A retrospective study of dyslipidaemia in patients with chronic kidney disease at Charlotte Maxeke Johannesburg Academic Hospital

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A research report submitted to the Faculty of Health Sciences, University of the Witwatersrand, in partial fulfilment for the degree of Master of Medicine (Internal Medicine)

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DECLARATION

I, Mohammed Rafique Essop, declare that this report is of my own work. It is being submitted for the degree of Master of Medicine in the Department of Internal Medicine, Faculty of Health Sciences, University of the Witwatersrand. It has not been presented for any other degree at any other University.

09.12.2021

Dr Mohammed Rafique Essop Date

MBBCh (Wits)

DEDICATION

To my wife, parents and siblings for their continuous support and patience during this difficult but rewarding period.

ETHICS COMMITTEE APPROVAL

This research was approved by the Ethics Committee for Research on Human Subjects, University of the Witwatersrand (Clearance Certificate number: M200760).

ABSTRACT

Background

Atherosclerotic cardiovascular disease (ASCVD) is a major cause of morbidity and mortality in patients with chronic kidney disease (CKD), whilst CKD itself is considered a coronary artery disease equivalent due to its atherogenic potential. Despite the role of CKD in ASCVD and recommendations to control lipid levels aggressively, landmark lipid studies have often excluded patients with CKD. Furthermore, there is little to no data examining the use and efficacy of lipid lowering therapy (LLT) in those with CKD in South Africa. We therefore undertook this study to further examine the prevalence and control of dyslipidaemia in a cohort of South African patients with CKD.

Methods

A retrospective, cross-sectional observational study of 250 patients with CKD attending the Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) renal clinic from 1 July 2019 to 31 July 2020. Lipograms, the use of lipid lowering therapy (LLT) and achievement of target lipid levels were examined.

Results

The median age of this cohort was 58 years (46-69, 95% CI); 50.4% were males and 64.4% were black African. The prevalence of dyslipidaemia in this study was 83.6% (N=209). Of the 250 patients enrolled 169 (67.6%) were on LLT, of these just 28 (16.6%) achieved the recommended low-density lipoprotein cholesterol (LDL-C) target. Of those not on LLT, 51 (63%) were eligible for LLT and almost all were classified as either very high risk (64.2%) or high risk (28.4%). Of those on LLT, all were on statin therapy, of which simvastatin at a mean dose of 21.2mg was the most commonly prescribed LLT.

Conclusion

This cohort comprised a large proportion of patients classified as high or very high risk by European Society of Cardiology criteria. Despite this, the use of LLT was inadequate and less than 20% of patients were at target LDL-C levels. These data suggest a greater need for awareness of initiating statin therapy and achieving target LDL-C levels in patients with CKD.

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ABBREVIATIONS

ACC	American College of Cardiology
ACS	Acute coronary syndrome
ART	Anti-retroviral therapy
ASCVD	Atherosclerotic cardiovascular disease
CKD	Chronic kidney disease
CVD	Cardiovascular disease
CMJAH	Charlotte Maxeke Johannesburg Academic Hospital
ESC	European Society of Cardiology
ESRD	End stage renal disease
GFR	Glomerular filtration rate
HDL-C	High density lipoprotein cholesterol
HMG-COA	Hydroxymethylglutaryl-Coenzyme A
hsCRP	High sensitivity C-reactive protein
KDIGO	Kidney Diseases Improving Global Outcomes
LDL-C	Low density lipoprotein cholesterol
LLA	Lipid lowering agent
LLT	Lipid lowering therapy
TC	Total cholesterol
TG	Triglycerides
Urine PCR	Urine protein: creatinine ratio

Chapter 1: Literature Review

1.1 Introduction

Atherosclerotic cardiovascular disease (ASCVD), including cerebrovascular disease, coronary artery disease, peripheral vascular disease and aortic aneurysm (1), contributes significantly to global morbidity and mortality, and is the leading cause of death in both developed and developing countries (2). In 2019, ASCVD was responsible for 32% or 17.9 million deaths globally (2), and in South Africa in 2014, ASCVD was responsible for 215 deaths daily, second only to HIV/AIDS (3). ASCVD is responsible for an increasing proportion of healthcare costs, and between 2014 and 2015, the economic cost of cardiovascular disease in the United States was estimated to be USD351.2 billion (4). Data from South Africa are sparse, but a publication from 1991 estimated that cardiovascular disease accounted for between ZAR4.1 billion and ZAR5 billion annually (5).

Dyslipidaemia is a major risk factor for ASCVD (6). Dyslipidaemia directly contributes to atherosclerosis due to lipid accumulation in the arterial wall which initiates an inflammatory cascade causing endothelial dysfunction. Apolipoprotein B containing lipoproteins are engulfed by macrophages producing foam cells that form the initial pathological fatty streak of atherosclerosis (7).

In a recent study from South Africa, 67% of the rural population met criteria for dyslipidaemia, while less than 1% were receiving lipid lowering therapy (LLT) (8). Furthermore, 60% of the patients in this study had hypertriglyceridemia (8). The Dyslipidaemia International Study (DYSIS) revealed that 50% of South African patients on statin therapy were not at low-density lipoprotein cholesterol (LDL-C) target and even more concerning was that 74% of these patients would have been classified as being at least high risk for ASCVD (9). Furthermore, against the background of a severely constrained public health system in which socio-economic factors limit access to healthcare, it is likely the extent of dyslipidaemia is underestimated. Additional factors also contribute to the growing burden of dyslipidaemia in South Africa. For example, increasing urbanisation that has resulted in reduced physical

activity and greater exposure to unhealthy diets (10). Dyslipidaemia also co-exists with traditional risk factors for ASCVD (diabetes, hypertension, smoking, obesity and gout) as well as HIV and antiretroviral therapy (ART) (10). The reported prevalence of dyslipidaemia in ART naïve patients and in those treated with ART is 90% and 85%, respectively (11).

Chronic kidney disease (CKD) is defined as a structural or functional abnormality of the kidney with a calculated glomerular filtration rate (GFR) of less than 60mL/min/1.73m^2 for more than three months (12). Markers of kidney damage include: albuminuria (albumin to creatinine ratio greater than 30mg/g); abnormalities in imaging, urine sediment and histology, renal tubular disorders or a history of renal transplantation (12). The stages of chronic kidney disease are determined by the glomerular filtration rate (GFR), albuminuria and the underlying cause of CKD. Stage 1 is defined as an GFR>90mL/min/1.73m^2 but with other evidence of kidney damage (as mentioned above), stage 2 GFR 60-89mL/min/1.73^2, stage 3a GFR 45-59 mL/min/1.73m^2, stage 3b GFR 30-44 mL/min/1.73m^2, stage 4 GFR 15-29 mL/min/1.73m^2 and stage 5 GFR <15mL/min/1.73m^2 (12). Albuminuria is graded based on the albumin to creatinine ratio (ACR). Stage 1 ACR <30mg/g, stage 2 ACR 30-300mg/g and stage 3 ACR>300mg/g (12). The figure below from KDIGO highlights the categories and severity of CKD based on the biochemical markers mentioned earlier.

Figure 1 illustrating the prognosis of CKD by GFR and albuminuria category (12).

Prognosis of CKD by GFR and albuminuria category

Prognosis of CKD by GFR and Albuminuria Categories: KDIGO 2012				Persistent albuminuria categories Description and range		
				A1	A2	A3
				Normal to mildly increased	Moderately increased	Severely increased
				<30 mg/g <3 mg/mmol	30-300 mg/g 3-30 mg/mmol	>300 mg/g >30 mg/mmol
GFR categories (ml/min/ 1.73 m^2) Description and range	G1	Normal or high	≥90			
	G2	Mildly decreased	60-89			
	G3a	Mildly to moderately decreased	45-59			
	G3b	Moderately to severely decreased	30-44			
	G4	Severely decreased	15-29			
	G5	Kidney failure	<15			

Green: low risk (if no other markers of kidney disease, no CKD); Yellow: moderately increased risk; Orange: high risk; Red, very high risk.

The worldwide prevalence of CKD is estimated to be between 8-16% (13). Approximately 5-10 million people die annually from CKD (14). In 2015 alone, in the United States, approximately USD64 billion was spent on care of patients with CKD (14). The epidemiology of CKD in South Africa is unclear but estimates note that 5 million South Africans above the age of twenty have CKD (15). In South Africa, risk factors for CKD include traditional risk factors such as hypertension, diabetes mellitus, dyslipidaemia as well as additional factors such as infectious glomerulonephritis and HIV (16) for example, in Southern Africa the prevalence of CKD in HIV is estimated to be approximately 3% (17).

CKD is a risk factor for ASCVD with a 10-fold higher prevalence of ASCVD in this population, moreover the risk of ASCVD progresses as renal function declines (18). Of all deaths amongst

those with end stage renal disease (ESRD) at least 50% are related to ASCVD (18). Existing data illustrates that patients with CKD have a much higher incidence, prevalence and severity of ASCVD. A prospective study by *Jungers et al*. found the incidence of de novo cardiovascular disease in patients with CKD to be 41% in males and 19% in females, respectively (19). The incidence of myocardial infarction was 2.5 times higher in men with CKD whilst, the prevalence and severity of cardiovascular disease is increased with the deterioration in renal function (19). The Atherosclerosis in Communities Study (ARIC) highlighted that the incidence of cardiovascular disease was 4.8% in stage 2 CKD and increased to 9.3% in stage 3-4 CKD (20). The ARIC study also revealed the incidence of recurrent cardiovascular events increased with the decline in renal function (20). Individuals with stage 2 CKD had a recurrent event rate of 20.4% vs 28.4% in stage 3-4 CKD (p=0.02) (20). Analysis of the Canadian, multicentre, observational cohort study reported that 35% of patients with pre-existing cardiovascular disease and CKD developed a new event or deterioration of cardiovascular disease (20). The presence of cardiovascular disease also increased the risk of ESRD requiring dialysis by 50% (21). A meta-analysis of patients with CKD in the Framingham Heart Study illustrated that the prevalence cardiovascular disease was 64% higher than that of the general population (20). The prevalence of cardiovascular disease in the Canadian, multicentric prospective cohort was 38% (20). In a study of black South African patients with ESRD, the investigators found that half the patients with CKD, half the patients on haemodialysis and three quarters of the patients on continuous ambulatory peritoneal dialysis had ASCVD (22). This observational study at a single point in time could not address the issue of incidence, but the overall prevalence of cardiovascular disease was 19%. The incidence of cardiovascular disease in subjects with renal impairment published in the Framingham Heart Study by *Cullaton et al* is 19% (23). The Chronic Renal Insufficiency Cohort (CRIC) Study reported a prevalence of 22% with coronary artery disease and 10% with heart failure (24).

