosus (M32, L93, L93.2) and ulcerative colitis (K51, K51.9).<sup>19</sup>

### **Statistical analysis**

Data management and analysis were carried out using the Statistical Analysis System® SAS 9.3® programme. To assist with the general computations, Microsoft® Office Excel 2010 was used. Variables were described using descriptive statistics such as frequencies, percentages, means, standard deviation (SD) and 95% confidence intervals (CI). One-way-analysis of variance (ANOVA) with Tukey's HSD post hoc test was used to compare mean values between groups. Cohen's *d*-value was used as effect size measure of the difference between means, with  $d \geq 0.8$  being regarded as practically significant. The chi-square test was used to test for associations between categorical variables and was deemed to be statistically significant with a probability of  $p \leq 0.05$ . Practical significance of the results were computed when *p*-values was statistically significant ( $p \leq 0.05$ ) by using the Cramer's *V* statistic. Cramer's  $V \geq 0.1$  was deemed to be weak association, Cramer's  $V \geq 0.3$  was seen to be a moderate association and Cramer's  $V \geq 0.5$  was regarded as a large effect/association.

### **Ethical considerations**

Permission to conduct the study was obtained from the Health Research Ethics Committee of the North-West University (NWU-00179-14-S1). Goodwill permission was furthermore obtained from the Board of directors of the PBM. Data was analysed anonymously.

### **Results**

Chronic kidney disease patients represented 0.10% to 0.14% of the total database from 2009 to 2013. The majority of these patients were males (male-to-female ratio 1:0.8) with prevalence ranging from 55% to 58% over the five year study period (see Table I). No association was found between the prevalence of CKD and gender over the study period ( $p=0.668$ ).

The mean age of the CKD patients over the study period varied between 58 and 61 years. The CKD patients were divided into different age groups (see Table I). Chronic kidney disease was mostly present in the age group 35-64 years, presenting prevalence rates of between 51% and 58% over the study period. A statistically significant association was found between the proportion of CKD patients per age group over the study period, with an increasing trend in most of the age groups ( $p \leq 0.05$ ). This association, however, was very weak (Cramer's  $V=0.039$ ).

Nearly one- in- three to one- in- four patients had at least one other CDL condition co-occurring with CKD. The majority (50% to 53%) of the CKD patients had either one or two other chronic conditions along with CKD, to a maximum of seven other chronic conditions (0.02%) over the study period. The prevalence of CKD patients with three comorbid chronic conditions (17.36% to 15.14%) was about double the prevalence of CKD patients with four co-occurring conditions (8.16% to 6.16%), whereas patients with only CKD and CKD along with one other condition had prevalence rates ranging from 20.16% to 24.11%, and 24.09% to 27.59%, respectively ( $p=0.263$ ; Cramer's  $V=0.039$ ). We observed no practical significant difference in the mean number of CDL conditions over the study period (2009-2013) ( $d=0.145$ ) (see Table I).

**Table I: CKD patient demographics**

Study variables	CKD prevalence by year (%)					p-value	Cramer's V
	2009	2010	2011	2012	2013		
<b>Total number of patients on database (N)</b>	1033057	968158	864977	815810	809857		
<b>CKD patients on database (%)</b>	1057(0.10)	1081(0.11)	1017(0.12)	1158(0.14)	1120(0.14)		
<b>Gender</b>							
<b>Male</b>	581(54.97)	600(55.50)	565(55.56)	648(55.96)	649(57.95)	p=0.668	0.021
<b>Female</b>	476(45.03)	481(44.50)	452(44.44)	510(44.14)	471(42.05)		
<b>Age groups (years)</b>							
<b>&gt;0 and ≤ 18</b>	17(1.61)	13(1.20)	13(1.28)	17(1.47)	25(2.23)	p=0.014	0.039
<b>&gt;18 and ≤ 34</b>	57(5.39)	57(5.27)	46(4.52)	62(5.35)	68(6.07)		
<b>&gt;34 and ≤ 65</b>	567(53.64)	556(51.43)	535(52.61)	626(54.06)	651(58.13)		
<b>&gt;65 years</b>	416(39.36)	455(42.09)	423(41.59)	453(39.12)	376(33.57)		
<b>Mean age (mean ± SD (95% CI))</b>	59.66±16.81 (58.65;60.68)	60.53±16.52 (59.54;61.51)	61.05±16.38 (60.04;62.05)	59.94±16.30 (59.00;60.88)	57.84±16.09 (56.90;58.78)		
<b>Number of co-occurring chronic conditions</b>							
<b>Only CKD</b>	222(21.00)	241(22.29)	205(20.16)	255(22.02)	270(24.11)	p=0.263	0.039
<b>CKD + 1</b>	275(26.02)	272(25.16)	261(25.66)	279(24.09)	309(27.59)		
<b>CKD + 2</b>	283(26.77)	270(24.98)	257(25.27)	289(24.96)	272(24.29)		
<b>CKD + 3</b>	160(15.14)	194(17.95)	181(17.80)	201(17.36)	177(15.80)		
<b>CKD + 4</b>	81(7.66)	78(7.22)	83(8.16)	87(7.51)	69(6.16)		
<b>CKD + 5</b>	31(2.93)	20(1.85)	23(2.26)	38(3.28)	21(1.88)		
<b>CKD + 6</b>	5(0.47)	5(0.46)	7(0.69)	9(0.78)	2(1.88)		
<b>CKD + 7</b>	0	1(0.09)	0	0	0		
<b>Mean number of co-occurring chronic conditions (mean ± SD (95% CI))</b>	1.73±1.35 (1.65;1.81)	1.70±1.34 (1.63;1.78)	1.78±1.35 (1.69;1.86)	1.77±1.40 (1.69;1.85)	1.59±1.30 (1.51;1.66)		

Hypertension was the most prevalent condition co-occurring with CKD, occurring in 47% to 55% of the CKD patients. Hyperlipidaemia's occurrence in CKD patients increased from 36% to 43% over the study period, whereas diabetes mellitus type 2 increased from 20% to 25% from 2009 to 2013. Table II lists the four most prevalent chronic conditions co-occurring with CKD. A statistically significant, but "weak" practical association was found between the occurrence of hypertension, hyperlipidaemia, diabetes mellitus type 2 and cardiac failure in CKD patients over the study period (see table II).

**Table II: Most prevalent co-occurring chronic conditions occurring with CKD**

Co-occurring chronic condition n (%)	2009	2010	2011	2012	2013	p-value	Cramer's V
<b>Hypertension</b>	581 (54.97)	576 (53.28)	552 (54.28)	620 (53.54)	525 (46.88)	0.001	0.060
<b>Hyperlipidaemia</b>	380 (35.95)	398 (36.82)	397 (39.04)	463 (39.98)	477 (42.59)	0.012	0.049
<b>Diabetes mellitus type 2</b>	204 (19.30)	228 (21.09)	232 (22.81)	280 (24.18)	275 (24.55)	0.017	0.047
<b>Cardiac failure</b>	146 (13.81)	142 (13.14)	162 (15.93)	185 (15.98)	102 (9.11)	<0.0001	0.074

The top five chronic condition pairings are listed in Table III. The CKD-hypertension pairing was the most prevalent combination, occurring in one in every six CKD patients. Hypertension and hyperlipidaemia were prevalent in 6% to 8% of the CKD population with two other CDL conditions. The top three co-occurring chronic conditions (hypertension, hyperlipidaemia and diabetes mellitus type 2) combined with CKD to double in prevalence from 3% to 6% over the study period.

**Table III: Most prevalent CKD and co-occurring chronic condition combinations**

CKD + chronic condition pairing	Prevalence of chronic conditions by year n (%)				
	2009	2010	2011	2012	2013
<b>Only CKD</b>	222 (23.72)	241 (25.18)	205 (22.75)	255 (25.15)	270 (24.50)
<b>CKD + hypertension</b>	156 (16.67)	154 (16.09)	141 (15.65)	158 (15.58)	164 (14.88)
<b>CKD + hyperlipidaemia</b>	40 (4.27)	44 (4.60)	40 (4.44)	47 (4.64)	68 (6.17)
<b>CKD + hypertension + hyperlipidaemia</b>	71 (7.59)	64 (6.69)	66 (7.33)	73 (7.20)	70 (6.35)
<b>CKD + hypertension + hyperlipidaemia+ diabetes mellitus type2</b>	24 (2.56)	37 (3.87)	39 (4.33)	55 (5.42)	66 (5.99)

## Discussion

The CKD prevalence of 0.10% to 0.14% found in our study was considerably lower than the estimated global CKD prevalence (8% to 16%)<sup>1</sup> and the prevalence rates of countries such as the United States (16%),<sup>20</sup> Canada (12.50%)<sup>21</sup> and England (6.76%)<sup>22</sup>. This prevalence was also significantly lower than the estimated CKD prevalence in South Africa.<sup>4</sup> Chronic kidney disease can be an underlying cause for several other chronic conditions.<sup>23</sup> The disease can also present differently, depending on the stage and cause of the disease, as well as individual factors such as age. This can result in a differential diagnosis for CKD<sup>24</sup> that is therefore not registered as CKD. Patients with chronic renal insufficiency could thus not have been diagnosed as having CKD.

In this study, CKD patients were predominantly male. Possible reasons for the gender differences in CKD could include diet, renal/nephron mass, glomerular hemodynamics and direct effects of sex hormones.<sup>12</sup> Similar results were found in the USA,<sup>20</sup> and that provided a good basis for comparison to our study, since data from the SANHANES<sup>25</sup> and NHANES<sup>26</sup> studies indicated that these two populations have similar obesity rates. Obesity increases the metabolic demand on the kidney, which results in greater glomerular capillary pressure, thus increasing the risk for CKD.<sup>27</sup> Some studies referred to male gender as being a risk factor for CKD,<sup>28,12</sup> because of the nephroprotective effect of oestrogen in females.<sup>29</sup> These are only true for reproductive years.<sup>30</sup> These findings contradicted findings in the CKD populations of Ireland<sup>31</sup> and England,<sup>22</sup> where CKD was more prevalent among females.

