

The Implementation Of Current Guidelines Regarding The Treatment Of Cardiovascular Risk In Type 2 Diabetics

Yacob Pinchevsky

The University of the Witwatersrand

Faculty Of Health Science

Department of Pharmacy and Pharmacology

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DECLARATION

I, Yacob Pinchevsky declare that this dissertation is my own work. It is being submitted for the degree of Master of Science in Medicine at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other University.

Signed at _____ on this _____ day of

_____ 2010.

Signature

DEDICATION

I dedicate this dissertation to my beloved and late grandfather, Boris Grin. I thank my parents for blessing me with the opportunity to study and the rest of my family and friends for their constant support.

PUBLICATIONS AND PRESENTATIONS

Presentations:

[2008]

- Attended “The Southern African Neuroscience Society Congress” in Rhodes University, Grahamstown, South Africa.
- Presented preliminary data in the form of a poster at “The Southern African Neuroscience Society Congress” at Rhodes University, Grahamstown, South Africa.

[2009]

- Attended “The International Student Congress Of Medical Sciences (ISCOMS)” at the University Medical Center Groningen, Groningen, The Netherlands.
- Presented preliminary data in the form of an oral presentation (category Endocrinology) at “The International Student Congress Of Medical Sciences (ISCOMS)” at the University Medical Center Groningen, Groningen, The Netherlands.
- Presented and received the “Runner Up” prize for the best poster presentation of preliminary data at the “Therapeutic Sciences Research Day” At the University Of The Witwatersrand, Johannesburg, South Africa.
- Presented an oral presentation at the University Of The Witwatersrand Inter-faculty Symposium, Johannesburg, South Africa.

ABSTRACT

Background: Type 2 diabetes mellitus (T2DM) is defined by an increase in serum glucose, however, this leads to the belief that only the serum glucose levels need be monitored and treated. Hence many other risk factors such as obesity, lipids and blood pressure which increase the risk of coronary heart disease, myocardial infarction, stroke and peripheral vascular disease are neglected. Consequently, T2DM patients that are at greater risk of developing cardiovascular disease (CVD), are often not receiving optimal comprehensive care.

Aims: To identify the treatment gaps of cardiovascular risk factors in patients with T2DM using both national and international current treatment guidelines.

Methods: Using a public sector database, data was obtained on the treatment of 666 T2DM patients. Records of patients were selected on the basis of established T2DM diagnoses, receiving oral hypoglycaemic and/or insulin therapy. The following patient data was recorded: demographics (age, gender, ethnicity), systolic blood pressure (SBP), diastolic blood pressure (DBP), glycated haemoglobin (HbA_{1c}), total cholesterol (TC), triglycerides (TG), HDL-cholesterol (HDL-C), LDL-cholesterol (LDL-C), family history, cardiovascular history and all chronic medications. The following parameters were applied to the cohort: SBP <130 mmHg, DBP <80 mmHg. In the event of proteinuria: SBP ≤120 mmHg, DBP ≤70 mmHg. HbA_{1c} <7.0%, TC <4.5 mmol/L, LDL-C <2.5 mmol/L, HDL-C >1.0 mmol/L (males), HDL-C >1.2 mmol/L (females) and TG <1.7 mmol/L. In patients with established CVD, LDL-C target: ≤1.8 mmol/L.

Results: The study cohort consisted of 666 T2DM-patients. 55% females. Mean age was 63 years (SD: 11.8), mean HbA_{1c} was 8.7% (SD: 2.4). The mean SBP and DBP readings for the cohort were 133.66 (SD: 19.9) and 78.07 mmHg (SD: 11.6), respectively. Mean LDL-cholesterol was 2.6 mmol/L (SD: 0.9). 26.2% reached HbA_{1c} of ≤7%, 45.8% reached ≤130/80 mm Hg blood pressure targets, 53.8% reached LDL-C of ≤2.5mmol/L and all 3 were reached by 7.5% of the cohort. TC ≤4.5 mmol/L was reached by 53.8%, 60.2% reached TG ≤1.7mmol/L, 58.6% males and 52.8%

females reached HDL-C targets of ≥ 1.0 mmol/L and ≥ 1.2 mmol/L, respectively. There were 17.9% of patients with CVD reaching targets of LDL-C ≤ 1.8 mmol/L whilst 16.4% of patients with nephropathy reaching targets of $\leq 120/70$ mm Hg. Almost half (48.2%) were not receiving lipid-lowering therapy, yet would be deemed eligible for therapy. Blood pressure targets may have been better reached with appropriate dosage reductions in addition to the introduction of further antihypertensive combination therapy. CVD was present in 15.5%.

Conclusions: T2DM patients are at high-risk for CVD. Many trials have demonstrated the benefits of targeting CVD risk factors (HbA_{1c}, blood pressure, serum lipids) in T2DM. Less than 10% of CVD risk factor targets were reached by the study cohort despite treatment guideline recommendations. The data from the study suggests poor control of modifiable cardiovascular risk factors and significant under treatment of T2DM in clinical practice. Whether improvement lies in the form of therapeutic titration adjustment or an increase in patient education, there needs to be a more aggressive multi-factorial therapeutic approach to treating this high risk group of patients in order to reduce overall morbidity, mortality and improve patient outcomes.