The risk factors and underlying mechanisms for development of ASCVD are unique in patients with CKD. GFR and proteinuria are independent predictors of cardiovascular risk and convey a higher risk of ASCVD than classic risk factors such as diabetes, dyslipidaemia, smoking and hypertension (25). Whilst, traditional risk factors such as hypertension, diabetes, smoking, obesity and dyslipidaemia are aggravated by CKD. Additional underlying mechanisms and non – traditional risk factors responsible for accelerated atherosclerotic disease in CKD include:

abnormalities in bone mineral metabolism, vascular calcification, uremic toxins, inflammation, oxidative stress and endothelial dysfunction (25). Reduced renal function and clearance of inflammatory mediators together with the increased generation of cytokines causes a state of systemic inflammation (25). The pro-inflammatory environment consists of circulating cytokines, C-reactive protein (CRP), monocytes and vascular cells (25). Raised high-sensitivity CRP (hsCRP) levels in patients with CKD have been associated with plaque deposition (25). In addition, uremic toxins stimulate macrophages causing damage to vascular walls, further contributing to the cycle of inflammation (25). At a cellular level, patients with CKD have been found to have extensive myocardial changes that include fibrosis, collagen deposition, hypertrophy and dilatation (26). These findings form the hallmark of the entity termed "uremic cardiomyopathy" (26). Up to one third of patients with CKD have left ventricular hypertrophy, and this increases to between 70-80% in patients with ESRD (26). Causes of cardiovascular mortality in CKD include sudden death, heart failure, stroke, myocardial infarction and peripheral vascular disease.

The pattern of dyslipidaemia in CKD comprises hypertriglyceridemia, reduced high-density lipoprotein cholesterol (HDL-C) and an elevated LDL-C (18). Quantitatively, CKD is associated with an accumulation of very low-density lipoprotein cholesterol (VLDL-C) and modest elevations of LDL-C, but with reduced LDL-C particle size. However, there are striking qualitative changes of lipoproteins in patients with CKD including glycation, oxidation and carbamylation, all of which may intensify the proatherogenic potential of these lipoproteins (25).

Statins and cholesterol absorption inhibitors are the mainstay of LLT in the public sector in South Africa. The mechanism of action of statins and ezetimibe in lowering LDL- C differ (27). Statins inhibit the rate limiting enzyme hydroxymethylglutaryl-coenzyme A (HMG-CoA) reductase resulting in reduced hepatic cholesterol production, and increased LDL receptor expression (27). This greater number of LDL-C receptors on the liver surface enhances uptake of LDL-C from the blood and ultimately reduces LDL-C plasma concentrations (27). Secondary cardiovascular benefits (pleotropic effects) include improved endothelial function, plaque stabilization, anti-inflammatory and immunomodulatory effects (27). The cholesterol absorption inhibitor Ezetimibe inhibits the absorption of cholesterol in the small intestine by

interacting with Niemann-Pick C1-like protein at the small intestine brush border (27). This results in decreased delivery of cholesterol to the liver, increased LDL receptor expression and LDL-C clearance from the bloodstream (27).

A number of trials have evaluated LLT in the setting of CKD. The Justification for the Use of Statins in Prevention: An Intervention Trial Evaluating Rosuvastatin (JUPITER) trial evaluated statin therapy with rosuvastatin 20mg in patients with low levels of LDL-C, that did not meet criteria for LLT, but had elevated levels of hsCRP. This trial included a subset of patients with stage 3 and 4 CKD, respectively (28). Subjects with renal dysfunction (GFR<60) were older, had more co-morbidities and worse cardiovascular outcomes as compared to those with normal renal function (28). Rosuvastatin was associated with a significant reduction in the primary endpoint in the group of patients with moderate CKD and this was similar to the reduction seen in patients with normal renal function (28). Notably, patients with moderate CKD had a greater absolute risk reduction in the primary endpoint compared to those with normal renal function (28). Unlike the JUPITER study, in The West of Scotland Coronary Prevention Study (WOSCOPS), evaluating primary prevention using 40 mg of pravastatin in patients with GFR<60 mL/min, there was no benefit with statin therapy (28). The Aggressive Lipid-Lowering Initiation Abates New Cardiac Events (ALLIANCE) study evaluated dyslipidaemia in patients with stage 3 CKD on atorvastatin and demonstrated a 28% reduction in the time to a first cardiovascular event (18). The Study of Heart and Renal Protection (SHARP) trial evaluated the impact of simvastatin 20mg and ezetimibe 10mg in pre-dialysis and dialysis requiring patients (29). The study concluded that there was a 17% risk reduction in major atherosclerotic events with a reduction in non-haemorrhagic stroke and arterial revascularization procedures in the treatment arm. The beneficial results of statin therapy were similar, regardless of whether participants were on dialysis or not (29).

The efficacy of LLT in patients already on renal replacement therapy (RRT) has not been well demonstrated. Only two trials have examined the efficacy of statin therapy in dialysis dependent patients with ESRD. The A Study to Evaluate the Use of Rosuvastatin in Subjects on Regular Haemodialysis: An Assessment of Survival and Cardiovascular Events (AURORA) trial studied the effect of 10mg of rosuvastatin on patients requiring haemodialysis and found no significant impact on cardiovascular outcomes despite a significant reduction in LDL-C (29).

The study did report a significant increase in the incidence of haemorrhagic stroke in diabetic patients (29). The results of the Deutsche Diabetes Dialysis Study (4D) study were similar concluding that 20mg of atorvastatin had no significant effect on cardiovascular outcomes and was associated with an increased risk of haemorrhagic stroke (29). These two studies suggest that as GFR declines statins have less of a role in reducing cardiovascular risk (30). As such, statins have not been shown to provide a clear benefit in dialysis requiring patients (30).

The concept of treating LDL-C to a particular target forms the backbone of all guidelines. Numerous trials have shown a relationship between reductions in LDL-C and a consequent reduction in cardiovascular events and mortality. The Treating to New Target Study (TNT) randomised patients with coronary heart disease to either high (80mg) or low dose (10mg) atorvastatin (31). The mean LDL-C in the high dose atorvastatin group was 2mmol/L and 2.6mmol/L in the low dose group (31). The overall incidence rate of major cardiovascular events was 8.7% and 10.9% in the high dose and low dose atorvastatin group, respectively ($p < 0.001$) (31). The Heart Protection Study (HPS) proved that lowering LDL-C below threshold from an LDL-C of 3.2mmol/L to less than 2 mmol/L reduced cardiovascular events by 24% ($p<0.0001$) and was associated with a reduction in overall mortality (12.9% in simvastatin arm vs 14.7% in placebo [p=0.0003]) (32). The Coronary Events in Cholesterol and Recurrent Events Trial (CARE) demonstrated a 24% decrease in coronary events with an LDL-C reduction from 4.5 mmol/L to 3.2 mmol/L (p-value=0.003) (33). The Scandinavian Simvastatin Survival Study (4S) found that LDL-C levels between 2.7mmol/L and 1.5mmol/L were associated with a lower incidence of coronary events (TNT STUDY) (31). Similar results were found in trials comparing LDL-C targets in patients with ischemic stroke. The Treat Stroke to Target (TST) compared a LDL-C target of less than 1.8mmol/L versus a level of 2.3-2.8mmol/L in patients with ischemic stroke and concluded that a lower LDL-C target was associated with a lower risk of cardiovascular events (9.6% LDL-C < 1.8mmol/L , 12.9% LDL-C 2.3-2.8mmol/L, p=0.015) (34). The risk of cerebral infarction and cerebral artery revascularisation was also reduced with a lower LDL-C level (6.7% LDL-C<1.8mmol/L, 9.1% LDL-C 2.3-2.8mmol/L p=0.046) (34).

The indications for LLT are based on a composite risk score assessing the presence of CKD, ASCVD complications and underlying risk factors. Patients are assigned a risk category ranging from low risk to very high-risk based on their estimated score. This method of risk

stratification prognosticates influences therapeutic decisions and forms the basis of the European Society of Cardiology (ESC) and South African dyslipidaemia guidelines (27, 35). The risk score and a patients untreated LDL-C determine which therapeutic intervention will be pursued and LDL-C targeted. Patients at low risk and normal levels are offered lifestyle modification before medical therapy, whilst patients at high-risk are offered concomitant lifestyle and LLT with lower LDL-C targets. Patients deemed to be high-risk include those with poorly controlled risk factors, CKD with a GFR less than 60mL/min and diabetics with target organ damage (27).

Current guidelines recommend LLT for all patients with CKD. However, recommendations across the guidelines are heterogenous. The ESC recommends initiating a statin with or without ezetimibe in all patients with stage 3-5 CKD that are non-dialysis dependent (27). In dialysis dependent patients already on a statin with or without ezetimibe, treatment should be continued (27). LLT is not routinely advised for patients on dialysis that have low ASCVD risk (27). Treatment targets are based on stratification scoring systems that divide patients into categories of risk. Patients at very high risk include CKD with a GFR under 30 ml/min/1.73m^2 (27). The therapeutic goal is to achieve an LDL-C less than 1.4 mmol/L and a 50% reduction in LDL-C from baseline (27). Patients with a GFR between 30-60 mL/min/1.73m^2 are considered high risk and a reduction of LDL-C to less than 1.8 mmol/L and 50% reduction from baseline is advocated (27). Patients considered to be at moderate risk include young patients with diabetes (type 1 diabetes age <35 years and type 2 diabetes age<50 years) with a duration of disease less than 10 years and no other ASCVD risk factors and a systematic coronary estimation score (SCORE) between 1 to 5% for 10 year ASCVD risk. In these patients, a target LDL-C of less than 2.6 mmol/L is advised. Patients at a low 10 year ASCVD risk based on a SCORE less than 1%, an LDL-C of less than 3mmol/L is recommended (27). In the 2020 South African dyslipidaemia guidelines, CKD is considered to be high risk if the eGFR is between 30-59 mL/min/1.73m^2 and very high risk if the eGFR is less than 30 mL/min/1.73m^2 (6). The recommended LDL-C targets are in keeping with those of the ESC guidelines. The recommended statin is based on the target LDL-C, starting LDL-C level and the percentage reduction in LDL-C (6). For patients at high to very high risk, high intensity statins such as atorvastatin 80mg or rosuvastatin 40mg are recommended (6). The American College of Cardiology (ACC) advises the use of a statin in all patients with CKD stage 1-5 not on

haemodialysis and patients post-transplant (36). The goal of lipid lowering treatment in patients at high risk of ASCVD is a 50% reduction in LDL-C from baseline (36). The ACC also recommends continuing statin treatment in those patients on dialysis who are currently receiving a statin, but advises against initiating statin therapy in patients requiring dialysis who are not already on LLT (36). The KDIGO guidelines recommend a statin for all CKD patients above the age of 50 years and in those under 50 years of age with the presence of an additional risk factor for coronary artery disease (18, 29). Similar to the ACC, statins are not recommended for patients with ESRD requiring dialysis unless they have already been initiated on treatment (29). The National Institute for Health and Care Excellence (NICE) guidelines recommend low dose atorvastatin 20mg in patients with CKD and eGFR measuring greater than 30mL/min/1.73m^2 and recommend the use of higher doses in patients with a GFR measuring less than 30mL/min/1.73m^2 in consultation with a nephrologist (37). The NICE guidelines do not address the role of statins in patients with CKD already on dialysis.