It is well known that kidney function decreases with an increase in age<sup>32</sup>, however, in our study the association between the prevalence of CKD was independent of the age group of the patient. The mean age of CKD patients (52.9±14.8 years) in a different South African<sup>33</sup> population (2008-2009) and studies conducted in Germany<sup>34</sup> and Canada<sup>21</sup>, showed results similar to those found in this study.<sup>34,21</sup> In our study, the youngest subject to be diagnosed with CKD was a mere one year old, with the oldest being 98 years of age. Chronic kidney disease in infants is not a common occurrence, with an estimated eight infants being registered with CKD (stages 3-5) globally each year.<sup>35</sup> Possible causes of CKD in infants could include renal dysplasia, obstructive uropathy, polycystic- and multicystic kidney disease, fetal hydronephrosis and connatal nephrotic syndrome.<sup>35-37</sup>

Chronic kidney disease is accompanied by several co-occurring chronic conditions and CKD-related complications<sup>23,38,39</sup> For instance, with hypertension, hyperlipidaemia and diabetes demonstrated high prevalence rates in our study as well as in the Australian,<sup>40</sup> USA<sup>41</sup> and German<sup>34</sup> CKD population. It is well supported that there is an association between the prevalence of hyperlipidaemia and a decline in renal function.<sup>34,42</sup> Although the mechanism is

not fully understood, oxidative stress and insulin resistance could contribute to further renal impairment in CKD patients.<sup>43</sup> Proteinuria associated with CKD could result in hypercholesterolemia, thus explaining the prevalence of hyperlipidaemia in CKD patients.<sup>43</sup>

Hypertension not only contributes to CKD and its progression, but plays an important role in the high cardiovascular morbidity and mortality of the disease.<sup>44</sup> The kidneys are protected from elevations in blood pressure through their autoregulatory mechanism in the glomerulus.<sup>45-47</sup> When the arterial pressure exceeds the autoregulatory threshold, even small further increases in arterial blood pressure can cause vascular and glomerular damage, resulting in a reduced kidney function.<sup>45-47</sup> In CKD patients, renal damage could result in hypertension that is difficult to control, which leads to more nephron loss and further renal damage.<sup>46</sup> An elevation in blood pressure in CKD patients thus increases the rate at which GFR (glomerular filtration rate) and resulting kidney function declines.<sup>44</sup> It is estimated that about 20%-40% of diabetes mellitus type 2 patients will encounter a moderate to severe decline in renal function.<sup>48</sup> Diabetes results in a rise in the body's blood sugar levels, which is referred to as hyperglycaemia.<sup>49</sup> This rise in blood sugar levels causes disturbances in protein metabolism, which results in several renal complications, such as retinopathy, diabetic nephropathy and neuropathy.<sup>50</sup> Diabetes can damage the kidneys through several mechanisms, including damage to blood vessels of the kidneys, which results in albuminuria and damage to the nerves around the bladder which increases the load on the kidneys.<sup>48,50-52</sup> Diabetes thus results in proteinuria, which causes a rise in blood pressure along with a decrease in kidney function and if not controlled can result in kidney failure.<sup>47</sup>

Taking the pathology into account, it seems that most of the above-mentioned comorbidities can be linked to non-modifiable or modifiable risk factors of atherosclerosis, such as age, male gender, smoking, obesity, physical inactivity, lipid disorder, hypertension, diabetes, and stress.<sup>53</sup> Following from this are relevant risk factors for CVD that include proteinuria and a decreased eGFR, with diet and gender having a definite influence on the decline in GFR again.<sup>30</sup>

### **Limitations of this study**

Since the study population was based solely on ICD codes, the results can be generalised only to this specific database and study population. The database employed in this study also lacked clinical data such as GFR, serum creatinine and blood urea nitrogen (BUN) levels. The extent to which risk factors such as age and co-occurring chronic conditions influenced the kidneys could therefore not be analysed.

### **Conclusion and Recommendations**

Our study showed that CKD co-occurs with several chronic conditions, particularly hypertension. This indicates that these patients are at serious risk of developing CKD and should be monitored closely, especially in the presence of atherosclerotic risk factors. In the management of CKD's comorbid conditions, lifestyle management such as a protein and salt-restricted diet and exercise should be emphasised, along with regular monitoring of blood sugar and blood pressure levels, a complete fasting lipid profile evaluation, GFR testing, and a measurement of proteinuria. Early detection and timely interventions are of the utmost importance in order to prevent CKD. An open-eyed approach to atherosclerosis and its risk factors, with good monitoring is what is required. There is room for research regarding the causes of early-life CKD, lifestyle interventions, and CKD screening in groups that are more at risk.

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### 3.3 Manuscript 2

#### **Prescribing patterns of non-steroidal anti-inflammatory drugs in chronic kidney disease patients**

##### **Article type**

Research article

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##### **Impact of findings**

- The lack of available information with regard to studies conducted on the prescribing patterns of NSAIDs in CKD patients is worrying, since results from these studies can contribute greatly to an improved outcome in renal insufficient patients.
- Emphasis should be put on the dosages of the NSAIDs prescribed to CKD patients, especially the dosages of ibuprofen and diclofenac. These dosages should accommodate the renal function of these patients with a renal insufficiency.
- Greater caution with regard to the type and dosage of drug prescribed should be exercised by general medical practitioners when treating pain in CKD patients.

**Keywords** non-steroidal anti-inflammatory drugs (NSAIDs), private health sector of South Africa, chronic kidney disease (CKD)

## Abstract

*Background* Non-steroidal anti-inflammatory drugs (NSAIDs) are among the most commonly used pharmaceutical agents worldwide. NSAIDs are considered nephrotoxic and should therefore be used with caution or be avoided completely in high-risk patients such as chronic kidney disease (CKD) patients. *Objective* This study aimed at investigating the prescribing of NSAIDs in CKD patients in order to generate awareness. *Setting* The study was conducted using medicine claims data in the private health sector of South Africa. *Method* A descriptive, quantitative study was performed, using retrospective data obtained from a pharmaceutical benefit management company (PBM). Data from 1 January 2009 to 31 December 2013 was analysed. The study population consisted of all patients with an ICD-10 code for a CKD (N18), in association with a paid claim for an NSAID. *Main outcome measure* The stratification of NSAID prescribing volume in the CKD population in terms of gender, age, NSAID type, dosage and prescriber type. *Results* The prescribing of NSAIDs in CKD patients varied between 26% and 40% over the five year study period. No association was found between gender and CKD patients who received NSAIDs vs. those who did not, with  $p > 0.05$  and Cramer's  $V < 0.1$  for each year of the study. The association between age groups and CKD patients who received NSAIDs vs. those who did not was statistically significant, but practically weak ( $p < 0.05$ ; Cramer's  $V \geq 0.1$ ). Most NSAID prescriptions (52%-63%) were for patients aged 35 to 64 years. Diclofenac (34.25%) was the single most frequently prescribed NSAID, but the COX-2-inhibitors (celecoxib, meloxicam and etoricoxib) were the preferred NSAID class to be prescribed. The majority (61.6%) of the NSAIDs were prescribed by general medical practitioners in dosages complying with and even exceeding the recommended daily dosage of patients with normal kidney function. *Conclusions* Even though NSAIDs are regarded as nephrotoxic drugs, they are still being prescribed to at-risk CKD patients, in particular, the elderly.

## **Introduction**

Non-steroidal anti-inflammatory drugs (NSAIDs) are regarded as the most commonly used pharmaceutical agents for the treatment of pain and inflammation [1] worldwide [2]. NSAIDs which include, *inter alia*, ibuprofen, celecoxib, diclofenac, and naproxen [1], inhibit (cyclooxygenase) COX-enzymes, thus inhibiting the release of prostaglandins and thereby exerting an anti-inflammatory, analgesic and antipyretic effect [1,3]. NSAIDs have several adverse effects including nephrotoxic effects on the kidneys, resulting in changes in the haemodynamics of the kidney, thus leading to renal failure [4]. NSAIDs should therefore be used with caution or even avoided in high-risk patients, such as chronic kidney disease (CKD) patients [5]. According to a recent study conducted in an American population with CKD, the mean number of NSAID agents taken per day was 3.0 for normal kidney patients, 3.3 for mild CKD (CKD stages 1 and 2) patients and 2.6 agents for moderate to severe CKD patients (CKD stages 3, 4 and 5) [6]. This stresses the fact that pain management in CKD patients is of concern to healthcare professionals.

In CKD and end-stage renal disease patients NSAIDs are mainly used to relieve pain experienced during the disease [7-9]. This pain can be the result of a variety of factors, such as polycystic kidneys, renal replacement therapy, pain from dialysis, pain resulting from comorbid illnesses (diabetic neuropathy, vascular diseases, etc.) [10] or several surgical procedures that require pain management [11]. The use of non-steroidal anti-inflammatory drugs in CKD patients is therefore a problem that needs to be addressed, as these drugs can cause several clinical renal syndromes such as nephrotic syndrome/proteinuria, glomerulonephritis, glomerulopathy, tubulo-interstitial nephritis, chronic interstitial fibrosis, hyponatremia, hyperkalaemia and podocyte injury [12-14]. These clinical renal syndromes may worsen the prognosis of patients with CKD [12].

It is evident that the risks of NSAID use in patients at risk, especially CKD patients, should be emphasised. In the absence of data on the prescribing patterns of NSAIDs in CKD patients in the South African private health sector, it is hoped that the findings of the study will generate awareness regarding the safe use of these drugs in patients with CKD.