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ABBREVIATIONS

4S	Scandinavian Simvastatin Survival Study
ACCEPT-D	Aspirin and Simvastatin Combination for Cardiovascular Events Prevention Trial in Diabetes
ADA	American Diabetes Association
ALLHAT	Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial
ANAES	National Agency for Health Care Accreditation and Evaluation (French National Guidelines)
ASCEND	A Study of Cardiovascular Events iN Diabetes
ASCOT-LLA	Anglo-Scandinavian Cardiac Outcomes Trial-Lipid Lowering Arm
ASPEN	Atorvastatin Study for Prevention of Coronary Heart Disease Endpoints in Non-Insulin-Dependent Diabetes Mellitus
Atorva	Atorvastatin
BMI	Body Mass Index
BP	Blood Pressure
CAD	Coronary Artery Disease
CARDS	Collaborative Atorvastatin Diabetes Study
CARE	Cholesterol and Recurrent Events trial
CHD	Coronary Heart Disease
CABG	Coronary Artery Bypass Graft
CRF	Case Report Form
CVD	Cardiovascular Disease
DIGAMI Study	Diabetes Insulin-Glucose in Acute Myocardial Infarction study
DBP	Diastolic Blood Pressure
DM	Diabetes Mellitus
ESC	European Society of Cardiology

EASD	European Association for the Study of Diabetes
FFA	Free Fatty Acid
FH	Familial Hypercholesterolaemia
GOAL	Global Opinion and Awareness of ChoLesterol
HbA _{1c}	Glycated Haemoglobin
HDL-C	High Density Lipoprotein Cholesterol
HMG CoA	3-Hydroxy-3-Methyl-Glutaryl-CoA
HOT Study	Hypertension Optimal Treatment Study
HPS	Heart Protection Study
HPT	Hypertensive
HREC	Human Research Ethics Committee
IDF	International Diabetes Federation
IHD	Ischaemic Heart Disease
IQR	Interquartile Range
ISCOMS	The International Student Congress Of Medical Sciences
ISH	Isolated Systolic Hypertension
JNC VII	The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure
LDL-C	Low Density Lipoprotein Cholesterol
LIPID	Long Term Intervention with Pravastatin in Ischaemic Disease Study
LIPS	Lescol Intervention Prevention Study
Mg	Milligrams
MI	Myocardial Infarction
MS	Metabolic Syndrome
NAG	Not At Goal
NCEP ATP	National Cholesterol Education Program Adult Treatment Panel
NHLS	National Health Laboratory Services
NSAM	Norwegian College of General Practitioners
NSTEMI	Non-ST Segment Myocardial Infarction

PROSPER	PROspective Study of Pravastatin in the Elderly at Risk
PVD	Peripheral Vascular Disease
RSA	Republic of South Africa
SA	South Africa
SBP	Systolic Blood Pressure
SCORE	Systematic Coronary Risk Evaluation
SD	Standard Deviation
SEMDSA	Society for Endocrinology, Metabolism, and Diabetes of South Africa
Simva	Simvastatin
Statin	HMG CoA Reductase Inhibitor / 3-Hydroxy-3-Methyl Glutaryl Coenzyme A Reductase Inhibitor
TC	Total Cholesterol
TG	Triglyceride
T1DM	Type 1 Diabetes Mellitus
T2DM	Type 2 Diabetes Mellitus
TIA	Transient Ischemic Attack
TNT	Treat to New Targets
UK	United Kingdom
UKPDS	United Kingdom Prospective Diabetes Study
US	United States of America
VLDL	Very Low Density Lipoprotein
WC	Waist Circumference

INTRODUCTION

Diabetes mellitus (DM) is a serious, multifaceted condition, which is also one of the most common life-threatening diseases around the globe. Diabetes Mellitus outweighs HIV/AIDS prevalence by 5 to 1; in 2000, there were approximately 36.1 million people living with HIV/AIDS, in the same year, approximately 171 million Diabetics.^{1 2} By 2025, an estimated 380 million people will be living with diabetes worldwide.³

Diabetes Mellitus Type 1

Type 1 diabetes mellitus (T1DM), previously known as “Insulin Dependent Diabetes Mellitus,” is thought to be caused by viral agent(s) or an interaction between genes and the immune system. In the autoimmune form, antibodies destroy the β cells of the pancreas, which leads to an absolute deficiency in insulin production. The autoimmune disorder form is the most common kind of type 1 diabetes mellitus and insulin administration is the therapeutic approach for all type 1 diabetics.⁴

Diabetes Mellitus Type 2

Type 2 diabetes mellitus (T2DM), was once known as “Non-Insulin Dependent Diabetes Mellitus” and is a metabolic disorder that is characterised by a diminished sensitivity of the target tissues to insulin. This results in “insulin resistance” which further leads to chronic hyperglycaemia. The progressive nature of this disease may also lead to the decreased β cell function of the pancreas,⁵ consequently leading to a state of relative insulin deficiency. Unlike type 1, most type 2 diabetics are overweight or obese at the time of diagnosis and may have the “metabolic

syndrome.” In order to combat this type of diabetes mellitus, lifestyle modifications such as decreased caloric intake, increased physical activity, weight loss and stress reduction are advocated. Despite these lifestyle modifications, the bulk of patients are still incapable of maintaining normoglycaemia without drug therapy. Oral hypoglycaemic agents are used to maintain glycemic control in type 2 diabetic patients. The major classes include:

- Insulin Secretagogues e.g. Sulphonylureas – stimulate insulin release from the pancreas.
- Meglitinides - structurally different from Insulin Secretagogues, yet also stimulate insulin release from the pancreas.
- Biguanides - enhance peripheral tissue sensitivity to insulin thereby increasing glycolysis and decreasing hepatic and renal gluconeogenesis.
- α -Glucosidase Inhibitors - divert and prolong the postprandial digestion and absorption of starch and disaccharides.
- Insulin Sensitizers e.g. Thiazolidinediones - correct insulin resistance by regulating genes involved in glucose, lipid metabolism and adipocyte differentiation.

When oral hypoglycaemic agents fail, insulin therapy is added in order to meet glycaemic target levels.

Microvascular Aspect of Type 2 Diabetes Mellitus

The high glucose load puts a huge strain on a number of different pathways. In type 2 diabetes, it has been clearly recognized that raised glucose levels ultimately result in microvascular complications.⁶ Microvascular complications include retinopathy,

which results in visual impairment or blindness, nephropathy, which leads to renal failure, and neuropathy, which can cause paresthesia.^{7 8}

The landmark UKPDS study enrolled over 5000 type 2 diabetic patients and showed a 25% decline in microvascular complications when intensive glycemic control was achieved. Hence, glycemic control is an essential factor in decreasing the risk of microvascular complications in diabetic patients.⁹ Poor glycemic control in type 2 diabetics is an independent predictor of vascular diseases.^{10 11} In the same study, in the group with tight glycaemic control, there was a 14% and 21% decline in myocardial infarcts and diabetes-related mortalities respectively. The Honolulu Heart Program determined that cardiovascular mortality in type 2 diabetics was proportional to long term serum glucose concentrations as measured by HbA_{1c}.¹² This suggests that tight glycemic control can reduce microvascular complications and at the same time, make an impact on macrovascular complications.

Macrovascular Aspect of Type 2 Diabetes Mellitus

The focus in the diabetes mellitus type 2 condition is serum glucose. This however, leads to the belief that only the serum glucose levels need be monitored and treated. Hence many other risk factors such as lipids, cholesterol and blood pressure which increase the risk of coronary heart disease, myocardial infarction, stroke and peripheral vascular disease are ignored.

Cardiovascular disease (CVD) is widespread in patients with type 2 diabetes mellitus.¹³ Type 2 diabetics have a 2 to 4 fold increased risk of cardiovascular episodes compared with non-diabetics.^{14 15} Haffner *et al.* concluded from

epidemiological data that type 2 diabetic subjects are as much at risk of suffering a myocardial infarction as non-diabetic subjects who previously suffered a myocardial infarction.¹⁴ At least 80% of people with type 2 diabetes mellitus die from some form of cardiovascular disease.^{16 17} This makes diabetes mellitus an independent risk factor for cardiovascular diseases.

The role of dyslipidaemia in coronary heart disease is well-described.¹⁸ The INTERHEART study conducted by Yusuf *et al.*, in 2004 showed that, amongst other risk factors, dyslipidaemia was associated with myocardial infarctions.¹⁹ Hyperlipidaemia results in cardiovascular complications such as premature progression of atherosclerosis, coronary artery disease, peripheral vascular diseases, thromboembolic stroke and myocardial infarctions.^{20 21}

Dyslipidaemia is common in type 2 diabetic patients due to genetic predispositions and/or obesity.²² Dyslipidaemia in type 2 diabetes is distinguished by small, dense atherogenic LDL cholesterol, high plasma triglycerides and reduced HDL cholesterol levels. This is frequently associated with coronary heart disease.²³ LDL cholesterol levels in type 2 diabetics are often similar to the levels in non-type 2 diabetics. Nonetheless, type 2 diabetics are still at higher risk for the development of atherosclerosis because of the absolute number of small dense LDL particles.^{24 25 26} An additional study demonstrated that coronary artery disease (CAD) was the foremost source of death among diabetic patients as a result of dyslipidaemia.²⁷ By treating dyslipidaemia in patients with Type 2 diabetes, cardiovascular diseases are considerably decreased in incidence.²⁸

Type 2 diabetics are particularly at risk of developing coronary heart diseases. This highlights how crucial primary prevention is within this population. The normal to slightly raised LDL cholesterol levels often makes lipid-lowering therapy unjustified for cardiovascular disease in type 2 diabetes. However, clinical trials have been conducted and support the contention that lipid-lowering treatment in diabetic patients reduces cardiovascular disease, regardless of LDL cholesterol levels at entry.²⁹ In the Collaborative Atorvastatin Diabetes Study (CARDS), type 2 diabetics with no prior history of cardiovascular disease were given atorvastatin (HMG-CoA reductase inhibitor) 10mg daily and showed a massive 37% reduction in major cardiovascular events.²⁹ Furthermore, there was a decline by 36% in acute coronary heart disease, 31% decline in revascularisations, 48% decline in strokes and overall mortality was reduced by a substantial 27%. This proves the benefit of lipid-lowering therapy in the primary prevention of cardiovascular disease in type 2 diabetics, despite the “normal” LDL cholesterol levels.