South Africa has a high burden of CKD and dyslipidaemia. However, there is little local data available regarding the prevalence, severity and therapy of dyslipidaemia in patients with CKD. The aim of this study is to examine the spectrum and treatment of dyslipidaemia in patients with CKD.

Chapter 2: Patients and Methods

2.1. Aim

To describe the prevalence, treatment and attainment of target levels of LDL-C in CKD patients in a South African hospital.

2.2. Study Objectives

Amongst a cohort of CKD patients attending the Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) renal clinic:

a) To determine the prevalence of dyslipidaemia
b) To determine the severity and pattern of dyslipidaemia
c) To determine the proportion of patients on LLT
d) To determine whether patients on LLT are at appropriate targets according to the 2019 ESC lipid guidelines
e) To evaluate the type and dose of LLT used to treat dyslipidaemia

2.3. Study Design

A cross-sectional retrospective observational study.

2.4. Study Setting

The Renal Clinic at CMJAH. The clinic sees approximately 350 patients monthly and approximately 4000 patients annually. Patients are either referred to the clinic from surrounding clinics and district hospitals or from specialist departments within CMJAH. The clinic sees a spectrum of CKD, including medical and non-medical aetiologies. Patients attending the renal clinic have routine bloods and follow up visits.

2.5 Definitions

CKD**:** Based on the KDIGO guidelines (12) was defined as any structural or functional renal abnormality persisting for more than three months. This includes albuminuria, electrolyte imbalances, tubular disorders, abnormal urine sediment, history of renal transplantation and abnormalities detected on imaging or histology. A reduction in GFR to less than 60ml/min/1.73^2 is also a criterion.

2.5.1. ASCVD risk stratification

Very high risk: defined according to the latest ESC guidelines (27), as the presence of ASCVD on imaging or clinically, risk SCORE greater than 10%, familial hypercholesterolemia with ASCVD or a major risk factor, severe CKD with a GFR below 30mL/min or diabetes mellitus with either target organ damage, 3 or more major risk factors, early onset or duration of type 1 greater than 20 years. In this category the LDL-C treatment target is less than 1.4 mmol/L and a 50% reduction from baseline LDL-C.

High risk: defined according to the latest ESC guidelines (27), as a risk SCORE between 5 and 10%, elevated total cholesterol greater than 8mmol/L Or LDL-C greater than 4.9 mmol/L, blood pressure greater than 180/110 mmHg, familial hypercholesterolemia without major risk factors, CKD with a GFR between 30-59 mL/min and diabetes mellitus without target organ damage and a duration greater than 10 years or with additional risk factors. In this category the target LDL-C level is less than 1.8 mmol/L and a 50% reduction from baseline LDL-C.

Moderate risk: defined according to the latest ESC guidelines (27), as a risk SCORE between 1 and 5 percent, type 1 diabetes diagnosed below the age of 35 with a duration of disease less than 10 years in the absence of any other risk factors, type 2 diabetes diagnosed below the age of 50 with a duration of disease less than 10 years in the absence of any other risk factors. In this category the target LDL-C level is less than 2.6 mmol/L.

Low risk: defined according to the latest ESC guidelines (27), as a risk score less than 1%. In this category the target LDL-C level is less than 3 mmol/L.

For this study, dyslipidaemia was defined as an elevated total cholesterol (TC) (>5 mmol/L), LDL-C (> 3mmol/L), or triglycerides (TG) (>1.7mmol/L) and a HDL-C (<1.0 mmol/L in males and <1.2 mmol/L in females) (38).

Severe dyslipidaemia was defined as total cholesterol greater than 7.5 mmol/L or a LDL-C greater than 4.9 mmol/L (38).

2.6 Study population

CMJAH is a quaternary hospital situated in Parktown in Johannesburg. The hospital serves a multitude of patients from a variety of backgrounds including black African, Asian, Indian, Caucasian and mixed race individuals.

a. Inclusion Criteria
    i. Patients with CKD, regardless of stage, attending the CMJAH Renal Clinic
    ii. Patients older than 18 years of age
    iii. A recent lipogram performed at least within the previous year from date of data extraction
    iv. Attended the Renal Clinic between 1 July 2019 to 31 July 2020.

b. Exclusion Criteria
    v. Insufficient clinical records available for data collection
    vi. Those attending the clinic for follow up after Acute Kidney Injury defined by the KDIGO guidelines (39)
        I. Increase in serum creatinine by more than 1.5 times the baseline, which is known to have occurred in the last 7 days
        II. Increase in serum creatinine greater than 26.5 umol/L within 48 hours
        III. Urine volume less than 0.5 ml/kg/h for 6 hours
        IV. Normalisation or recovery of serum creatinine following discharge

2.7 Sampling Method

All patients who attended the renal clinic with CKD and fulfilling the inclusion criteria without evidence of exclusion criteria will be eligible for enrolment.

2.8 Measurement Instruments/Tools

Patient clinic files were used to obtain patients age, gender, race, weight, height and whether a patient is on RRT. Haematology and biochemistry results were extracted and analysed. These included: haemoglobin, mean corpuscular volume, albumin, urea and electrolytes, creatinine, eGFR, corrected calcium, magnesium, phosphate, TC, LDL-C, HDL-C, TG, HbA1c and urine albumin to creatinine ratio or urine protein to creatinine ratio. Co-morbidities including diabetes, hypertension, smoking, alcohol use, HIV status, obesity, dyslipidaemia and gout were noted. Complications such as stroke, peripheral vascular disease and coronary artery disease were recorded. The use of immunosuppressive agents, steroids and LLT were noted in addition to the dose and duration of treatment. The data extraction form was used for reviewing and extracting data from the patients file is attached as Appendix 1.

2.9. Sample Size

A total of 310 patients records were analysed, however, only 250 records had adequate data and met the inclusion criteria for this study. Data was extracted over a period of 3 months. This sample size provided 80% power to measure a prevalence of dyslipidaemia of between 50-60% assuming α-level of 0.05 and that 30% of patients did not have lipograms documented in their files.

2.10. Ethics

Ethics approval was submitted to the Human Research Ethical Committee of the University of the Witwatersrand and approved. See approval letter in Appendix B. The retrospective design of the study, with all the data collected from clinic files, did not require individual patient consent. Consent for access to patient files was obtained from the Head of the Renal Clinic, Head of Department of Medicine and hospital manager at CMJAH. Data was only made

available to primary investigator and supervisors. All data was anonymised as each data sheet (Appendix A) was assigned a study number and no identifiable characteristics were recorded.

2.11. Funding

The study was self-funded by the primary investigator and the only cost incurred was the photocopying of data sheets.

2.12. Statistics

Completed data extraction forms were entered into an Excel® spreadsheet and subsequently exported into Stata 14.2 for analysis. The demographic and clinical profiles of patients included were described using descriptive statistics- frequencies and proportions for categorical data as well medians and interquartile ranges for continuous variables. Data analysis methods for the different objectives are described below:

I *To determine the prevalence of dyslipidaemia*: the prevalence of dyslipidaemia was determined as the number of patients with CKD who had dyslipidaemia at the most recent lipogram divided by the total number of patients with CKD included in the analysis. The prevalence was determined as a percentage with a 95% confidence interval. The prevalence of dyslipidaemia was determined by age, gender, presence of other co-morbidities and whether lipid lowering agents were being utilized or not. Dyslipidaemia was determined as LDL-C > 3.0 OR LDL-C > 1.8 and CVD High Risk OR LDL-C >1.4 and CVD very high risk. Severe dyslipidaemia was determined as having TC≥7.5mmol/L OR LDL-C≥5 mmol/l OR TG≥4.5mmol/l.

II *To determine the severity and pattern of dyslipidaemia:* the pattern of dyslipidaemia was determined from the distribution of TGs, HDL-C and LDL-C levels among patients with CKD.

III *To determine the proportion of patients on lipid lowering therapy:* the proportion of patients taking lipid lowering drugs was determined as the number of patients taking LLT as a fraction of all patients with CKD enrolled. The proportion was calculated as a percentage with a 95% confidence interval.

IV *To determine whether patients on lipid lowering therapy are at appropriate targets according to the 2019 ESC/EAS Guidelines for the management of dyslipidaemias*. The proportion of patients receiving lipid lowering drugs at the appropriate target level was determined as the number of patients taking LLT and having a lipogram in the desired range as a fraction of all patients on LLT. Binary logistic regression was used to determine factors associated with meeting the 2019 ESC/EAS targets for dyslipidaemia.

V *To evaluate the type and dose of LLT used to treat dyslipidaemia*: the number and percentage of patients taking different types and doses of LLT was determined. These were determined as percentages.

Chapter 3: Results

3.1 Baseline clinical and biochemical characteristics

The records of 310 patients were reviewed. 250 were included in the final analysis and 60 records were excluded from the study due to missing lipogram data (n = 28, 46%), failure to have attended the clinic in the preceding year (n = 18, 30%) or failure to meet the age criteria (n = 14, 24%). The median age of patients attending the renal clinic was 58 years (interquartile range [IQR]: 46-69; p=0.032) (Table 1). Regarding the racial demographics of this cohort, the majority of participants in the study were black Africans (64%), followed by Caucasian (23%) and Indians (9%) and mixed race (4%). When considering the underlying aetiology of CKD, hypertension was the leading cause (76.4%) followed by type two diabetes (32%), non-steroidal anti-inflammatory drug use (4%) and lupus nephritis (3.6%) (figure 2). Hypertension (83%), diabetes (35%) and obesity (23%) were the most common co-morbidities, followed by cardiac disease (19%) and HIV infection (31%) (Figure 3).