## **Aim**

This study aimed to stratify NSAID prescribing in CKD patients in terms of age, gender, NSAID type, NSAID dosage and prescriber speciality.

## **Ethical approval**

The Health Research Ethics Committee of the North-West University provided permission to conduct the study (NWU-00179-14-S1). Goodwill permission was obtained from the Board of directors of the PBM.

## **Method**

### *Study design*

A descriptive, quantitative drug utilisation review was performed, using depersonalised retrospective data obtained from a medicine claims database of a Pharmaceutical Benefit Management company (PBM). Data from 1 January 2009 to 31 December 2013 was used to conduct the research. The database contained information on 1 033 057, 968 158, 864 977, 815 810 and 809 857 patients respectively over the five year study period (2009 to 2013), representing 9% to 13% of the total medical schemes industry in South Africa [15]. The data fields that were used in the study included the date of birth and gender of patient, date of treatment, ICD-10 codes of claims, NAPPI (National Pharmaceutical Product Index) codes (active ingredient) of drugs, quantity of medicine items prescribed, days supplied of items and prescriber speciality.

### *Study population*

The study population was identified as all patients with an ICD-10 code for a CKD (N18), in association with a paid claim for an NSAID, during the study period of 1 January 2009 to 31 December 2013. The ICD-10 codes are based on the World Health Organization's (WHO) 10th edition of International Statistical Classification of Diseases and Related Problems [16]. The NSAIDs were identified on the database by their NAPPI codes. These are unique codes given to a surgical or a consumable product that enables electronic transfer of information right through the healthcare delivery chain and are used to distinguish not only between different medicine items, but different dosage forms of the same active ingredient [17].

### *Data and Statistical analysis*

The independent variables that were analysed in this study included age, gender, time periods (study period), presence of disease, name of the active ingredient and prescriber type. The prescribers were grouped according to which prescribers are most likely to engage in the consultation and/or treatment of renal insufficient patients. The age of the patients was calculated using the date of birth of the patient and the date of treatment and patients were categorised into four age groups:

- >0 years and ≤18 years
- >18 years and ≤34 years

- >34 years and ≤65 years
- >65 years

The dependent variables were the prevalence of CKD and prescribed daily dosage (PDD). The PDD was defined as the average daily dose prescribed, as obtained from a representative sample or prescription [18]. This was calculated by dividing the product of the strength of a drug and the quantity dispensed, by the number of days for which the medicine was supplied. The NSAIDs were classified according to the Monthly Index of Medical Specialties (MIMS®) classification system. The dosages of the NSAIDs prescribed to CKD patients were compared to the recommended daily dosage of these NSAIDs in patients with a normal kidney function. The recommended daily dosages for these NSAIDs, as listed in the MIMS® [19] and the South African Medicines Formulary (SAMF®) [20] are listed in Table 1.

'Insert Table 1 here'

Data analysis was performed with the SAS programme Version 9.3® (SAS Institute, Cary, NC). Variables were expressed using descriptive statistics such as frequencies, percentages, means, standard deviations (SD) and 95% confidence intervals (CI). One-way-analysis of variance (ANOVA) with Tukey's HSD post hoc test was used to compare mean values between groups, with Cohen's *d*-value measuring the effect size of the difference between these means ( $d \geq 0.8$  was viewed as practically significant). The chi-square test ( $\chi^2$ ) tested for associations between proportions of two or more groups and was regarded as statistically significant at  $p \leq 0.05$ . Cramer's *V* statistic was then used to test the practical significance of these associations (Cramer's  $V \geq 0.1$  was deemed as a weak association, Cramer's  $V \geq 0.3$  was seen as a moderate association and Cramer's  $V \geq 0.5$  was regarded as a large effect/association).

## Results

Non-steroidal anti-inflammatory drugs were prescribed to 39.7% (n=492), 36.0% (n=435), 33.6% (n=381), 31.9% (n=409) and 25.6% (n=309) of the CKD patients from 2009 to 2013 respectively. The majority of these patients were male, receiving 52% to 59% of the NSAID prescriptions over the five year study period (see Table 2). There was no significant association between males/females with CKD and whether or not they received NSAIDs over the study period ( $p > 0.05$ ; Cramer's  $V < 0.1$ ).

'Insert Table 2 here'

The NSAID prescribing volume in CKD patients increased with an increase in age and was the highest in the 35-64 year age group, representing 52% to 63% of the total number of NSAID prescriptions for CKD patients during the study period. A statistically significant association

seemed to exist between age and CKD patients who received NSAIDs vs. those who did not with  $p$ -values  $< 0.05$  in 2009 (0.002), 2010 (0.013), 2011 (0.001) and 2012 ( $<0.001$ ). This had a weak practical significance, with Cramer's  $V > 0.1$  in 2009 (0.11), 2011 (0.12) and 2012 (0.13) (see Table 2).

The NSAID most frequently prescribed to CKD patients was diclofenac (34.25%), followed by the three COX-2-inhibitors meloxicam (19.5%), celecoxib (18.8%) and etoricoxib (9.5%) (see Table 3). The mean PDD over the study period of the most prescribed NSAIDs is listed in Table 3. The results indicate that 80.0% of the celecoxib prescriptions were prescribed in dosages of 200 mg or less, whereas 87.2% of the diclofenac prescriptions were for 150 mg or less.

The PDD of NSAIDs in CKD patients was similar to the recommended daily dosage of NSAIDs in patients with a normal kidney function [19,20], and in some cases exceeded these dosages. This was especially prominent with indomethacin, diclofenac and ibuprofen, where 39.1%, 12.8% and 44.9% of the active ingredient, respectively, was prescribed in dosages greater than the recommended daily dosage of these NSAIDs.

'Insert Table 3 here'

There was a clear statistical significant association between the different prescribers and the prescribing of NSAIDs in CKD patients ( $p=0.0028$ ). General medical practitioners prescribed NSAIDs most frequently (61.6%), followed by physicians, immunologists, rheumatologists, nephrologists, diabetologist and endocrinologists together, at 18.8%. A total of 157 (7.8%) NSAIDs were prescribed by pharmacists (see Table 4). Registered nurses, pulmonologists, dentists, etc. (other group) were responsible for 5.6% of the NSAID prescriptions in CKD patients (see Table 4). Tukey's HSD test also revealed a significant difference in the mean number of NSAID prescriptions prescribed between general medical practitioners, pharmacists and a group that consisted of physicians, immunologists, rheumatologists, nephrologists, diabetologists and endocrinologists, with  $d \geq 0.8$ .

'Insert Table 4 here'

## **Discussion**

Non-steroidal anti-inflammatory drug use by CKD patients ranged from 25% to 39% over the study period. This finding is higher than the NSAID use in a United States CKD population [6] and lower than the CKD populations of the UK [21], and Italy [22]. By mechanism, NSAIDs reduce prostaglandin synthesis [23], which could cause alterations in renal blood flow [24]. These effects are more likely to occur in patients with volume depletion, a depleted kidney function or high levels of angiotensin, such as CKD patients [25]. Renal complications caused

by NSAIDs are therefore more likely to occur in CKD patients than in patients with a normal kidney function.

We found no association between the prescribing of NSAIDs and patients' gender or age. Varying information on gender and NSAID use in CKD patients is currently available. Females are regarded to be more at risk of developing renal side effects through NSAID use, because they tend to have less lean body mass, a lower GFR and more prevalent hypoalbuminemia than their male counterparts, which all results in an increased free-drug concentration [12]. Males can also be seen as being more at risk because of oestrogen's nephroprotective effects in females [26]. We found no association between gender and NSAID prescribing in CKD patients.

Age is regarded as a strong risk factor for developing CKD [27-29], as an increase in age is associated with a decline in kidney function [30]. Chronic kidney disease patients in Italy (2006-2011) who used NSAIDs for less than six months had a mean age of  $72.1 \pm 12.3$  years, with patients over 65 years (76.1%) being responsible for most of the NSAID prescriptions, followed by the 45-64 year group (21.1%) [22]. The results from our study also showed an increase in NSAID use in CKD patients, as a statistical and "weak" practical association was found.

In our study, diclofenac had the highest prescribing prevalence. Similar results were found in studies conducted in Scotland (2005-2007) and Southern Italy [22]. It is unclear exactly why diclofenac is so commonly used, but reasons for its use could include the availability of diclofenac in over-the-counter (OTC) formulation and its availability in a wide variety of generics and dosage forms, which includes tablets (Panamor<sup>®</sup>), dispersible tablets (Cataflam D<sup>®</sup>), capsules (Veltex<sup>®</sup>), drops, injections, gels and suppositories (all Voltaren<sup>®</sup>) [20]. According to the MIMS<sup>®</sup>, diclofenac compares very well to other NSAIDs in terms of cost and is among the less expensive NSAIDs available in South Africa [19]. However, it has been found that there is no clear difference between NSAIDs in terms of their adverse effects on renal function, as all NSAIDs and COX-2 inhibitors have similar adverse effects on the kidneys [31].

The dose of NSAIDs should be adjusted in accordance with the renal function of the patient, especially CKD patients in stage 3 and above [32]. We found that NSAIDs were being prescribed predominantly by general medical practitioners in dosages similar to and even exceeding the recommended daily dosage of NSAIDs in normal kidney function patients. The use of these nephrotoxic drugs could cause a decrease in kidney function and worsen the prognosis of the disease in CKD patients, even causing death [23].