Other studies have also shown similar trends, including the Cholesterol and Recurrent Events (CARE),³⁰ Long-term Intervention with Pravastatin in Ischemic Disease (LIPID),³¹ the Lescol Intervention Prevention Study (LIPS),³² the Anglo-Scandinavian Cardiac Outcomes Trial-Lipid Lowering Arm (ASCOT-LLA)³³ and the Atorvastatin Study for Prevention of Coronary Heart Disease Endpoints in Non-Insulin-Dependent Diabetes Mellitus (ASPEN).³⁴ These studies had diabetic subgroups large enough to prove the efficacy of lipid-lowering therapy in secondary prevention of heart diseases.

The Heart Protection Study (HPS) enrolled over 20 000 patients, which consisted of 5963 diabetic patients, of which 2912 patients had no prior cardiovascular disease.²⁸ Lipid lowering therapy led to the entire diabetic group showing a 27% reduced risk of major coronary events (20% reduction in coronary mortality and 37% reduction in first non-fatal myocardial infarction), 17% reduction in revascularisations and a highly noteworthy 22% reduction in major vascular events. In the 2912 diabetic subgroup without documented coronary or other occlusive arterial diseases, a striking 33% proportional reduction in first major vascular events occurred. The HPS provided an indication of how cholesterol-lowering therapy in type 2 diabetics reduces the risk of heart attacks, strokes, and revascularisations, especially in primary prevention. The benefit was also seen in patients with LDL below 3.0 mmol/L in particular- by showing reductions in vascular events by as much as 27%. This further demonstrated how lipid-lowering therapy should be used consistently for all type 2 diabetics, irrespective of their initial cholesterol levels.

The Scandinavian Simvastatin Survival Study (4S), one of the first studies to establish the effectiveness of HMG-CoA reductase inhibitors in secondary prevention, demonstrated that diabetic patients being treated with simvastatin (an HMG-CoA reductase inhibitor) lowered the relative risk of death by 43%, as well as lowered their relative risk of any atherosclerotic event by 37%.³⁵ This confirms the potential of lipid-lowering therapy with regards to decreasing the risk of major coronary events in secondary prevention, in spite of baseline risk factors such as diabetes mellitus. It is clear that there is a robust relationship between type 2 diabetes mellitus and cardiovascular disease.

The Treatment Of Cardiovascular Risk Factors In Type 2 Diabetes Mellitus

Cardiovascular disease is common in South Africa.³⁶ In a study conducted at 9 South African township communities of 1691 subjects (an estimated 0.2% of the total population), 78% of subjects screened positive for at least one major cardiovascular risk factor for CVD.³⁷ Not only is CVD prevalent in South Africa but also often left undiagnosed. A South African health survey revealed that Nearly 6 million South Africans aged 15 years and older suffered from hypertension, of which only 26% of men and 51% of women knew that they had had hypertension.³⁸ CVD left untreated results in many complications. In another South African study (at a hypertension clinic), congestive heart failure was the most common form of mortality.³⁹

The link between CVD and T2DM is clear.¹⁴ T2DM is an established and highly prevalent risk factor for cardiac morbidity and mortality. Long considered a disease of minor significance to world health, T2DM is now taking its place as one of the main threats to human health in the 21st century.⁴⁰ Changes in human environment, behaviour and lifestyle have accompanied globalization and these have resulted in escalating rates of both obesity and diabetes. Hence the adoption of the term “diabesity.”⁴¹

The treatment in patients with T2DM has traditionally centred around correcting blood glucose levels and this claims most of the resources. Yet, as many as 80% of people with T2DM will die from some form of CVD, highlighting the need for more aggressive intervention.¹⁶ This makes T2DM an independent risk factor for CVD. Targeting blood glucose levels may reduce microvascular complications, but this will

only slightly improve patient outcomes if other cardiovascular risk factors, namely blood pressure and serum lipids are left untreated.^{28 42}

Blood pressure and serum lipid targets are far more stringent in this group than in non-diabetics, thus requiring more intensive therapy.⁴³ The accelerated atherosclerosis which predisposes T2DM patients to increased incidence of premature cardiovascular events has been demonstrated in epidemiological studies and major clinical trials.^{28 29 44 45} Risk factors in T2DM such as dyslipidaemia, hypertension and obesity which are commonly associated with T2DM have increased the incidence and progression of cardiovascular related events. Not surprisingly, T2DM has been classified as a “CVD-equivalent” necessitating secondary prevention treatment.¹⁴

In T2DM, premature morbidity and mortality associated with the disease warranted a way in which complications could be averted.⁴⁰ Over the last decade, major studies such as the UKPDS and DCCT established the need for stricter control of blood glucose in order to reduce or prevent the risk of both the microvascular and (to a lesser degree) macrovascular complications.^{6 9} However, recent evidence has shown that over treating glucose levels may in fact negatively impact patient outcomes through episodes of hypoglycaemia.⁴⁶ Similarly, a recent review by the Cochrane Collaboration concluded with: “Treating patients to lower than standard BP targets, ≤ 140 - $160/90$ - 100 mmHg, does not reduce mortality or morbidity.”⁴⁷ Neglecting or over treating the cardiovascular risk factors in T2DM will lead to complications, perhaps a more careful approach is the way forward.