Table 1 : Description of patient cohort stratified by taking LLA (N=250)

Characteristic	On LLA n=169	Not on LLA n=81	Total n=250	p-value
Age in years (median, IQR)	59 (48- 71)	54 (39- 66)	58 (46 – 69)	0.032
Age ≥50 years				
No	45 (26.6)	31 (38.3)	76 (30.4)	0.061
Yes	124 (73.4)	50 (61.7)	174 (69.6)	
Ethnicity				
Black African	101 (59.8)	60 (74.1)	161 (64.4)	
Coloured	5 (3.0)	4 (4.9)	9 (3.6)	0.069
Indian	19 (11.2)	4 (4.9)	23 (9.2)	
White/ Other	44 (26.0)	13 (16.1)	57 (22.8)	
Weight (kg) (median, IQR)	82.5 (69.4- 95.5)	76.7(63.5 – 88)	81 (68- 93)	0.014
Year of first visit to renal clinic (median, IQR)	2018 (2016- 2019)	2019 (2017 -2019)	2018 (2017- 2019)	0.014
Renal replacement therapy	9 (5.3)	1 (1.2)	10 (4.0)	0.122
Risk status				
Very High risk	100 (59.2)	52 (64.2)	152 (60.8)	
High risk	55 (32.5)	23 (28.4)	78 (31.2)	0.747
Low/ Moderate risk	14 (18.3)	6 (7.4)	20 (8.0)	

CKD stage				
1	10 (6.0)	6 (7.4)	16 (6.5)	
2	6 (3.6)	1 (1.2)	7 (2.8)	0.157
3a	22 (13.2)	7 (8.6)	29 (11.7)	
3b	51 (30.5)	17 (21.0)	68 (27.4)	
4	49 (29.3)	26 (32.1)	75 (30.2)	
5	29 (17.4)	24 (29.6)	53 (21.4)	
Type of LLA				
Simvastatin	148 (87.5)	--	148 (87.5)	
Atorvastatin	18 (10.7)	--	18 (10.7)	---
Simvastatin then Atorvastatin	2 (1.2)	--	2 (1.2)	
Simvastatin then Bezafibrate	1 (0.6)	--	1 (0.6)	

Figure 2: Frequency of causes of Chronic Kidney Disease (n=250)

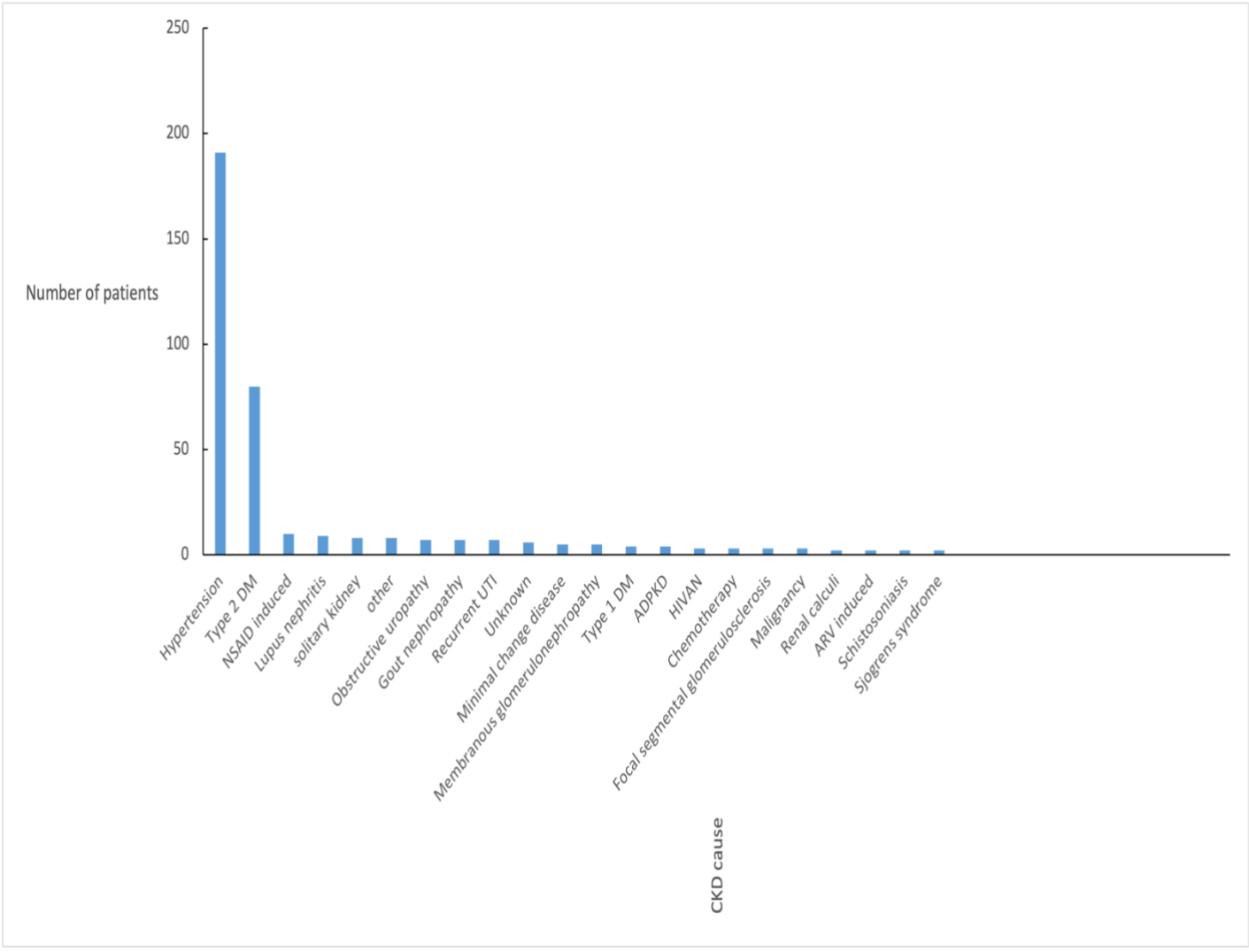
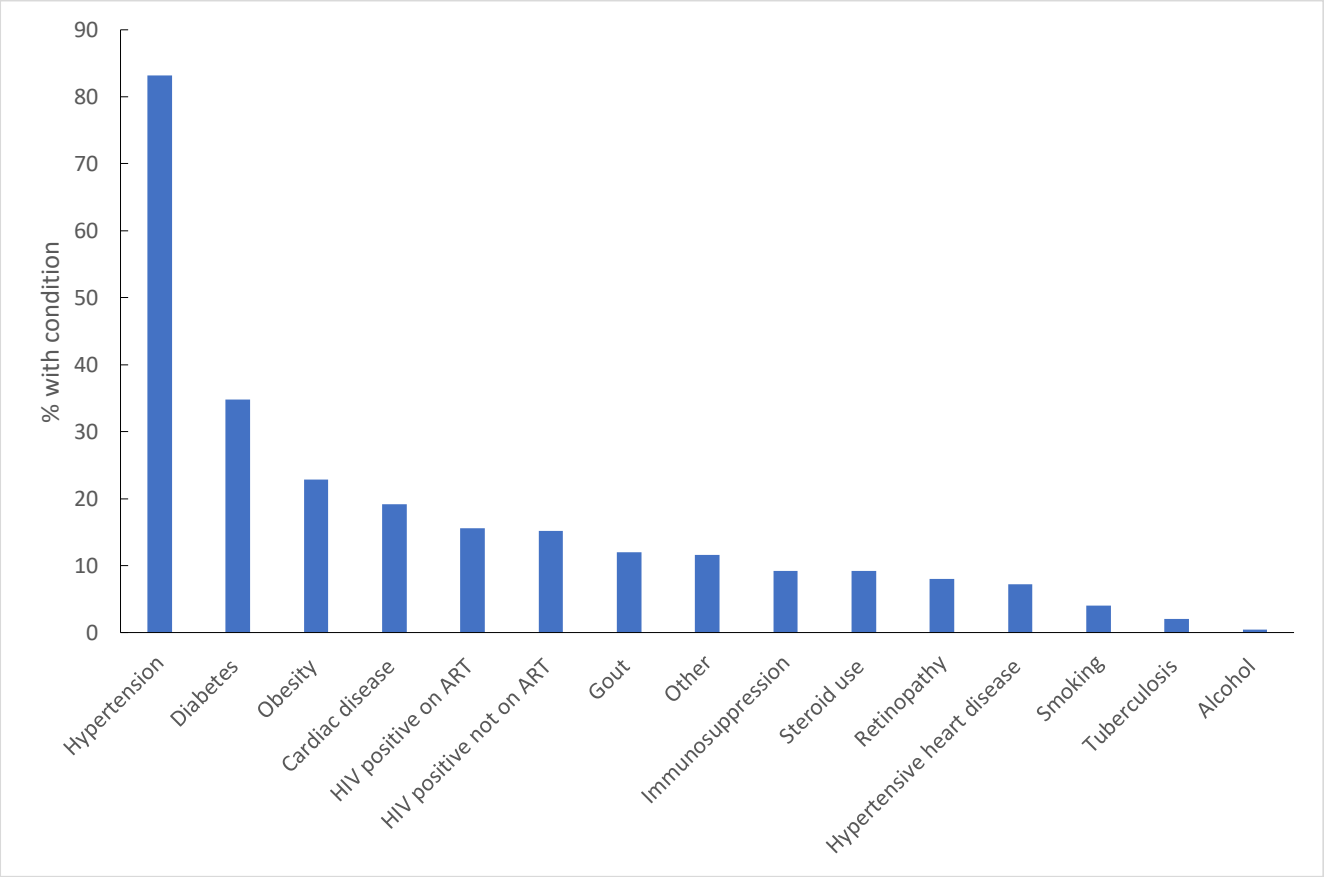


Figure 3: Prevalence of underlying co-morbidities (n=250)



The majority of patients attending the renal clinic were males (50.4%) (Table 2). Males were younger than females (male median age 57.5 vs 58.5 for females). More black African, Indian and mixed race females attended the renal clinic, with the exception of white females who comprised 19% as compared to 26% of white males. Males had a marginally higher cardiovascular risk profile (very high-risk 61% vs females 60.5%, and high-risk 31% vs females 30%). The majority of patients receiving LLT were males (72%) as opposed to females (62%).