## **Conclusions and Recommendations**

The study revealed that one in every three to four CKD patients was being prescribed NSAIDs in dosages similar to and exceeding the recommended daily dosages for patients with a normal

kidney function. This remains a worrying statistic if one considers that NSAIDs can result in adverse renal effects [23]. The increase in NSAID use with an increase in age is a cause for concern, since both age and NSAID use are regarded as risk factors for CKD. We could conclude that few dosing adjustments on NSAIDs such as diclofenac and COX-2 inhibitors had been made to facilitate the declined kidney function of CKD patients. Greater caution should therefore be exercised by prescribers (such as general medical practitioners and pharmacists) when NSAIDs are issued and provided to at-risk patients such as CKD. This study leaves room for further research regarding the clinical impact of NSAID prescribing in CKD patients to create more awareness among prescribers.

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## **Conflict of interests**

We declare that we have no financial or personal relationship(s) that may have inappropriately influenced us in writing this paper.

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**Table 1: Recommended daily dosage of NSAIDs in patients with normal kidney function over the study period**

<b>Active ingredient of NSAID</b>	<b>Recommended daily dosage</b>
Diclofenac	100 mg-150 mg
Meloxicam	7.5 mg-15 mg
Celecoxib	200 mg-400 mg
Etoricoxib	60 mg-120 mg
Ibuprofen	800 mg-1600 mg
Piroxicam	10 mg-40 mg
Indomethacin	75 mg-150 mg

**Table 2: CKD patients with a script for NSAIDs vs. CKD patients without a NSAID script**

Study variables	CKD patients without a NSAID script (0) vs. CKD patients with a NSAID scripts (1)									
	n(%)									
	2009 (N=1238)		2010 (N=1210)		2011 (N=1135)		2012 (N=1282)		2013 (N=1207)	
	0 (n=746)	1 (n=492)	0 (n=775)	1 (n=435)	0 (n=754)	1 (n=381)	0 (n=873)	1 (n=409)	0 (n=898)	1 (n=309)
<b>Gender</b>										
<b>Male</b>	417(55.9)	258(52.4)	439(56.7)	226(52.0)	412(54.6)	223(58.5)	48(55.6)	239(58.4)	378(42.1)	173(56.0)
<b>Female</b>	329(44.1)	234(47.6)	336(43.4)	209(48.1)	342(45.4)	158(41.5)	388(44.4)	170(41.6)	520(57.9)	136(44.0)
<b>p-values</b>	0.232		0.116		0.213		0.332		0.556	
<b>Cramer's     V</b>	0.034		0.045		0.037		0.027		0.017	
<b>Age groups (years)</b>										
<b>&gt;0 and ≤     18</b>	16(2.1)	1(0.2)	11(1.4)	2(0.5)	12(1.6)	1(0.3)	1(2.0)	0(0.0)	22(2.45)	3(1.0)
<b>&gt;18 and     ≤ 34</b>	47(6.3)	16(3.3)	48(6.2)	11(2.5)	41(5.4)	5(1.3)	54(6.2)	11(2.7)	58(6.5)	13(4.2)
<b>&gt;34 and     ≤65</b>	400(53.6)	285(57.9)	399(51.5)	230(52.9)	400(53.1)	215(56.4)	460(52.7)	259(63.3)	514(57.24)	195(63.1)
<b>&gt;65</b>	283(37.9)	190(38.6)	317(40.9)	192(44.1)	301(39.9)	160(42.0)	342(39.2)	139(34.0)	304(33.9)	98(31.7)
<b>p-values</b>	0.002		0.013		0.0016		<0.0001		0.108	
<b>Cramer's     V</b>	0.109		0.095		0.116		0.132		0.071	
<b>Mean number of NSAID prescriptions per CKD patient (mean ± SD (95% CI))</b>	2.36±2.67 (2.11;2.61)		2.27±2.5 (2.02;2.52)		2.16±2.30 (1.91;2.40)		2.00±2.04 (1.80;2.21)		1.89±1.92 (1.67;2.11)	

**Table 3: NSAIDs by total prescriptions and PDD per year**

Active ingredient (Top 7)	Total prescriptions n(%)	Mean PDD per year ( $\pm$ SD;95% CI)					Number of NSAID items in CKD patients exceeding recommended daily dosage n(%)
		2009	2010	2011	2012	2013	
<b>Diclofenac</b>	694 (34.3)	95.0 $\pm$ 62.32 (87.6;102.5)	107.8 $\pm$ 60.7 (100.4;115.2)	100.7 $\pm$ 65.2 (91.0;110.4)	91.1 $\pm$ 61.0 (83.4;98.9)	97.0 $\pm$ 62.3 (88.0;105.0)	148 (12.8%)
<b>Meloxicam</b>	394 (19.5)	14.6 $\pm$ 16.2 (12.9;16.3)	14.0 $\pm$ 2.6 (13.6;14.3)	13.8 $\pm$ 2.8 (13.4;14.1)	13.7 $\pm$ 6.6 (12.8;14.7)	13.0 $\pm$ 3.3 (12.5;13.6)	3 (0.3%)
<b>Celecoxib</b>	381 (18.8)	247.2 $\pm$ 151.4 (228.3;266.1)	230.0 $\pm$ 95.6 (218.0;242.0)	212.9 $\pm$ 85.2 (199.8;225.9)	231.4 $\pm$ 91.3 (217.2;245.6)	230.0 $\pm$ 91.7 (211.5;248.3)	7 (0.8%)
<b>Etoricoxib</b>	192 (9.5)	92.4 $\pm$ 21.4 (87.6;97.1)	93.5 $\pm$ 23.6 (87.8;99.1)	87.3 $\pm$ 24.3 (82.1;92.4)	91.6 $\pm$ 19.1 (87.3;96.0)	87.8 $\pm$ 18.0 (83.1;92.6)	-
<b>Ibuprofen</b>	99 (4.9)	1861.8 $\pm$ 515.9 (1596.5;2127.0)	1745.7 $\pm$ 506.4 (1572.0;1920.0)	1598.5 $\pm$ 678.3 (1354.0;1843.1)	1248.6 $\pm$ 643.5 (976.8;1520.3)	1549.4 $\pm$ 657.1 (1233.0;1866.1)	57 (44.9%)
<b>Piroxicam</b>	67 (3.3)	28.8 $\pm$ 19.1 (22.5;35.2)	27.8 $\pm$ 10.0 (22.8;32.8)	30.8 $\pm$ 10.4 (24.5;37.0)	26.3 $\pm$ 9.4 (22.4;30.2)	34.6 $\pm$ 9.3 (28.3;40.8)	2 (1.9%)
<b>Indomethacin</b>	67 (3.3)	141.1 $\pm$ 51.6 (118.2;164.0)	139.3 $\pm$ 65.1 (79.1;199.5)	159.6 $\pm$ 50.5 (134.4;184.7)	115.0 $\pm$ 49.3 (95.5;134.5)	97.0 $\pm$ 43.0 (75.6;118.4)	36 (39.1%)

**Table 4: NSAIDs prescribed in CKD patients by prescriber over the study period**

<b>Prescriber</b>	<b>Number of NSAIDs prescribed (%)</b>
<b>Cardiologist</b>	14(0.7)
<b>General medical practitioner</b>	1248(61.6)
<b>Oncology</b>	4(0.2)
<b>Orthopaedics</b>	60(3.0)
<b>Pharmacotherapist</b>	3(0.2)
<b>Pharmacist</b>	157(7.8)
<b>Physicians/immunologists, rheumatologists/nephrologists/ diabetologist/endocrinologists</b>	380(18.8)
<b>Rheumatologist</b>	2(0.1)
<b>Surgery/Paediatic surgery</b>	32(1.6)
<b>Urologist</b>	13(0.6)
<b>Other</b>	113(5.6)

### **3.4 Chapter summary**

This chapter contained the results of the study and was presented in the form of two manuscripts. Chapter 4 will provide conclusions and recommendations from this study, as well as discuss the limitations and strengths of the research.

## **CHAPTER 4: CONCLUSIONS AND RECOMMENDATIONS**

### **4.1 Introduction**

In this chapter, conclusions are drawn regarding the specific objectives that were indicated in Chapter 1. The limitations as well as the strengths of the study are listed and recommendations are made for future studies surrounding this topic.

The general aim of this study was to investigate and determine the prescribing patterns of NSAIDs in CKD patients in the private health sector of South Africa. The study consisted of a literature review and an empirical investigation. In order to achieve the general objective of the study, each individual research objective specifically led to certain conclusions. The conclusions drawn from these objectives are discussed in paragraphs 4.2 and 4.3, followed by the limitations (paragraph 4.4) and strengths (paragraph 4.5) of the study. Recommendations for further studies are given in paragraph 4.6. A reflection on the entire study is done at the end of the chapter in paragraph 4.8.

### **4.2 Literature review**

Research was conducted to review available literature information in order to reach specific literature objectives (refer to Chapter 2). The prevalence of impaired renal function, along with the prevalence of NSAID use in South Africa and in other countries, was investigated. Research was done on the safety concerns regarding the use of these NSAIDs, especially their effect on the kidneys. The final objective of the literature review investigated the prevalence of NSAID use in patients with impaired renal function (CKD) in South Africa and other countries. The conclusions drawn from these objectives are presented in paragraphs 4.2.1 to 4.2.4.

#### **4.2.1 To investigate the prevalence of impaired renal function in South Africa and other countries**

The prevalence of CKD in a variety of countries with different socio-economic environments was studied (Annexure A). It was found that CKD is a prevalent global condition, with a worldwide prevalence of 8 to 16% (see paragraph 2.3.3). Chronic kidney disease was found to be prevalent in both developed and developing countries, with prevalence rates ranging from 6% in Spain to 16% in the USA (refer to Annexure A). Very little research has been done regarding the prevalence of CKD in the private and/or public healthcare sectors of South Africa, but an estimated prevalence of 14.3% was found in 2014 (Stanifer *et al.*, 2014:e177). It was also found that the prevalence of CKD increased with age, since an increase in age was associated with a decrease in kidney function. It was established that CKD co-occurred with several other chronic

conditions such as diabetes, hyperlipidaemia and hypertension (refer to 2.3.4.1). This objective concluded that CKD was a prevalent global condition.