Global Treatment Of Cardiovascular Risk Factors In Type 2 Diabetics

With T2DM patients being at a markedly increased risk for CVD, the latest evidence has resulted in T2DM treatment guidelines being more “cardiovascular risk factor” focused with regards to patient treatment and management.⁴⁸ Treatment guidelines in general are designed to influence the practitioner’s method of treating patient risk factors in order to help better patient outcomes. Optimal management of T2DM risk factors offered in various treatment guidelines advocate stricter goals or treatment targets for T2DM patients in order to reduce patient morbidity and mortality.

However, many T2DM patients, even those in resource rich countries still lack control of the key risk factors leading to complications. The following studies have been selected and carefully reviewed for the purposes of comparison. Although the studies may have varied by location, demographic population and national targets (specific to the country), all studies chosen have a core purpose and that is of investigating the treatment of cardiovascular risk factors in T2DM patients in practice.

Italy. In an Italian 2004 observational study where 2465 patients were recruited from 10 different hospitals across the country, 5% of the total targets were achieved by patients for LDL-C, BP, HbA_{1c} and smoking habits with mean lipid and BP readings significantly higher than recommended cardiovascular guidelines.⁴⁹ Gender difference studies revealed that women were worse off than men with regards to their weight, HbA_{1c}, LDL-C, SBP, but not smoking habits. Patients with a longer duration of diabetes tended to have a higher HbA_{1c} and SBP, but were less obese, had lower DBP and smoked less than patients with shorter duration of diabetes. Evidently, despite clear recommendations from the Italian Diabetes Society,⁵⁰ the majority of

T2DM patients in Italy aren't being treated appropriately for their cardiovascular risk factors.

Norway. This study, recommended by the Regional Ethics Committee and Research Board of the Norwegian College of General Practitioners (NSAM) comprised of 975 T2DM patients which were recruited from 5 major regions across Norway.⁵¹ Some 13% and 6% of the total cohort achieved goals for glucose, BP and cholesterol control using national and IDF guidelines, respectively. No major gender differences were found. 79% had metabolic syndrome according to WHO definition. 65% and 35% of the total cohort achieved NSAM and IDF glucose targets, respectively. BP targets ($\leq 140/85$ mmHg) were reached by 52%, whilst 32% achieved LDL-C targets (< 3 mmol/L). 73% of patients with CVD, whilst 27% of patients without CVD but with other risk factors such as hypertension, microalbuminuria and smoking received lipid-lowering therapy. Conclusions from the study reflect on compliance with national targets being more often achieved with glycaemic control than with BP and cholesterol.

Spain. A 2003 cross-sectional study was conducted in order to assess the “degree of control of modifiable cardiovascular risk factors” in 501 T2DM patients.⁵² The cohort comprised of patients recruited from a specialized secondary referral centre that provides healthcare to 31 districts in Madrid, Spain. With no significant differences between genders, 41% of the total population achieved both HbA_{1c} ($< 7\%$) and LDL-C targets (< 2.6 mmol/L). More patients with CAD received statins than those without CAD, which explains why more of these patients were at goal for LDL-C (53% vs. 31%, $p = 0.0006$). 27% and 72% of patients were at goal for SBP (< 130 mmHg) and

DBP (<80 mmHg), respectively. Amongst glucose-related levels (HbA_{1c}, fasting plasma glucose, postprandial capillary glucose), lipid levels and BP readings, other parameters included in the study consisted of body mass index (BMI), waist circumference (WC), smoking status and medications. None of the 501 patients achieved target for all the risk factors tested. A correlation was seen in patients with established CAD; these patients tended to receive more insulin than oral hypoglycaemics as well as had more risk factors present, which may be indicative of the progressive nature of DM and its impact on heart disease. Overall, in view of the poor control achieved and none of the patients being at targets for risk factors tested, the study investigators called for a more aggressive approach to combating “modifiable cardiovascular risk factors” in T2DM patients.

Czech Republic. This study comprised of 3206 randomly selected patients from 89 outpatient clinics across the Czech Republic.⁵³ Conducted in 2002, retrospective patient data such as lipids, BP and HbA_{1c} were captured from records. Using ADA-based national T2DM guidelines,⁴⁸ results revealed the following: 42% of patients achieved HbA_{1c} <7.0%, 31% achieved SBP <130 mmHg, 63% achieved DBP <80 mm Hg, 27% achieved TC <5.0 mmol/L, 55% achieved HDL-C above 1.1 mmol/L and finally 56% achieved triglycerides below 2.0 mmol/L. Combined, only 1% of all study T2DM patients achieved goals for all three parameters. The investigators also investigated the use of pharmacological treatment and found that patients were largely under-treated. It was clear that T2DM treatment guidelines simply were not being implemented properly. It was also mentioned that patients need to be evaluated more intensely for their risk factors, “to minimize the number of unrecognized cases.” Non-pharmacological advice such as lifestyle modifications

and better self-monitoring was also re-enforced. It was concluded that improved outcomes are expected through increased guideline adherence using readily available non-drug and drug technologies in order to target under-treatment of T2DM.