Table 2: Description of patients who had record review and data abstraction stratified by biological sex (n=250)

Characteristic	Female n=124 (49.6%)	Male n=126 (50.4%)	Total n=250	p-value
Age in years (median, IQR)	58.5 (46 – 69)	57.5 (46- 69)	58 (46 – 69)	0.919
Age ≥50 years				
No	35 (28.2)	41 (32.5)	76 (30.4)	0.458
Yes	89 (71.8)	85 (67.5)	174 (69.6)	
Ethnicity				
Black African	81 (65.3)	80 (63.5)	161 (64.4)	
Coloured	7 (5.7)	2 (1.6)	9 (3.6)	0.237
Indian	12 (9.7)	11 (8.7)	23 (9.2)	
White/ Other	24 (19.4)	33 (26.2)	57 (22.8)	
Most recent weight recorded in kilograms (median, IQR)	79.8 (64.7- 90)	83 (70- 90)	81 (68- 93)	0.017
Year of first visit to renal clinic (median, IQR)	2018 (2017- 2019)	2019 (2017- 2019)	2018 (2017- 2019)	0.381
On renal replacement therapy	2 (1.6)	8 (6.4)	10 (4.0)	0.056
Risk profile				
Very High risk	75 (60.5)	77 (61.1)	152 (60.8)	
High risk	38 (30.7)	40 (31.8)	78 (31.2)	0.877
Low/ Moderate risk	11 (8.9)	9 (7.1)	20 (8.0)	
CKD stage*				
1	10 (8.1)	6 (4.8)	16 (6.5)	
2	3 (2.4)	4 (3.2)	7 (2.8)	
3a	15 (12.2)	14 (11.2)	29 (11.7)	0.811
3b	33 (26.8)	35 (28.0)	68 (27.4)	
4	39 (31.7)	36 (28.8)	75 (30.2)	
5	23 (18.7)	30 (24.0)	53 (21.4)	
On LLA	77 (62.1)	92 (72.0)	169 (67.6)	0.065
Type of LLA				
Simvastatin	68 (88.3)	80 (87.0)	148 (87.5)	
Atorvastatin	8 (10.4)	10 (10.9)	18 (10.7)	0.371
Simvastatin/ Atorvastatin	1 (1.3)	1 (1.1)	2 (1.2)	
Simvastatin/ Bezafibrate	0	1 (1.1)	1 (0.6)	

*data available for 248/250 patients

The median haemoglobin of patients in the cohort was 10.5g/dL (IQR:10.5-13.8). The median urea was 10,9 mmol/L (IQR: 7.9-17), creatinine 178 umol/L (IQR: 129-292) and estimated GFR 29 mL/min/1.73m^2 (IQR: 17-41) . The majority of patients (n=75 [30%]) were stage 4 CKD, followed by stage 3 (n=68 [27%]) and stage 5 (n=53 [21%]). The mean haemoglobin A1c was 6.1% and urine PCR 0,05 g/mmol (Table 3).

Table 3: Haematological and blood chemistry profile of patients

Investigation	**n**	**Result (median, IQR)**
Haemoglobin (g/dL)	249	12.2 (10.5- 13.8)
Mean Corpuscular Volume (fL)	242	89.4 (84.8- 93.4)
Sodium (mmol/L)	249	141 (138- 143)
Potassium (mmol/L)	249	4.4 (4- 5)
Chloride (mmol/L)	249	103 (99- 105)
Bicarbonate (mmol/L)	248	21 (18- 23)
Urea (mmol/L)	249	10.9 (7.9- 17)
Creatinine (umol/L)	249	178 (129- 292)
Estimated GFR (mL/min/1.73m^2)	248	29 (17- 41)
Corrected Calcium (mmol/L)	249	2.28 (2.16- 2.39)
Magnesium (mmol/L)	245	0.86 (0.79- 0.94)
Phosphate (mmol/L)	248	1.1 (0.94- 1.36)
Haemoglobin A1c (%)	207	6.1 (5.6- 7.3)
Urine protein creatinine ratio (g/mmol)	235	0.05 (0.014- 0.146)
Albumin (g/L)	209	41 (37- 45)
CKD Stage**		
1	248	16 (6.5)
2		7 (2.8)
3a		29 (11.7)
3b		68 (27.4)
4		75 (30.2)
5		53 (21.4)

** n (%)

In this study, the prevalence of dyslipidaemia was 84%. Males and females were almost equally affected (85% vs 81%, respectively), the majority were above the age of 50 (87%, p=0.015), classified as very high-risk (92%, p=<0.001), and had HIV infection treated with ART (87%). Dyslipidaemia was most prevalent amongst the mixed race group (88.9%), followed by Indians (87%), and black Africans (83%). Dyslipidaemia was least prevalent in Caucasian patients (82.4%). Patients not receiving LLT had a high prevalence of dyslipidaemia (84%). The prevalence of dyslipidaemia increased with the progression of CKD. The prevalence of dyslipidaemia in patients with stage 1 CKD was 12.5%, stage 2 71%, stage 3a 96.6%, stage 3b 77.9%, stage 4 92% and 96.2% in patients at stage 5 (p=<0.001) (Table 4).

Table 4: Prevalence of dyslipidaemia stratified by different patient characteristics

Characteristic	**n/N**	**% Prevalence of dyslipidaemia (95% CI)**	**X^2 p-value**
Gender			
Female	101/124	81.5 (73.6- 87.4)	0.363
Male	108/126	85.7 (78.4- 90.8)	
Age ≥50 years			
No	57/76	75.0 (64.0- 83.5)	0.015
Yes	152/174	87.5 (81.5- 91.6)	
Ethnicity			
Black African	134/161	83.2 (76.6 - 88.3)	
Coloured	8/9	88.9 (46.6- 98.7)	0.931
Indian	20/23	87.0 (65.7- 95.9)	
White/ Other	47/57	82.4 (70.2 – 90.4)	
Risk profile			
Low/ Moderate	4/20	20.0 (7.5- 43.6)	
High risk	64/78	82.1 (71.8 – 89.1)	<0.001
Very High Risk	141/152	92.8 (87.3 - 96.0)	
CKD stage			
1	2/16	12.5 (3.0- 39.9)	
2	5/7	71.4 (29.6- 93.7)	
3a	28/29	96.6 (78.5- 99.5)	<0.001
3b	53/68	77.9 (66.4- 86.3)	
4	69/75	92.0 (83.2- 96.4)	
5	51/53	96.2 (85.9- 99.1)	
HIV positive on ART			
No	123/153	82.9 (77.2 - 87.5)	0.511
Yes	34/89	87.2 (72.3 - 94.6)	
On LLT			
No	68/81	84.0 (74.2- 90.5)	0.917

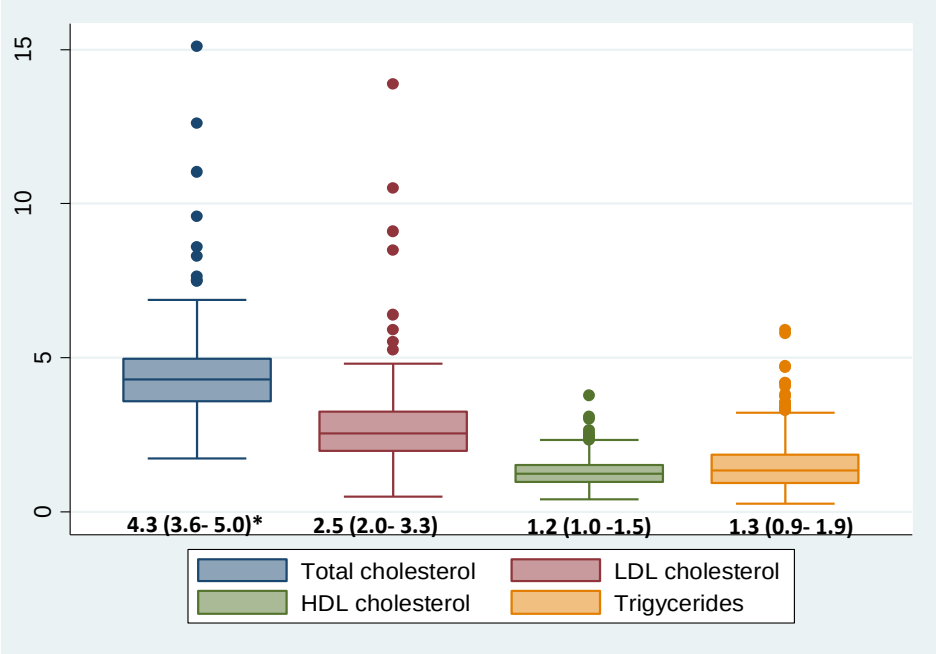
Yes	141/169	83.4 (77.0- 88.3)	

ART= antiretroviral therapy; CKD= Chronic Kidney Disease; LLA= lipid lowering therapy

The box and whisker plots (Figure 4) illustrate the patterns of dyslipidaemia in this study. The median TC was 4.3mmol/L, LDL-C 2.5mmol/l, HDL-C 1.2mmol/L and TGs 1.3 mmol/L. In the low-moderate risk category the median TC was 3.6mmol/L and LDL-C 2mmol/L. The median TC and LDL-C were greater in the very high-risk and high-risk group compared to the low-moderate group. The HDL-C was higher in the low-moderate risk group and lower in the high to very high-risk groups. There was no clear pattern associated with TGs.

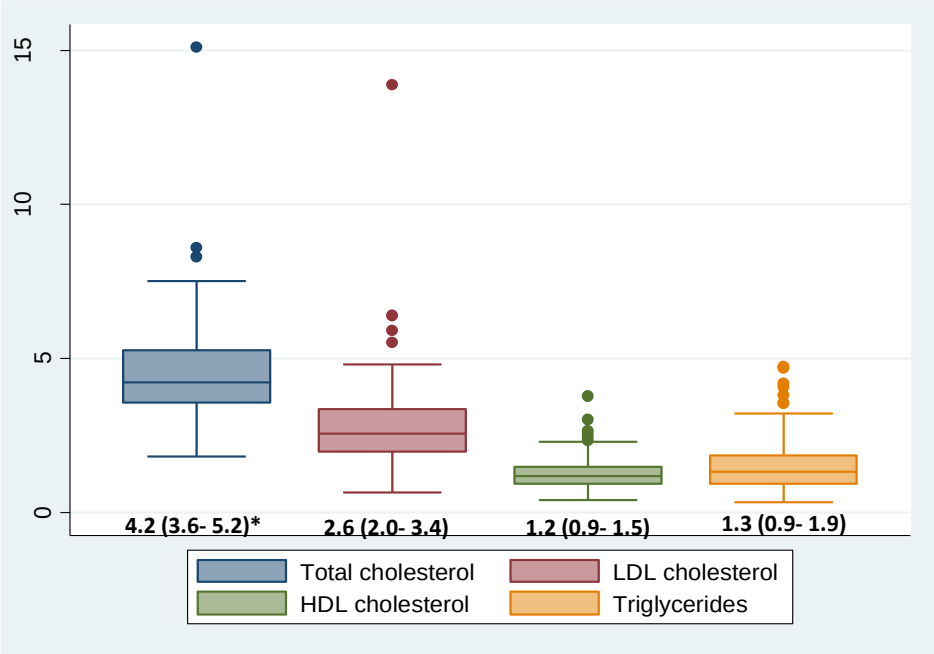
Figure 4: Median values of total cholesterol, LDL-cholesterol, HDL- cholesterol and triglycerides at most recent lipogram overall (A) and by cardiovascular risk profile (B, C, D)