#### **4.2.2 To investigate the prevalence of NSAID use in South Africa and other countries**

This literature confirmed that NSAIDs were among the most frequently used drugs worldwide. The NSAIDs were found to be widely used across all countries; from Chile (33.2%) to the USA (65%) (refer to Table 2-9). In South Africa, non-selective NSAIDs (29.6%) and COX-2 inhibitors (48.7%) were widely used (Beeka, 2008). In general it was found that diclofenac and ibuprofen were the most commonly prescribed NSAIDs, followed by COX-2 inhibitors such as celecoxib. If one considers prescribers, general medical practitioners were responsible for prescribing NSAIDs most frequently (see paragraph 2.2.5). NSAID use seemed to increase with age, as it was found that older patients claimed an NSAID prescription more frequently than their younger counterparts. It was therefore clear that NSAIDs were being consumed in both developed and developing countries at a rapid rate, with no indication of decline in its prescribing volume in the near future.

#### **4.2.3 To investigate the safety concerns regarding NSAID use, especially the effect on the kidneys**

Literature on the safety concerns regarding NSAID use, especially the effect on the kidneys, showed that several safety concerns existed regarding NSAIDs, although they were extremely efficient in the treatment of pain and inflammation. These adverse effects included gastrointestinal damage, adverse cardiovascular events, the possibility of inducing asthma, hypertension, certain effects they had on platelets, possible liver toxicity and adverse renal effects (refer to paragraph 2.2.6). This study especially focused on the renal effects of the NSAIDs. Non-steroidal anti-inflammatory drugs were indeed confirmed to be nephrotoxic drugs, with an ability to inhibit the COX enzymes and eventually decrease prostaglandin production (refer to paragraph 2.4.3). This then results in a reduced kidney function, which could eventually cause severe kidney damage, especially in CKD patients. Renal syndromes that could result from the use of NSAIDs included hyperkalaemia, hyponatremia, congestive heart failure and acute renal failure. The objective concluded that NSAIDs were highly efficient, but their accompanied adverse effects should be considered and evaluated more carefully before the onset of treatment.

#### **4.2.4 To investigate the prevalence of NSAID use in patients with impaired renal function in South Africa and other countries**

With regard to the prevalence of NSAID use in patients with impaired renal function in South Africa and other countries, the study found that the literature regarding the use of NSAIDs in

CKD patients was inadequate. This was especially true for South Africa. However, it was found that NSAIDs were frequently being used in CKD patients (refer to paragraph 2.4.2). Global prevalence rates on NSAID use in CKD patients ranged from 10% to 74,8% (see paragraph 2.4.2). There did not seem to be a difference in the use of NSAIDs in CKD patients compared to patients with normal kidney function, especially with regard to the dosage of these drugs. These statistics are worrying indeed, as these drugs can worsen the prognosis of the disease and lead to several complications such as glomerulonephritis, nephrotic syndrome, podocyte injury, etc. (Choudhury & Ahmed, 2006:83; Loh & Cohen, 2009:241; Perazella, 2009:1281).

### **4.3 Empirical investigation objectives**

The empirical investigation was conducted in the form of two manuscripts (refer to Chapter 3) and its objectives were achieved by using data obtained from the medicine claims database of a nationally represented PBM company (refer to paragraph 1.4.2). The objectives included the determination of the CKD prevalence and the proportion of these CKD patients receiving NSAIDs in the private healthcare sector of South Africa. The disease profile of CKD was determined in terms of age, gender, number and type of other CDL conditions, etc. Finally the prescribing patterns of NSAIDs were characterised, stratified by prescriber specialty. The conclusions drawn on these objectives are summarised in paragraphs 4.3.1 to 4.3.2.

#### **4.3.1 To determine the prevalence of CKD over the study period using the data of a medicine claims database, stratified by age, gender and co-occurring chronic conditions**

With regard to determining the prevalence of CKD over the study period, it was found that CKD patients represented 0.10% to 0.14% (from 2009 to 2013) of the total number of patients on the database. This prevalence might seem extremely low, and was much lower than other prevalence rates of CKD found in the literature review (refer to paragraph 4.2). The male-to-female ratio (1:0.8) of the CKD patients in the present study agreed with results from the USA (US Renal Data System, 2007), but contradicted results from the UK (Kearns *et al.*, 2013:52). No association between CKD prevalence and gender was found in our study. It was observed that CKD increased with an increase in age, with the 35–64-year age group being the most prevalent. However, this association was not found to be of practical significance. The mean age of the CKD patients ranged from 59.66 ± 16.82 years (95% CI: 58.65;60.68) in 2009 to 57.84 ± 16.09 years (95% CI: 56.90;58.78) in 2013. The results indicated that several chronic conditions co-occurred with CKD, with hypertension occurring in more than half the CKD patients. Other prevalent co-occurring conditions included hyperlipidaemia and diabetes mellitus 2 (refer to manuscript 1, paragraph 3.2).

#### **4.3.2 To determine the proportion of CKD patients receiving NSAIDs, stratified by age, gender, type of NSAID, PDD and prescriber type by using the medicine claims database**

One in every three to four CKD patients was prescribed NSAIDs over the study period. The mean number of NSAID prescriptions in CKD patients ranged from  $2.36 \pm 2.67$  (95% CI: 2.11;2.61) in 2009 to  $1.89 \pm 0.92$  (95% CI: 1.67;2.11) in 2013. No association between CKD patients to whom NSAIDs were prescribed vs. those who did not receive NSAIDs and gender was found, although males were responsible for the majority of the prescriptions (varying male-to-female ratio 1:0.8). A weak association between age and CKD patients with an NSAID prescription vs. those without was found. General medical practitioners prescribed more than half the NSAIDs prescriptions in CKD patients. Diclofenac was the NSAID prescribed most frequently in CKD patients (diclofenac-to-other NSAIDs ratio 1:2). These NSAIDs were prescribed to CKD patients in dosages similar to and in some instances exceeding the recommended daily dosage of the drug for patients with a healthy kidney. Ibuprofen and indomethacin were prescribed in dosages exceeding the recommended daily dosage of the drug in 44.88% and 39.13% of the prescriptions respectively. It can be concluded that NSAIDs were frequently used by CKD patients with an increased age in dosages not supportive to their renal function (refer to manuscript 2 in paragraph 3.3).

#### **4.4 Limitations**

This research had several limitations, which included:

- Chronic kidney disease has several chronic conditions co-occurring with it and could possibly be an underlying cause for several other chronic conditions (refer to paragraph 2.3.4.1). Chronic kidney disease can also present differently during different stages of the disease, it could be influenced by several risk factors and the presentation of the disease can be influenced by its etiology. This could all result in patients with renal insufficiency not being diagnosed with CKD, resulting in the underreporting of CKD prevalence on the database.
- The database employed in the study lacked clinical data (such as GFR, serum creatinine and blood urea nitrogen (BUN) levels). The clinical effects of different NSAID dosages and risk factors on the renal function of CKD patients could therefore not be analysed.
- Since most NSAIDs are available in over-the-counter (OTC) formulation, they could possibly have been consumed by CKD patients without being claimed on the patients' medical scheme. Not all registered CKD patients could consequently have had a paid claim for an NSAID and data would then be lost to analysis, resulting in the underreporting of NSAID use in CKD patients.

## 4.5 Strengths

The strengths of this study included the use of a large, nationally representative study population extracted from a pharmaceutical claims database. By using retrospective, depersonalised data from a PBM company, this study was a low-risk study, with little ethical implications.

The indirect benefits of this study included:

- This study can facilitate an improvement in healthcare delivery to CKD patients, as well as an improved assessment of these patients' health needs (Brink *et al.*, 2012:43).
- An improvement in preventive health measures can be achieved, which will improve the treatment outcome of these patients and contribute to greater quality of life (Brink *et al.*, 2012:43).

It is important to ensure that all information is gathered from a reliable source to ensure that the data is valid and reliable. The research was conducted assuming that all the data was correct and accurate. However, checks were in place to assure data quality, such as checking for data outliers, and performing random data checks. A statement was therefore designed to provide guidance on how to conduct research well in epidemiological studies. This statement is called Strengthening the Reporting of Observational Studies in Epidemiology (STROBE). The items from the checklist (Von Elm *et al.*, 2008:346-347) relevant to this study are indicated in Annexure I and provide a guideline to improve the validity and reliability of this study.

## 4.6 Recommendations

This study recommends that future studies be conducted that investigate the prescribing of NSAIDs in high-risk patients, such as those with CKD. This research could especially be conducted in South Africa, where there is very little information regarding this matter available. More clinical studies can be conducted to examine the effect that different dosages of NSAIDs have on the renal function of the CKD patient. The extent of the renal damage NSAIDs might cause could thus be measured by using several parameters, including GFR, serum creatinine and blood urea nitrogen levels. These future studies will provide more insightful information to prescribers, and even provide helpful guidelines for the prescribing of NSAIDs in renal-insufficient patients.

## 4.7 Chapter summary

This chapter stated the general aim of the research and discussed the conclusions drawn from the specific objectives of both the literature review and empirical study. The limitations and the

strengths of this research were listed and recommendations for future research completed the chapter.

#### **4.8 Study reflection**

This study used retrospective medicine claims data obtained from a PBM company to investigate the prescribing patterns of NSAIDs in CKD patients in the private health sector of South Africa from 2009 to 2013. The introduction to the study was presented in Chapter 1, followed by a literature review on NSAIDs and CKD in Chapter 2. The results of the study were then presented in the form of two manuscripts in Chapter 3 and the conclusions and recommendations were provided in Chapter 4.