South Africa. Two local South African studies were conducted to determine cardiovascular risk factor treatment in T2DM patients in 1996 and 2006, respectively.^{54 55} In the former study, eighty-two patients were recruited and tested for obesity, smoking status, lipid, HbA_{1c} and blood pressure levels. Results indicated that 82% of total patients were obese, 66% had hypertriglyceridaemia, 46% had hypercholesterolaemia and 20% had uncontrolled hypertension. Other cardiovascular risk factors such as smoking were present in 27%. Outcomes from the study indicated that patients were not receiving adequate treatment for their cardiovascular risk factors. Similar findings were present in the 2006 study. In spite of the wealth of clinical evidence available and latest guideline recommendations, it appears that DM treatment in practice has largely remained confined to glycaemic control.

The latest guidelines issued by the “Society for Endocrinology, Metabolism, and Diabetes of South Africa (SEMDSA),⁵⁶ American Diabetes Association (ADA),⁴⁸ International Diabetes Federation (IDF)⁵⁷ and European Society of Cardiology / European Association for the Study of Diabetes (ESC/EASD)⁵⁸ suggest aggressive targeting of HbA_{1c} but also blood pressure and dyslipidaemia. But how well do treatment guidelines translate into clinical practice and are goals being met?

In developing countries with so much competition for scarce resources such as antiretrovirals for HIV/AIDS, we wished to document how well T2DM patients were being treated in a South African, public sector setting.

The outcome of the two previous South African studies conducted at the Johannesburg Academic Hospital revealed that the management of cardiovascular risk factors in T2DM patients remains suboptimal.^{54 55} Results from both these studies showed that there is still a significant gap in the management of cardiovascular risk factors in T2DM. Following these last two studies, the current study was designed to further address the ongoing problem with the management cardiovascular risk factors in T2DM. Both previously conducted studies consisted of smaller sized cohorts and there has since been emergence of newer evidence regarding the management of cardiovascular risk factors in T2DM. The idea behind the current study was to augment our understanding of the problems T2DM patients face in the management of their cardiovascular risk factors and to see where the shortfalls lie. To the knowledge of the author of the current study, no audit of this magnitude regarding the treatment of cardiovascular risk factors in T2DM has ever been conducted at the Charlotte Maxeke Johannesburg General Hospital.

The cohort of this study comprised of patients initially referred from their primary local clinics to a tertiary public sector clinic. This reflects the quality of care the State can provide, especially to those in the lower socio-economic class who cannot afford private health care. Given that these patients have been referred to the Johannesburg Hospital from smaller clinics, these patients which comprise the study cohort tend to be more burdened with disease or have a more “advanced form” of

diabetes requiring further attention and management. Targeting of cardiovascular risk factors such as blood glucose, blood pressure and serum lipids will most likely determine patient outcomes. For these reasons, the current study will enable us to determine the extent to which guidelines are being implemented with regards to cardiovascular risk factor management in more “complicated” South African T2DM patients.

Study Objectives

1. The objectives of this study are to:
 - 1.1 Determine the current treatment strategies of cardiovascular risk factors (HbA_{1c}, blood pressure, serum lipids) in type 2 diabetic patients by practitioners at a Johannesburg State Hospital.
 - 1.2 Determine whether current diabetes treatment guidelines are being adhered to by practitioners.
 - 1.3 Determine the frequency and type of glucose-lowering, anti-hypertensive and lipid-lowering treatment in type 2 diabetic patients.
 - 1.4 Determine the extent to which lipid, glucose and blood pressure targets have been achieved in type 2 diabetic patients according to the latest national and international diabetes treatment guidelines.
 - 1.5 Determine the prevalence of cardiovascular disease in type 2 diabetic patients and the extent to which lipid levels are controlled in this high-risk group.
 - 1.6 Determine the prevalence of diabetic nephropathy in type 2 diabetic patients and the extent to which blood pressure levels are controlled in this high-risk group.
 - 1.7 Compare the attainment of cardiovascular risk factor targets (HbA_{1c}, blood pressure, serum lipids) with those of similar studies.

STUDY METHODOLOGY

Study Design

This was a cross-sectional study conducted at the Charlotte Maxeke Johannesburg General Hospital between June 2008 and March 2009. The Johannesburg General Hospital is an academic tertiary hospital that provides healthcare services to patients across the Gauteng province. Patients that were enrolled in this clinic are generally not covered by the private health care industry and are generally from lower socio-economic strata that cannot afford private healthcare. In addition patients are only treated once their treating physician at the local clinics have referred them. Complete diabetes management is carried out at the hospital's diabetic clinic and patients attend the clinic for the purposes of initial and follow-up visits.