A -Overall



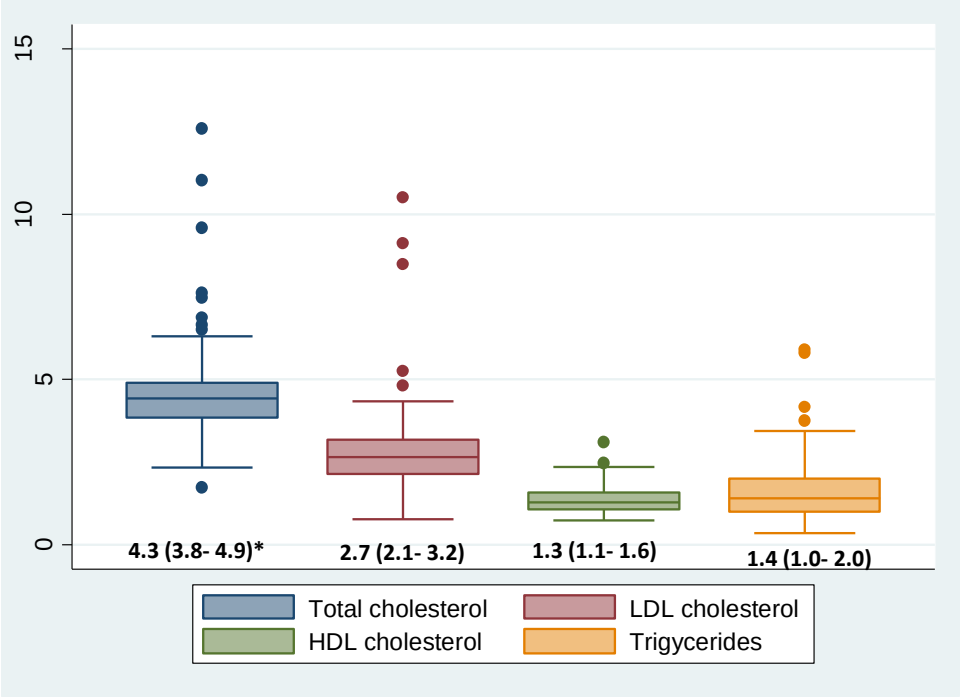
*median (IQR)

B- Very high-risk



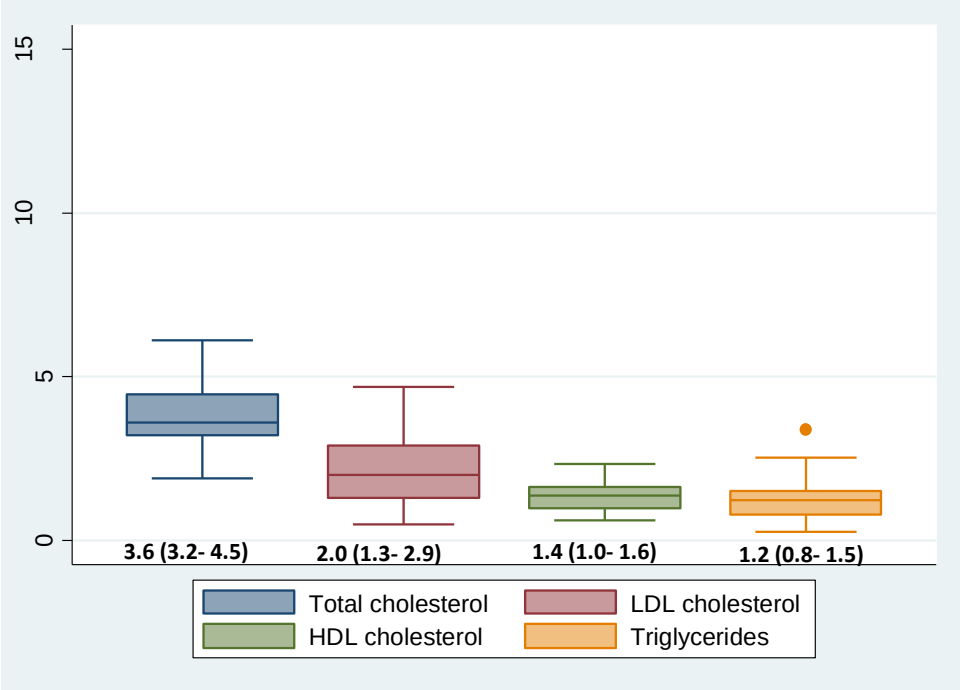
*median (IQR)

C- High-risk



*median (IQR)

D- Low- moderate risk



*median (IQR)

In this study, 5.6% of patients met the criteria for severe dyslipidaemia. Severe dyslipidaemia was more prevalent amongst females(p=0.258), Indians (p=0.093), high-risk participants (0.207) and those with CKD stage 2/3a (p=0.607). HIV positive patients on ART (p=0.536) and those uninitiated on LLT were also at increased risk of severe dyslipidaemia (p=0.78)(Table 5).

Table 5: Prevalence of severe dyslipidaemia stratified by different patient characteristics

Characteristic	**n/N**	**% Prevalence of dyslipidaemia (95% CI)**	**X^2 p-value**
Gender			
Female	101/124	81.5 (73.6- 87.4)	0.363
Male	108/126	85.7 (78.4- 90.8)	
Age ≥50 years			
No	57/76	75.0 (64.0- 83.5)	0.015
Yes	152/174	87.5 (81.5- 91.6)	
Ethnicity			
Black African	134/161	83.2 (76.6 - 88.3)	0.931
Coloured	8/9	88.9 (46.6- 98.7)	
Indian	20/23	87.0 (65.7- 95.9)	
White/ Other	47/57	82.4 (70.2 – 90.4)	

Risk profile			
Low/ Moderate	4/20	20.0 (7.5- 43.6)	<0.001
High risk	64/78	82.1 (71.8 – 89.1)	
Very High Risk	141/152	92.8 (87.3 - 96.0)	
CKD stage			
1	2/16	12.5 (3.0- 39.9)	<0.001
2	5/7	71.4 (29.6- 93.7)	
3a	28/29	96.6 (78.5- 99.5)	
3b	53/68	77.9 (66.4- 86.3)	
4	69/75	92.0 (83.2- 96.4)	
5	51/53	96.2 (85.9- 99.1)	
HIV positive on ART			
No	123/153	82.9 (77.2 - 87.5)	0.511
Yes	34/89	87.2 (72.3- 94.6)	
On LLA			
No	68/81	84.0 (74.2- 90.5)	0.917
Yes	141/169	83.4 (77.0- 88.3)	

ART= antiretroviral therapy; CKD= Chronic Kidney Disease; LLA= lipid lowering agent

3.2 **Utilisation of statin therapy**

The most common LLT used was simvastatin (87%) at a median dose of 20mg (Table 6). 10% of patients received atorvastatin at a median dose of 30mg. Just 2 patients had their LLT adjusted from simvastatin to atorvastatin and only one patient received simvastatin and a fibrate.

Amongst the 81 patients not on LLT, 86% met criteria for the use of LLT. By risk categories, two-thirds (64%) were high-risk, 28% very high-risk and 7% low-moderate risk (Table 6). In the high-risk group, just 9.6% had an LDL-C level at the appropriate target of 1.8 mmol/L or less and no patients met the LDL-C target of 1.4mmol/L or less. 40% had an LDL-C that was between 3-4.9 mmol/L, 35% had an LDL-C level that measured between 1.8-2.64 mmol/L. All 6 patients at low to moderate risk were at the appropriate LDL-C target.

Table 6: Doses of LLA among those taking LLA (N=169)

LLA	**Number taking**	**Median dose in mg (IQR)**	**Mean dose in mg (SD)**
Simvastatin	148	20 (20- 20)	21.2 (6.4)
Atorvastatin	18	30 (20- 40)	38.9 (24.2)
Bezafibrate	1	400	400

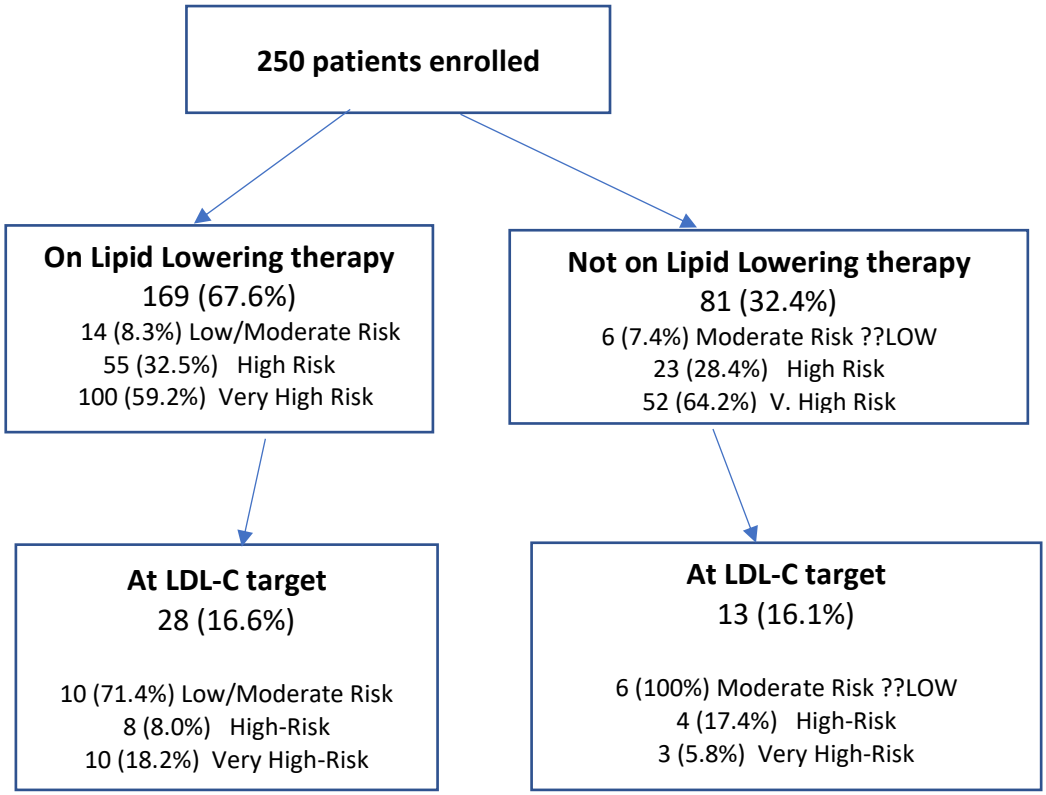
Table 7: Cardiovascular risk profile and LDL-C levels among those not on LLA (N=81)

Risk profile	LDL-C levels						
	<1.4 mmol/L	**1.4- <1.84 mmol/L**	**1.8- <2.64 mmol/L**	**2.6- <3.04 mmol/L**	**3.0- <4.9 4mmol/L**	**≥4.94 mmol/L**	**N**
Low/moderate n(%)	2 (33.3)	2 (33.3)	2 (33.3)	0	0	0	6
High n(%)	3 (5.8)	2 (3.9)	15 (28.9)	9 (17.3)	21 (40.4)	2 (3.9)	52
Very high n(%)	0	4 (17.4)	A 8 (34.8)	6 (26.1)	5 (21.7)	0	23
All	5 (6.2)	8 (9.9)	25 (30.9)	15 (18.5)	26 (32.1)	2 (2.5)	81

3.3 Analysis of lipid profiles

Of the 250 patients, 67% were on LLT. Of those on LLT, 59% were classified as very high-risk, 32.5% as high-risk and 8.3% as low to moderate risk based on the ESC risk score (Table 1). Of those not on LLT 62.4% were very high risk, 28.4% high risk and 7.4% low to moderate risk respectively (Table 1). 84% of patients on LLT did not meet the recommended target LDL-C for their risk group. Of the 16% whose LDL-C levels were at target, 10 participants were very high-risk and 8 were high-risk (Figure 5).