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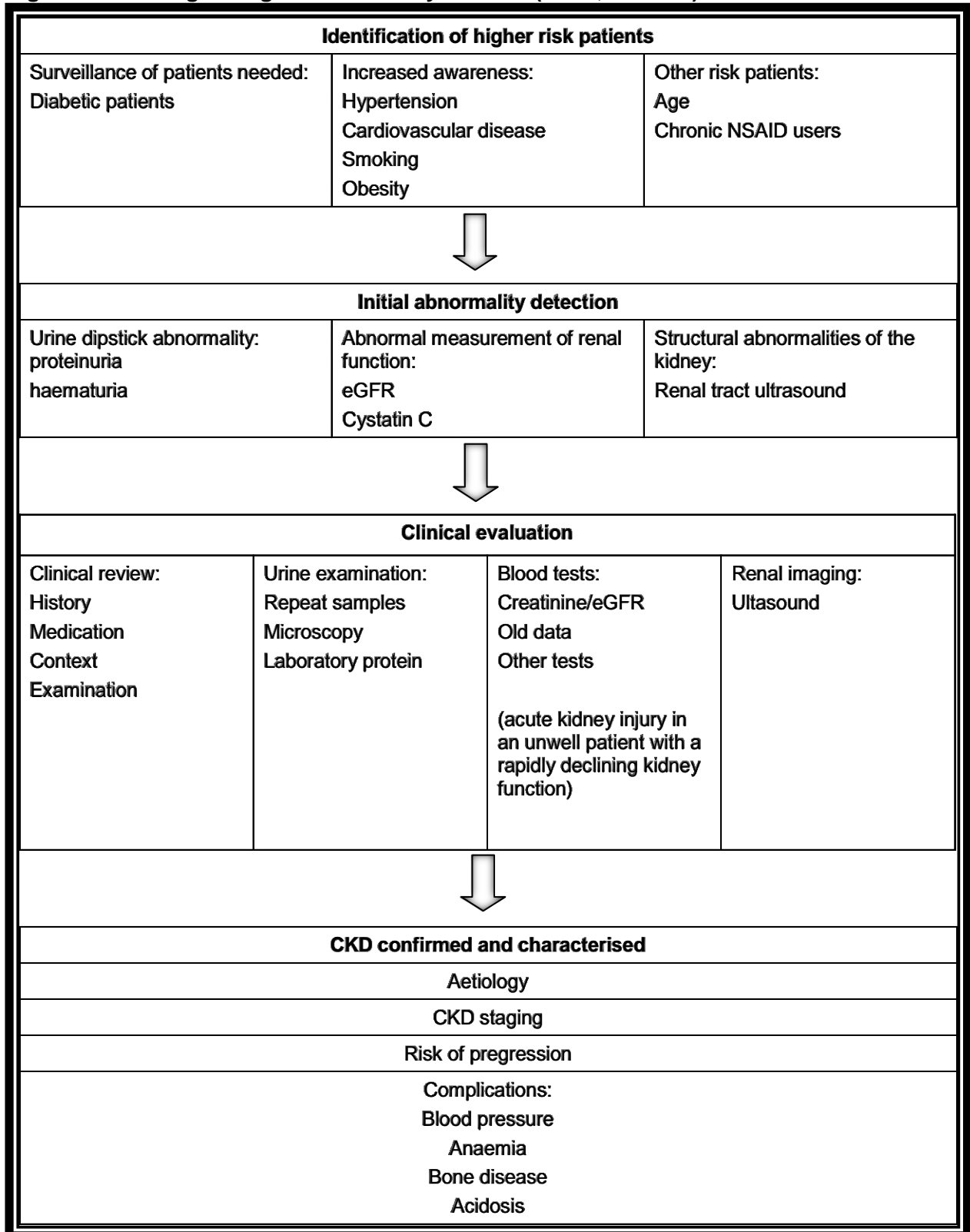
## ANNEXURE A

### Summary of studies on prevalence of chronic kidney disease

Source	Study period	Study participants (n)	Setting	Units of measurement	Main/key findings
Warnock <i>et al.</i> (2005:1428)	May 2004–Mar. 2005	6 807	USA	Portion of the study population diagnosed with CKD	CKD was present in 1 081 (16%) of the participants
Otero <i>et al.</i> (2010:79)	Jan. 2004–Jan. 2008	2 746	Spain	Prevalence of CKD among the study population	A CKD prevalence of 6.8% was found during the study
Imai <i>et al.</i> (2007:162)	2000–2004	527 594	Japan	Predicted portion of the general Japanese population with CKD Stages 3–5	Approximately 20% of the general adult population is predicted to have CKD Stages 3–5
Covic <i>et al.</i> (2006:420)	1995–2004	635	Romania	The portion of renal biopsies caused by CKD	10.1% of renal biopsies performed is caused by CKD
Zhang <i>et al.</i> (2012:819)	Sep. 2009–Sep. 2010	47 204	China	Overall prevalence of CKD in study population	10.8% of study population has CKD
Sumaili <i>et al.</i> (2009:18)	9 Jan. 2007–25 May 2007	527	Democratic Republic of Congo	Prevalence of CKD in patients at high risk for CKD	A CKD prevalence of 36% among the high-risk study population
Ingsathit <i>et al.</i> (2010:70)	Aug. 2007–Jun. 2008	3 459	Thailand	Prevalence of CKD among the study population	17.5% of study population was identified to have CKD
Zhang <i>et al.</i> (2009:125)	Jul. 2000–Dec. 2002	9 806	Germany	Proportion of study population with CKD	17.4% of the study population has CKD
Stanifer <i>et al.</i> (2014:e177)	1962–2011	64 307	South Africa	Overall prevalence of CKD in meta-analysis done on 17 studies	Overall CKD prevalence of 14.3% found in studies
Arora <i>et al.</i>	2007–2009	3 689	Canada	Prevalence of CKD in the study population	A CKD prevalence of 12.5% was identified

## ANNEXURE B

### Algorithm for diagnosing chronic kidney disease (SIGN, 2008:14)



## ANNEXURE C

### Treatment of chronic kidney disease

Underlying disease	Treatment goal	Pharmacotherapy		
		Class	Active ingredient	Trade names
Hypertension	<125–130 mmHg/ 75–80 mmHg	ACE inhibitor (Snyman, 2012:122-135)	Quinapril  Perindopril  Captopril  Lisinopril  Enalapril  Ramipril  Verapamil	Accumax Accuretic Prexum Vectoryl Adco-Captomax Zapto Lisoretic Zestomax Enap Pharmapress Rampil Tri-Plen VeraHexal Rarka
		Angiotensin-receptor blocker (Snyman, 2012:135-142)	Irbesartan  Candesartan Losartan  Valsartan  Amlodipine	Irbewin Aprovel Atacand Cozaar Zartan Co-Diovan Exforge Amlate Amloc

### Treatment of chronic kidney disease

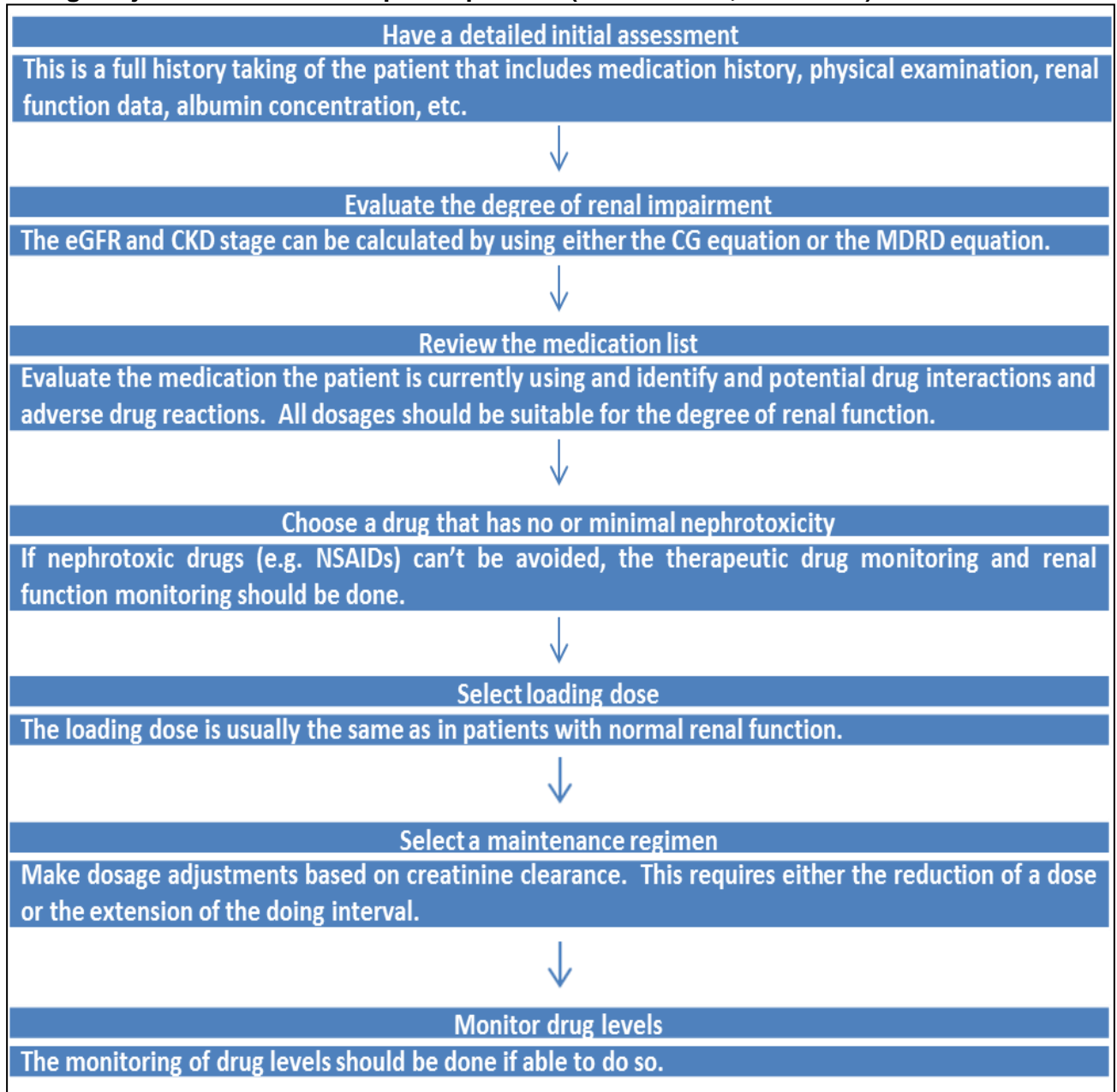
Underlying disease	Treatment goal	Pharmacotherapy		
		Class	Active ingredient	Trade names
Hypertension	<125–130 mmHg/ 75–80 mmHg	Thiazide diuretic (Snyman, 2012:244-248)	Indapamide  Hydrochlorothiazide	Adco-Dapamax NatriliX Adco-retic Amiloretic
		Beta blocker	Bisoprolol  Acebutolol  Atenolol	Bilocor Cardicor Butobloc Sectral Adco-Atenolol Ten-Bloka
		Long-acting calcium-channel blocker (Snyman, 2012:143)	Nifedipine	Adalat Adco-Vascard
Diabetes mellitus	HbA <sub>1c</sub> < 7.0% Fasting plasma glucose of 4–7 mmol/L	Biguanide (Snyman, 2012:330-342)	Metformin	Glucophage Mylan-Metformin
		Meglitinides (Snyman, 2012:330-342)	Repaglinide	NovoNorm
		Sulphonylureas (Snyman, 2012:330-342)	Glimepiride  Gilbenclamide  Gilclazide  Glipizide	Amaryl Glamaryl Glucovance Glycomin Diagluclide Diamicron Minidiab
			Insulin (Snyman, 2012:330-342)	Insulin glulisine Insulin glargine Insulin detemir Insulin lispro Biosynthetic human insulin