Patients

Patients that met the inclusion criteria of being > 18 years of age and having a positive diagnosis for Type 2 Diabetes Mellitus were enrolled into the study. For the purposes of this study, patients were assumed to have a positive diagnosis for Type 2 Diabetes Mellitus as indicated in their medical history (in their hospital files). For the current study, the definition of Type 2 Diabetes Mellitus is defined as in any of the recognized guidelines as seen under appendices VIII, IX, X and XI. The guidelines were assumed to have been followed by the diagnosing registered nurse or practitioner at the referral clinic or at the Charlotte Maxeke Johannesburg General Hospital at the time of patient diagnosis. To establish an appropriate diagnosis for Type 2 Diabetes Mellitus, patients are required to be diagnosed according to recognized guidelines such as those under appendices VIII, IX, X and XI. Patients

comprising the cohort of the current study were assumed to have been diagnosed using recognized guidelines such as those under appendices VIII, IX, X and XI.

Patients comprising the cohort were selected on the basis of previous T2DM diagnosis, eliminating the chance of patient-selection bias in the study. From 782 patients, the following patients were excluded from the study: 109 Type 1 Diabetic patients (study exclusion criteria), 1 gestational Diabetes patient (study exclusion criteria) and 1 steroid-induced Diabetes patient (study exclusion criteria). As one of the primary measurements was serum lipid readings, it was decided to exclude the 5 patients with triglyceride levels > 5 mmol/L as this may have been a source of error for the calculation of LDL-C or could possibly be non-compliance with overnight fasting leading to anomalous lipid readings and in particular, low LDL-cholesterol readings. Thus, data from a total of 666 patients which attended the hospital's diabetic clinic between July 2008 and July 2009 was used for this study.

All patients seen at the diabetes clinic of the Charlotte Maxeke Johannesburg General Hospital are provided with a file where all information regarding hospital visits, treatment and medical history is documented. Patient laboratory reports are also kept within these files. The files are physically kept at the clinic and are maintained by hospital administration clerks. The files are organized into the filing cabinets by a unique hospital number given to patients at the hospital, as well as the first letter of the patient's surname.

For the purposes of this study, patients were recruited based on the hospital's filing system which used patient's hospital numbers as well as the first letter of their surname. Patient files were selected in an alphabetical order, starting from the letter A (followed by the assigned hospital number). This method of selecting participants

ensured a non-bias selection of participants and to the knowledge of the investigator, did not allow for any patients to be favoured over others.

Using patient records, the following data was captured into case report forms (CRF): demographics (age, gender, ethnicity), systolic blood pressure (SBP), diastolic blood pressure (DBP), glycated haemoglobin (HbA_{1c}), total cholesterol (TC), triglycerides (TG), HDL-cholesterol (HDL-C), LDL-cholesterol (LDL-C) , family history, cardiovascular history and all chronic medications (Figure 50). Only the most recent records and laboratory reports of the patient were utilised for the purposes of this study.

Clinical Parameters

Where blood samples were required for laboratory tests, registered nurses were in charge of drawing of study patient's bloods using standardised techniques at the diabetes clinic. Patients were informed of the mandatory fasting requirements of tests before having their blood drawn for specific tests (fasting lipids) in prior appointments/visits.

As Charlotte Maxeke Johannesburg Academic Hospital is a state hospital, the National Health Laboratory Services (NHLS) was responsible for all the laboratory measurements of study patients. Once the results were available, the NHLS issued laboratory results delivered by hospital staff to the diabetes clinic and filed under respective patient files by clinic administration staff.

HbA_{1c} was measured using the Tina-Quant Haemoglobin A1c II immunological assay, fasting LDL-C was determined indirectly using the Friedewald formula,⁵⁹ fasting HDL-C was measured by direct enzymatic methods (HDL-C plus 3rd

generation), fasting TC was also measured by direct enzymatic methods (CHOD-PAP) and TG were measured by enzymatic colorimetric methods (GPO-PAP). All measurements were done using the Modular Analyser P800 System (Roche Diagnostics-Hitachi, Mannheim, Germany).

Blood pressure readings used for the study were measured by registered nurses or treating doctors at the clinic. It is advised for treating nurses or practitioners whilst performing a blood pressure examination to ensure standardised brachial cuff techniques in accordance with the latest South African Hypertension Guidelines⁶⁰ and The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC VII).⁶¹ However, in the current study, blood pressure reading data (SBP and DBP) for each patient was extracted from patient hospital files meaning that these blood pressure readings were measured prior to the study. The initial blood pressure measurement, number of blood pressure measurements taken for each patient and whether the mean of two or more measurements were used to work out a final measurement was not available to the study investigator. The study investigator is not able to confirm proper blood pressure technique employed at the time of blood pressure examination. The single latest blood pressure measurement, if available, for each patient, from the patient's respective file was extracted for the purposes of this study.