Figure 5: Summary of LLT and target LDL-C levels in the overall cohort



3.4 **Predictors of achieving LDL-C target**

Univariate and multivariate analysis of the factors that determined whether patients were at target LDL-C levels was performed (Table *7*). Only cardiovascular risk status predicted the likelihood of achieving the recommended target LDL-C level following both univariate and multivariate analysis.

Table 8: Factors associated with meeting 2019 ESC/EAS LDL-C targets among patients attending renal clinic at CMJAH, N=250

Variable	Met LDH-C target n/N (%)	Univariable OR (95% CI)	p-value	Multivariable OR (95% CI)	p-value
Age ≥50 years					
No	19/76 (25.6)	1.00			
Yes	22/174 (12.6)	0.43 (0.22-0.86)	**0.017**	0.92 (0.37-2.26)	0.853
Gender					
Female	23/124 (18.6)	1.00			
Male	18/126 (14.3)	0.73 (0.37-1.44)	**0.364**	0.77 (0.34-1.70)	0.511
Ethnicity					
Black African	27/161 (16.8)	0.95 (0.43-2.10)	0.894	--	--
Coloured/ Indian	4/32 (12.5)	0.67 (0.19-2.34)	0.532	--	--
White/ Other	10/57 (17.5)	1.00			
Year of first visit to renal clinic					
≥2018	27/170 (15.9)	1.00		--	--
<2018	14/80 (17.5)	1.12 (0.53-2.28)	0.747	--	--
CVD risk status					
Very High-risk	11/152 (7.2)	0.02 (0.01-0.07)	**<0.001**	0.03 (0.01-0.11)	**<0.001**
High-risk	14/78 (18.0)	0.05 (0.02-0.19)	**<0.001**	0.07 (0.02-0.27)	**<0.001**
Low/ Moderate risk	16/20 (80.0)	1.00			
On LLA					
No	12/81 (16.1)	1.00		--	--
Yes	28/169 (16.6)	1.04 (0.51-2.13)	0.917	--	--
On ISD					
No	29/219 (11.9)	1.00			
Yes	15/31 (48.4)	6.96 (3.08-15.71)	**<0.001**	1.83 (0.59-5.71)	0.293
HIV positive					
No	36/211 (17.1)	1.00		--	--
Yes	5/39 (12.8)	0.71 (0.26-1.95)	0.513	--	--

Year of lipogram					
≤2019	19/167 (17.8)	1.00		--	--
2020	22/143 (15.4)	0.84 (0.43-1.65)	0.616	--	--
Duration on LLA					
<3 years	7/60 (11.7)	1.00			
≥3years	12/68 (17.7)	1.62 (0.59-4.43)	0.345	--	--
Unknown	22/122 (18.0)	1.67 (0.67-4.15)	0.274	--	--

OR= odds ratio; aOR = adjusted odds ratio; CVD= cardiovascular; LDL-C= low density lipoprotein cholesterol; LLA= Lipid lowering drugs; ISD= Immunosuppressive drugs;

Chapter 4: Discussion

In this retrospective analysis of 250 patients attending the specialist renal clinic at the CMJAH, a high prevalence of dyslipidaemia was noted. In addition, the majority of patients had high LDL-C levels necessitating the introduction of LLT. Of concern, despite a large proportion of patients who met ESC guidelines for LLT, 32% remained untreated. Furthermore, of those who were treated with a statin, just 16% met the appropriate LDL-C target for their respective risk group.

4.1 Prevalence of dyslipidaemia

The prevalence of dyslipidaemia in our study was 83.6%. Dyslipidaemia was more common in males, the elderly, non-Caucasian patients and patients with HIV infection on ART. This study revealed that the prevalence of dyslipidaemia increased with deterioration in GFR from CKD stage 1 to 5. In the NHANES study the prevalence of dyslipidaemia in patients with CKD was 53.9% and increased from 45% from stage 1 ESRD to 67.8% in stage 4 (40). The results indicate a higher prevalence of dyslipidaemia from stage 2 to 4 CKD when compared with the NHANES study. Furthermore, the prevalence of dyslipidaemia was higher in this study despite a lower median age than in the NHANES study (median age of 58 years old vs 64.2 years old) (40). Analysis of the PREdialysis PAtient REcord-2 (PREPARE 2) cohort similarly revealed the majority of patients with dyslipidaemia and CKD had a mean age of 66 years and the majority were males (71%) (41). The prevalence of dyslipidaemia in the PREPARE 2 cohort was 66% (41). The prevalence of dyslipidaemia is also higher in the current study than previously described in local literature. In a cross-sectional study by *Madala et al.* examining CKD in rural Kwa-Zulu Natal, the prevalence of dyslipidaemia was 39.1% (42). Unlike the findings in this study, the prevalence of dyslipidaemia was significantly lower in males, 29.2% and 47.9% in females compared to our study in which dyslipidaemia was noted in 85.7% in males and 81.5% in females (42).

The high prevalence of dyslipidaemia in this study may be due to numerous factors. Since CMJAH is the only quaternary hospital in Gauteng, most patients are managed at peripheral hospitals where infrequent lipogram testing may result in fewer patients detected with dyslipidaemia. The majority of patients attending CMJAH renal clinic had severe renal

impairment with a mean eGFR of 29 mL/min/1.73^2. This alone would place these patients at high risk for ASCVD, apart from the other multiple comorbidity that that they may have had. More than two thirds of patients attending the renal clinic were deemed to be high-risk with approximately one third very high-risk. The majority of patients in this study were non-Caucasian, in whom it is traditionally believed that dyslipidaemia is infrequent. A meta-analysis conducted by *Noubiap et al.* published in the Lancet found a high prevalence of dyslipidaemia in African adults, especially those with cardiovascular risk factors such as hypertension, diabetes and HIV (43). Furthermore, the cohort of patients included in this study were predominantly urban residents in whom dietary and other factors such as access to fast food and a sedentary lifestyle may have resulted in much higher cholesterol levels than in rural populations.

4.2 Patterns of dyslipidaemia

This study demonstrated the following pattern of dyslipidaemia: an elevated LDL-C relative to the treatment target and reduced HDL-C especially in the higher risk categories. This pattern of dyslipidaemia is similar other studies examining dyslipidaemia in CKD. The PREPARE -2 study found patients with CKD had low levels of HDL-C and elevated levels of TC, LDL-C and TGs (41). The TG levels in this study were not elevated. The aetiology is unclear, but may be related to underlying autoimmune disease, thyroid disease, malabsorption, HIV or malnutrition.

4.3 Risk factors for dyslipidaemia

This study revealed that the leading risk factors for dyslipidaemia were similar to those previously described in the literature. Hypertension, diabetes and obesity were the top three modifiable risk factors for dyslipidaemia in this study. One third of patients in this study had hypertension, 14% had diabetes and 9% were obese. 31% of patients were HIV positive, only half of whom received ART. The overall prevalence of dyslipidaemia and severe dyslipidaemia was higher in patients who were HIV positive on ART. The findings in this study were similar to the a meta-analysis by *Noubiap et al.* which reported a high prevalence of dyslipidaemia amongst African patients with diabetes, hypertension and HIV (43). The prevalence of

dyslipidaemia in statin-treated patients in South Africa: results of the dyslipidaemia international study (DYSIS) study also noted a high prevalence of dyslipidaemia amongst African patients with hypertension, diabetes and obesity (9).

The non-modifiable risk factors present in this study were advanced age, male gender and Asian or mixed ancestry. The prevalence of dyslipidaemia was higher in males, individuals older than 50 years of age and amongst non-Caucasian patients. The prevalence of dyslipidaemia was highest in mixed race patients followed by Indians and black Africans. Severe dyslipidaemia had a higher prevalence in Indian patients and mixed race patients. The DYSIS trial also found that Asian and mixed-ancestry were risk factors for dyslipidaemia in South African patients (9). However, it is unclear if these racial differences are statistically significant due to the small size of the study.

4.4 Patterns of lipid lowering treatment

The majority of patients enrolled in this study were treated with LLT. Patients receiving treatment were in the very high risk and high risk group of ASCVD. The majority of patients receiving LLT were above the age of 50 years, males and were of black African race. The most commonly prescribed LLT was simvastatin followed by atorvastatin. Only 2 patients had their treatment escalated from simvastatin to atorvastatin and only one patient received combination therapy consisting of a statin and fibrate. The prevalence of severe dyslipidaemia was lower in patients receiving LLT.

Despite the recommendations of the SA Lipid Society that the majority of high-risk patients be treated with high dose atorvastatin or rosuvastatin this study revealed these agents were infrequently used in those belonging to the very high or high-risk group. This maybe a reflection of the lack of availability of these agents in the state sector.

4.5 Failure of prescription of statin therapy

Of the 250 patients enrolled in this study, 32.4% did not receive LLT, however, based on the ESC/SA guidelines 63% of this group patients were eligible for therapy. Most of the statin eligible patients who did not receive therapy fell into the very high-risk category.