### Treatment of chronic kidney disease

Underlying disease	Treatment goal	Pharmacotherapy		
		Class	Active ingredient	Trade names
Dyslipidaemia	Serum total cholesterol < 4 mmol/L	Statins (Snyman, 2012:150-156)	Simvastatin	Adco-Simvastatin Simvacor
			Atorvastatin	Aspavor
			Pravastatin	Atolip
			Lovastatin	Aspen Pravastatin
		Fibrates (Snyman, 2012:149-150)	Bezafibrate	Lovachol
			Fenofibrate	Bezachole Dyna-Bezafibrate Lipanthyl

## ANNEXURE D

### Dosage adjustments in renal impaired patients (Hassan *et al.*, 2009:1099)



## ANNEXURE E

### AUTHOR GUIDELINES FOR SOUTH AFRICAN FAMILY PRACTICE

Obtained from: <http://www.safpj.co.za/index.php/safpj/about/submissions#authorGuidelines>.

#### Author Guidelines

Submissions can only be made online at [www.editorialmanager.com/safpj](http://www.editorialmanager.com/safpj). Authors need to register online with the journal prior to submitting a manuscript. Once registered, simply log in and begin an easy 5 step process to upload your manuscript. All manuscripts must be submitted in MS Word®, Open Office, or RTF format using Times New Roman font size 10 and single-spacing. Headings must be in Bold.

The author must always retain a copy. All the named authors must have approved the final manuscript. Pages should be numbered consecutively in the lower right corner. Please note that the Original Research section will follow a ";print-short, web-long"; policy, which means that only the abstracts will be published in print, with the full article published on the web. Some review articles may also be published under these provisions.

The following contributions are accepted (word counts exclude abstracts, tables and references):

1. *Original research* (Between 1000 and 3500 words):
2. *Letters to the Editor* (Up to 400 words):
3. *Scientific Letters* (Less than 600 words): A short abstract is required (125-150 words) and should be structured under the following headings: background, methods, results and conclusion. One table or graph and not more than 5 references.
4. *Review/CPD articles* (Up to 1800 words): Most review articles are published as part of the continuous professional development (CPD) programme of SAFFP. A scientific editor is appointed to approve topics, invite authors and to review the articles before they are independently peer-reviewed. All articles are reviewed by a family physician as well a topic specialist. Review articles outside the CPD programme are welcomed. Once accepted they may be published in full in the printed journal OR a 250 word abstract will be published in print with the full article available online.
5. *Opinions (Open Forum)* (Between 1000 and 3500 words).
6. *Editorials* (Between 600 - 800 words): Scientific editorials can be used to highlight progress in any scientific field related to family medicine.

Please consult the Section Policies for more details regarding CPD articles.

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**Title page:** All articles must have a title page with the following information and in this particular order: Title of the article; surname, initials, qualifications and affiliation of each author; The name, postal address, e-mail address and telephonic contact details of the corresponding author; at least 5 keywords. Please do not use capital letters only for headings and names, but stick to the normal use of capital letters.

**Abstract.** All articles should include an abstract. The structured abstract for an Original Research article should be between 200 and 250 words and should consist of four paragraphs labelled "Background, Methods, Results, and Conclusions".

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The following are sample references:

1. London L, Baillie R. Notification of Pesticide Poisoning: Knowledge, Attitudes and Practices of Doctors in the Rural Western Cape. *S A Fam Pract* 1999;20(1):117-20.
2. FDA Talk Paper: <http://www.fda.gov/bbs/topics/ANSWERS/2002/ANS01151.html> (Accessed 04/10/2002).

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**Figures.** All figures must be inserted in the appropriate position of the electronic document. Symbols, lettering, and numbering (in Arabic numerals e.g. 1, 2, etc. in order of appearance in the text) should be placed below the figure, clear and large enough to remain legible after the figure has been reduced. Figures must have clear descriptive titles.

**Photographs and images:** If photographs of patients are used, either the subject should not be identifiable or use of the picture should be authorised by an enclosed written permission from the subject. The position of photographs and images should be clearly indicated in the text. Electronic images should be saved as either jpeg or gif files. All photographs should be scanned at a high resolution (300dpi, print optimised). Provision is made to upload individual images on the website as *supplementary files*. Please number the images appropriately.

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3. All URL addresses in the text (e.g., <http://pkp.sfu.ca>) are activated and ready to click.
4. The text is single-spaced; uses a 10-point font; employs italics, rather than underlining (except with URL addresses); and all tables and figures are placed within the text at the appropriate points, rather than at the end.
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## ANNEXURE F

**South African Family Practice**  
**Prevalence of chronic kidney disease (CKD) and co-occurring chronic conditions in the private health sector of South Africa**  
--Manuscript Draft--

<b>Full Title:</b>	Prevalence of chronic kidney disease (CKD) and co-occurring chronic conditions in the private health sector of South Africa
<b>Manuscript Number:</b>	
<b>Article Type:</b>	Original Research
<b>Keywords:</b>	Prevalence, chronic kidney disease, risk factors, comorbid chronic conditions, South Africa
<b>Manuscript Classifications:</b>	Allied Health; Clinical Pharmacology & Therapeutics; General Medicine; Nephrology; Nursing; Pharmacy & Dispensing; Specialist Community Public Health Nursing
<b>Abstract:</b>	<p>Background: Chronic kidney disease (CKD) is a public health problem, with increasing global prevalence. Several factors could influence the prognosis of CKD, including co-occurring chronic conditions. This study determined the prevalence of CKD in the private health sector of South Africa and the co-occurring chronic conditions.</p> <p>Methods: Retrospective medicine claims data from a pharmaceutical benefit management (PBM) company was used to perform this descriptive, quantitative study. The study population consisted of all patients identified with an ICD-10 code for CKD (N18) during the study period of 1 January 2009 to 31 December 2013.</p> <p>Results: CKD patients represented 0.10% to 0.14% of the total patients on the database from 2009 to 2013. The mean age of the CKD patients over the study period varied between 58 and 61 years. Prevalence was higher in males (male-to-female ratio 1:0.8) and in patients aged 35-64 years (<math>p=0.014</math>; Cramer's <math>V=0.039</math>). The occurrence of chronic conditions in the CKD population was prevalent, with hypertension occurring in more than half the CKD patients.</p> <p>Conclusion: Several chronic conditions, especially those regarding atherosclerotic risk factors, frequently co-occurred with CKD. Lifestyle management and frequent screening tests of these patients are of the utmost importance to improve the outcome of CKD.</p>

## **ANNEXURE G**

### **AUTHOR GUIDELINES FOR INTERNATIONAL JOURNAL OF CLINICAL PHARMACY**

Obtained from: <http://www.springer.com/medicine/internal/journal/11096>.

#### **Aims & Scope**

The aim of International Journal of Clinical Pharmacy is to provide a medium for the publication of articles on clinical pharmacy and related practice-oriented subjects in the pharmaceutical sciences. The scope of the journal is clinical pharmacy, its research and its application in e.g. pharmaceutical care. The editors therefore welcome contributions on the above-mentioned topics and especially on the following:

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- Clinical pharmacy
- Pharmacoepidemiology
- Pharmacoeconomics
- Pharmaceutical care
- Medicines and medical devices utilisation
- Medicines and medical devices information
- Pharmacy services research
- Medication management
- Other clinical aspects of pharmacy

The journal welcomes papers in the following categories: Review articles, Research articles, Case reports, Short research reports, Commentaries, and Letters to the Editor. All submissions (including Commentaries and, if necessary, Letters) will be peer-reviewed by experts.

Until 2010 the journal was entitled Pharmacy World & Science.

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International Journal of Clinical Pharmacy has a fully web-enabled manuscript submission and review system. This system offers authors the option of tracking the review process of their manuscripts in real time. The online manuscript and review system offers easy and straightforward log-in and submission procedures. It supports a wide range of submission file formats, including Word, WordPerfect, RTF, TXT and LaTeX for article text and TIFF, EPS, PS, GIF, JPEG and PPT for figures. PDF manuscripts cannot be accepted.

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Please describe the article type of your submission (see 'Article types' below) and the reason why International Journal of Clinical Pharmacy should publish your article in your cover letter. This letter should also contain a submission statement with a sentence that the paper has not been submitted elsewhere in similar form, and should state that all authors have contributed significantly to the publication. There should also be a statement concerning the fact that all authors are aware of the submission and agree with it.

Additionally we expect all authors' details in the cover letter, as well as the number of words of the article, of the abstract, and of the references. Please do not insert author details in the manuscript itself.

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We appreciate any efforts that you make to ensure that the language is corrected before submission. This probably will greatly improve the legibility of your paper if English is not your first language. It will improve the chances of the manuscript being accepted by the reviewers.

#### **What happens after submission?**

You will receive an acknowledgement of receipt of the submission. The paper will be checked for adherence to the instructions and the editorial policy of the journal. Sometimes a plagiarism check will be performed and all references will be checked. If approved, the submission will be sent to reviewers. The review procedure should be finished in approx. 6 weeks, but may sometimes take up to 3 months. You will then receive information about acceptance, needed revisions or rejection of your submission. Unless otherwise stated in the cover letter, the corresponding author will be regarded as the author for correspondence and proofs. You can follow the progress of the reviewing process on line in Editorial Manager.

Once your paper is accepted for publication, you will receive an edited version electronically for proofreading. The authors are responsible for checking and correcting the proofs. The main author will receive 25 offprints free of charge of the article within 8 weeks after its publication. More offprints can be ordered, at additional costs, when returning the proofs to the publisher. Consent to publish forms should be signed by the corresponding author and returned to Springer prior to publication. The copyright will be established in the name of Springer.

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Review articles should not exceed 3000 words, excluding abstract and references. Reviews should be structured as follows: Introduction, Aim of the review, Method, Results, Discussion and Conclusion. Please provide a structured abstract of max. 350 words with the headings: Background, Aim of the Review, Method, Results, and Conclusion.

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Research articles should not exceed 3000 words, excluding tables, figures, abstract, or references. Research articles should be structured as follows: Introduction, Aim of the study, Ethical approval, Method, Results, Discussion, and Conclusion. Please provide a structured abstract of max. 350 words with the headings: Background, Objective, Setting, Method, Main outcome measure, Results, Conclusion. Articles describing qualitative research may be 4000 words in length.

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### *Commentaries*

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## **Abbreviations**

Abbreviations should be explained upon first occurrence. Do not use abbreviations in the

abstract.

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Please use the recommended SI units.

### **Section headings**

First-, second-, third-, and fourth-order headings should be clearly distinguishable but not numbered.

### **Appendices**

Supplementary material (like very large tables) should be collected in an Appendix and placed after the Reference section. Questionnaires should not be added to the manuscript, but made available on-line, and a reference should be inserted in the article.

### **Notes**

Please use footnotes sparingly. Footnotes should be indicated by means of superscript marks (\*, #, \$) in the text and listed at the bottom of the appropriate page. Endnotes functions may be used to insert references.

### **Acknowledgements**

Acknowledgements should be placed in a separate section after the conclusion. If external funding has been obtained for the study, then this should be mentioned under a separate header 'Funding', after the acknowledgements.

### **Conflict of interests**

Conflicts of interest (also if there are none) should be stated in a separate section before the References.

### **References**

In the text, a reference is identified by means of a number between square brackets, that should be placed at the end of a sentence before the punctuation. Please use cross-referencing if the same reference is used more than once.

According to the ICMJE, references to books, journal articles, articles in collections and conference or workshop proceedings, and technical reports should be listed at the end of the article in numbered order according to 'Citing Medicine: The NLM Style Guide for Authors, Editors, and Publishers. Abbreviations of journal names should be according to Index Medicus. We expect a maximum of 6 author names before 'et al.'. Articles in preparation or articles

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### **Tables**

Each table should be numbered consecutively (1, 2, etc.). In tables, footnotes are preferable to long explanatory material in either the heading or body of the table. Such explanatory footnotes, identified by superscript letters, should be placed immediately below the table. Please provide a caption (without abbreviations) to each table, refer to the table in the text and note its approximate location as 'Insert Table... here' in the text. Finally, please place the tables after the figures at the end of the manuscript.

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# ANNEXURE H

**International Journal of Clinical Pharmacy**  
**Prescribing patterns of non-steroidal anti-inflammatory drugs in chronic kidney disease patients**  
 --Manuscript Draft--

Manuscript Number:	
Full Title:	Prescribing patterns of non-steroidal anti-inflammatory drugs in chronic kidney disease patients
Article Type:	Research Article
Keywords:	non-steroidal anti-inflammatory drugs (NSAIDs); private health sector of South Africa; chronic kidney disease (CKD)
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Funding Information:	
Abstract:	<p>Background Non-steroidal anti-inflammatory drugs (NSAIDs) are among the most commonly used pharmaceutical agents worldwide. NSAIDs are considered nephrotoxic and should therefore be used with caution or be avoided completely in high-risk patients such as chronic kidney disease (CKD) patients. Objective This study aimed at investigating the prescribing of NSAIDs in CKD patients in order to generate awareness. Setting The study was conducted using medicine claims data in the private health sector of South Africa. Method A descriptive, quantitative study was performed, using retrospective data obtained from a pharmaceutical benefit management company (PBM). Data from 1 January 2009 to 31 December 2013 was analysed. The study population consisted of all patients with an ICD-10 code for a CKD (N18), in association with a paid claim for an NSAID. Main outcome measure The stratification of NSAID prescribing volume in the CKD population in terms of gender, age, NSAID type, dosage and prescriber type. Results The prescribing of NSAIDs in CKD patients varied between 26% and 40% over the five year study period. No association was found between gender and CKD patients who received NSAIDs vs. those who did not, with <math>p &gt; 0.05</math> and Cramer's <math>V &lt; 0.1</math> for each year of the study. The association between age groups and CKD patients who received NSAIDs vs. those who did not was statistically significant, but practically weak (<math>p &lt; 0.05</math>; Cramer's <math>V \geq 0.1</math>). Most NSAID prescriptions (52%–63%) were for patients aged 35 to 64 years. Diclofenac (34.25%) was the single most frequently prescribed NSAID, but the COX-2-inhibitors (celecoxib, meloxicam and etoricoxib) were the preferred NSAID class to be prescribed. The majority (51.6%) of the NSAIDs were prescribed by general medical practitioners in dosages complying with and even exceeding the recommended daily dosage of patients with normal kidney function. Conclusions Even though NSAIDs are</p>

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	<p>regarded as nephrotoxic drugs, they are still being prescribed to at-risk CKD patients, in particular, the elderly.</p> <p><b>Impact of findings</b>          *The lack of available information with regard to studies conducted on the prescribing patterns of NSAIDs in CKD patients is worrying, since results from these studies can contribute greatly to an improved outcome in renal insufficient patients.          *Emphasis should be put on the dosages of the NSAIDs prescribed to CKD patients, especially the dosages of ibuprofen and diclofenac. These dosages should accommodate the renal function of these patients with a renal insufficiency.          *Greater caution with regard to the type and dosage of drug prescribed should be exercised by general medical practitioners when treating pain in CKD patients.</p>
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## ANNEXURE I

### Checklist to ensure validity and reliability of the research process

Considerations	Checklist item	Approach followed
Title and abstract	<p>The study's design should be indicated in the title or abstract with commonly used terms.</p> <p>The abstract should also contain an informative summary of what was done in the study and what was found.</p>	The abstract contains a summary of what was done during this research.
Introduction	The rationale and the scientific background of the study should be explained in the introduction.	All the key features regarding the study were pointed out in the introduction
Objectives	Any specific objectives and hypotheses of the researcher must be included.	Objectives for both the literature and empirical phase were stated, as was the general research aim.
Methods	The key elements of the study should be included early in the paper.	<p>Data analysis plan was included.</p> <p>Rationale for this study design was given in paragraph 1.4.2.1</p>
Variables	<p>All outcomes, exposures, predictors, potential confounders and effect modifiers should be clearly defined and explained.</p> <p>For every variable, the measurements involving the study should be mentioned and explained.</p>	All study variables were named and all measurements described in Table 1-3.
Bias	Any source of potential bias should be listed and efforts explained to address it.	<p>In selecting subjects, bias should be avoided.</p> <p>The selection of subjects in the study was ethically appropriate, since they were not selected by race, gender, age, etc., because the only selection criterion was that all subjects be on treatment for a CKD.</p> <p>This removed any biases that might have occurred during the selection of the subjects.</p>

### Checklist to ensure the validity and reliability of the research process

Considerations	Checklist item	Approach followed
Results	<p>The number of individuals should be reported at each stage of the study.</p> <p>Unadjusted estimates should be reported, e.g. 95% confidence interval.</p> <p>Any other analyses must be reported, e.g. the analyses of subgroups.</p>	<p>All analyses done during the research is reported in Chapter 3 of this study.</p>
Discussion	<p>Key results should be summarised and be put in perspective with study objectives.</p> <p>Any limitations of the study should be discussed.</p>	<p>Discussions of results were done in Chapter 3 of this research, along with the conclusions drawn from the respective objectives in Chapter 4. .</p>