The majority of statin eligible patients who were not treated were black African, female and elderly. These constitute the usual group of patients in cardiovascular trials who fail to be treated appropriately as recommended by standardised guidelines. This failure may be a reflection of either prejudicial behaviour or a genuine but misguided belief that these are low risk patients who do not merit therapy. A further factor which may account for the failure to prescribe appropriate statin therapy may relate to financial constraints in the public sector healthcare system that is already under severe pressure by diseases considered more pressing by policy makers, such as HIV and TB. The lack of recognition of CKD as a major risk factor of ASCVD by physician trainees may be a contributing factor, as well as the lack of practising evidence based medicine published by the ESC and SA Lipid society.

There is a reluctance amongst physicians to prescribe statin therapy in CKD due to concern for adverse effects such as: hepatoxicity, myotoxicity and the development of diabetes mellitus (44). Statin therapy has numerous drug interactions that combined with the generation of active metabolites and decreased excretion in patients with CKD may lead to increased risk of adverse side effects particularly in the elderly (44).

4.6 Achievement of target LDL-C levels

In this study based on ESC recommendations only 16.6% of patients were at target levels of LDL-C. The mean LDL-C was 2.5mmol/L. The majority of patients that met LDL-C target were in the low to moderate risk category (71.4%). Only 8% of patients in the high-risk and 18% in the very high-risk group met the appropriate LDL-C target. On univariate analysis, younger age (< 50 years), low cardiovascular risk status and presence of immunosuppressive therapy were associated with a higher likelihood achieving target LDL-C. However, in the multivariate analysis only cardiovascular risk status remained as a predictor of achievement of target LDL-C. Gender, ethnicity and HIV status did not predict attainment of target LDL-C.

There are numerous factors affecting achievement of LDL-C targets. The International Cholesterol management Practice Study (ICLPS) revealed that patients failing to attain appropriate LDL-C targets were high-risk ASCVD, overweight, hypertensive, female, active smokers and had statin intolerance (45). Patients at high ASCVD risk were 1.5-3 times less likely to achieve LDL-C target (45). In the (ICLPS) study 51.4% of patients met the goal LDL-C

target (45). The Lipid Treatment Assessment Project (L-TAP) found that only 38.4% of patients were at LDL-C target (46). The majority of patients at target LDL-C were low risk (68%) (46). Caucasian and Hispanic patients were also more likely to attain goal LDL-C (39 and 40% success rate) (46). Only 29% of African Americans were successful in attaining target LDL-C (46). A study conducted by Zhang et al. determined that female sex (37.9% vs 28.7% males P<0.001), high levels of baseline LDL-C levels (2.82+-0.75 vs 2.08+-0.70 mmol/L P<0.001) and younger age (66.7 +-10.6 vs 68.9+-10.1 years, p=0.009) were factors that were associated with patients not reaching target LDL-C in a cohort that was diagnosed with ACS and treated with statins post percutaneous coronary intervention (47).

In this analysis, achievement of target LDL-C levels was much lower than in the studies previously mentioned. This may be in part due to the fact that this study was a cohort of patients with CKD as opposed to the comparative studies, none of which specifically examined patients with CKD. The safety and efficacy of high intensity statin therapy remains a concern in patients with CKD especially in those with ESRD (48). Whether the failure to prescribe high intensity statin therapy was based on physician reluctance could not be determined, although a more likely explanation would be the lack of availability of potent statins in the public sector healthcare setting of South Africa. A further factor impeding achievement of target LDL-C would be low patient compliance amongst patients with CKD. Similar to other studies, high cardiovascular risk was found to be a predictor of failure to reach target LDL-C. The reason for this would be the lower target LDL-C in higher risk patients making it more difficult to achieve the lower LDL-C target level. Unlike the findings in the LTAP study, older age was also found to be predictive of failure of achieving LDL-C control. The reason for this remains unclear. It is unclear why patients in this study who were on immunosuppressive therapy achieved better LDL-C control.

In this study, 77 of the 250 patients were HIV positive with just half on ART. Although ART is well documented, in particular the protease inhibitors, to raise LDL-C , the presence of HIV or its treatment did not appear to have an impact on the degree of dyslipidaemia. However, as numbers were small and the majority of patients were not receiving protease inhibitors, the study may have been underpowered in this regard.

Compliance with medical therapy amongst patients with ESRD in general has been previously documented to be quite low ranging from 19-99% (49). It is possible that the inability to achieve target LDL-C may have been related to lack of compliance.

4.7 Limitations

Although this analysis allowed us to make some significant observations, there are certain limitations which need to be mentioned. Firstly, this was a retrospective observational study which may have entailed certain biases in terms of patient selection and management, which we may have not accounted for. Also, a significant limitation of all retrospective studies is the lack of complete data for all patients. Secondly, although the overall number of patients included in this study was moderately large, subgroup analysis could not allow definitive conclusions because of relatively small numbers. Thirdly, only single lipid estimations were obtained at one point in time with no baseline pre-treatment lipid levels. Observations with respect to eligibility for statin therapy and degree of control may have been jeopardised. Fourthly, most patients received suboptimal statin therapy in the form of low dose simvastatin despite their high ASCVD risk. Finally, compliance with statin therapy could not be accessed. In other studies non-compliance with statin therapy occurred in up to 50% of patients resulting in an underestimation of the benefits of LLT(50).

Chapter 5: Conclusion

In this retrospective analysis of 250 patients with CKD, a high prevalence of dyslipidaemia was noted in the cohort. Of concern, a large number of patients who required LLT were untreated and even in those on LLT in only a minority were recommended LDL-C targets achieved . These findings highlight the need to improve the management of dyslipidaemia in patients with CKD in South African public sector in order to reduce the high burden of ASCVD contributing morbidity and mortality in the CKD population. These goals could be achieved by increasing education of clinicians involved in the management of patients with CKD and by placing recent evidence based guideline derived protocols for the treatment of dyslipidaemia in place to assist in this regard.

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Appendix A: Data Collection Sheet

Dyslipidaemia in CKD: Data Sheet

1.	Study number	
2.	Age	|___|___|
3.	Gender	Male|___| Female|___|
4.	Ethnicity	Black |___| White |___| Indian |___| Other|___|
5.	Weight (kg)	
6.	Height (cm)	
7.	Date of first visit to renal clinic (DD/MM/YYYY)	|___|___|/|___|___|/|___|___|___|___|
8.	CKD cause	Unknown (UNK)|___|
9.	On RRT?	Yes|___| No|___| Unknown (UNK)|___|
10.	If on RRT	Duration (months): _____ Modality: HD |___| PD |___|
11.	Co-morbidities	- Underlying cardiac disease Yes|___|No|___|UNK|___| - Hypertension Yes|___| No|___|UNK|___| - Gout Yes|___|No|___|UNK|___| - Tuberculosis Yes|___|No|___|UNK|___| - HIV positive, not on ART Yes|___|No|___|UNK|___| - HIV positive on ART Yes|___|No|___|UNK|___| If on ART: detail regimen _____ - Obesity (as defined by clinical staff: NOT BMI) Yes|___|No|___|UNK|___| - Diabetes Yes|___|No|___|UNK|___| - If yes: T1DM|___| T2DM|___| - Smoking Current smoker|___|Former|___|None|___| - Alcohol Yes|___|No|___|UNK|___| - Immunosuppression Yes|___|No|___|UNK|___| -Steroid use Yes|___|No|___|UNK|___| - Other relevant CVD risk factor Yes|___|No|___|UNK|___| Specify_____
12.	Year of diagnosis of co-morbidity	- Underlying cardiac disease |___|___|___|___| - Hypertension |___|___|___|___| - Gout |___|___|___|___| - Tuberculosis |___|___ |___|___| - HIV positive, not on ART (year of + test) |___|___|___|___| - HIV positive on ART (year of ART start) |___|___|___|___| - Obesity (as defined by clinical staff: NOT BMI) |___| ___|___|___| - Diabetes |___| ___ |___|___| - Smoking |___|___|___|___| - Other relevant CVD risk factor |___|___|___|___|

13.	Complications	- Stroke / Cerebrovascular accident Yes|___| No|___| UNK|___| - Congestive heart failure Yes|___| No|___| UNK|___| - Coronary Artery Disease Yes|___| No|___| UNK|___| - Cardiac arrhythmia Yes|___| No|___| UNK|___| - Peripheral vascular disease Yes|___| No|___| UNK|___| - Other Specify_____
14.	Immunosuppression or steroid use	
15.	Documented lipid lowering medications (LLA)	
16.	Date of lipogram (DD/MM/YYYY)	|___|___|/|___|___|/|___|___|___|___|
17.	Results of lipogram	

Drug	Dose	Start date	Stop date

Drug	Dose	Start date	Stop date

Total Cholesterol (mmol/L)	
LDL-C (mmol/L)	
HDL-C (mmol/L)	
Triglyceride (mmol/L)	

18.	Other chemistry tests	

Hemoglobin (g/dL)	
MCV (fL)	
Sodium (mmol/L)	
Potassium (mmol/L)	
Chloride (mmol/L)	
Bicarbonate (mmol/L)	
Urea (mmol/L)	
Creatinine (umol/L)	
eGFR (mL/min/1.73m^2)	
Corrected Calcium (mmol/L)	
Magnesium (mmol/L)	
Phosphate (mmol/L)	
HBA1c (%)	
Urine ACR (mg/mmol)	
U-PCR (g/mmol)	
Albumin (g/L)	
CKD Stage	

Appendix B: Ethics Approval Letter

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

R14/49 Dr Mohammed RafiqueEssop

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M200760 MED20-04-067

NAME: (Principal Investigator)	Dr Mohammed RafiqueEssop
DEPARTMENT:	Internal Medicine Charlotte Maxeke Johannesburg Academic Hospital
PROJECT TITLE:	A retrospective study of dyslipidaemia in patients with chronic kidney disease at Charlotte Maxeke Johannesburg Academic Hospital
DATE CONSIDERED:	31/07/2020
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Prof Federick Raal and Dr Faheem Seedat
APPROVED BY:	Dr C Penny, Chairperson, HREC (Medical)
DATE OF APPROVAL:	14/09/2020

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office Secretary in Room 301, Third floor, Faculty of Health Sciences, Phillip Tobias Building, 29 Princess of Wales Terrace, Parktown, 2193, University of the Witwatersrand. I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated, from the research protocol as approved, I/we undertake to resubmit the application to the Committee. **I agree to submit a yearly progress report**. The date for annual re-certification will be one year after the date of convened meeting where the study was initially reviewed. In this case, the study was initially reviewed July
and will therefore be due in the month of
July each year. Unreported changes to the application may invalidate the clearance given by the HREC (Medical).

Principal Investigator Signature Date

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

Appendix C: Turn it in report

ORIGINALITY REPORT

18%	14%	13%	6%
SIMILARITY INDEX	INTERNET SOURCES	PUBLICATIONS	STUDENT PAPERS

PRIMARY SOURCES

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