As previously mentioned, due to the referral nature of the Charlotte Maxeke Johannesburg General Hospital, many patients already presented with previously diagnosed complications. Defining patients, for the purposes of this study as having diabetic nephropathy using laboratory data, i.e. micro-albumin-to-creatinine ratios, serum creatinine concentrations or glomerular filtration rate (GFR) often proved inconsistent due to many patients not having these laboratory reports available in

their records. It was also found that some patients were concurrently being managed at the hospital's renal clinic, separate to the diabetic clinic. For the purposes of this study, patients deemed as having nephropathy were those patients who had one or more of the following in their records: chronic kidney disease (CKD), chronic renal disease (CRD), chronic renal failure (CRF), nephropathy and diabetic nephropathy. Where patient clinical data (e.g. Blood Pressure readings) was missing from records, no random values were registered into the database for those patients. For the purposes of calculations, patients with missing clinical data values were excluded from certain calculations (Figure 52). Table 1 shows the total number of patient clinical parameters available for use in the study for the entire cohort.

Parameter	Readings (n)	(%)
Serum Glucose		
HbA _{1c}	623	93.54
Blood Pressure	540	81.08
Systolic (No Nephropathy)	485	72.82
Diastolic (No Nephropathy)	485	72.82
Systolic (Nephropathy)	55	8.26
Diastolic (Nephropathy)	55	8.26
Plasma Lipids		
Total Cholesterol	595	89.34
LDL-Cholesterol (No CAD/Stroke)	481	72.67
LDL-Cholesterol (CAD/Stroke)	94	14.26
HDL-Cholesterol	580	87.09
Triglycerides	578	86.79

Table 1 Total clinical data obtained from patient records; Glycated Haemoglobin (HbA_{1c}), Coronary Artery Disease (CAD)

In statistical calculations, where appropriate, only the necessary variables required were used for calculations.

Most patient files had incomplete details of weight, height, diet details and smoking status. These parameters, especially the first two, would have been used to work out Body Mass Index (BMI). Since this data was unavailable, no calculations were possible. On the same note, due to missing waist measurements, patient classification of Metabolic Syndrome (MS) ⁶² was also omitted from the study.

Once data was captured into case reports, the SEMDSA 2009, American Diabetes Association 2008, IDF 2005 and European Society of Cardiology / European Association for the Study of Diabetes (ESC/EASD) ⁵⁸ 2007 treatment guidelines were applied to the cohort. As treating practitioners within South Africa use local guidelines (SEMDSA) to treat patients, the national guidelines were primarily used for NAG (Not At Goal) and AG (At Goal) studies). At the time of collection (July 2008-July 2009) the practitioners may have used the previous SEMDSA 2003 guidelines to manage their patients.

For this study, hypercholesterolaemia was defined as total cholesterol >4.5mmol/L and hypertriglyceridaemia as triglycerides >1.7 mmol/L. Patients receiving lipid-lowering therapy were not classified as having hyperlipidaemia as therapy could have been instituted for either primary or secondary prevention purposes. Patients were considered hypertensive if they were being treated with hypertensive medication, as many patients on therapy had controlled blood pressure levels. In instances where patients were not being treated with an oral hypoglycaemic or

insulin therapy or a combination of both, lifestyle modification in the form of diet was assumed as the mechanism of glucose lowering therapy.

It was not possible to risk rate or classify patients by means of the Framingham risk scoring system as T2DM patients are already considered high risk i.e. necessitating secondary treatment.⁶³

According to the latest T2DM guidelines (see appendix vii)^{48 56 57 58} T2DM patients:

without previously established vascular disease (such as ischaemic heart disease, cerebrovascular disease or peripheral vascular disease), the LDL-C target of ≤ 2.5 mmol/L is recommended.

with established vascular disease (such as ischaemic heart disease, cerebrovascular disease or peripheral vascular disease), the LDL-C target of ≤ 1.8 mmol/L is recommended.

For the purposes of this study, as per the latest guidelines (see appendix vii)^{48 56 57 58} the following thresholds were defined:

Patients *without* previously established vascular disease were classified as “Lower Risk” and have an LDL-C target threshold: 2.5 mmol/L.

Patients *with* established vascular disease were classified as “Higher Risk” and have an LDL-C target threshold: 1.8 mmol/L.

For patients in both “lower risk” and “higher risk” not achieving LDL-C goals or targets as set by guidelines (see appendix vii),^{48 56 57} using an adaptation from previous guideline studies,^{64 65} LDL-C calculations for “Lower Risk” and “Higher risk” patients was conducted as follows:

Mean “Off” Target level or “Gap” =

The population mean of the patients not at goal (mmol/L) - Guideline recommended LDL-C goal level (mmol/L) X 100

The population mean of the patients not at goal (mmol/L)

Mean “Off” Target level or “Gap” for “Lower Risk” Patients =

$$\frac{\text{The population mean of the patients not at goal (mmol/L)} - (2.5 \text{ mmol/L})}{\text{The population mean of the patients not at goal (mmol/L)}} \times 100$$

The population mean of the patients not at goal (mmol/L)

Mean “Off” Target level or “Gap” for “Higher Risk” Patients =

$$\frac{\text{The population mean of the patients not at goal (mmol/L)} - (1.8 \text{ mmol/L})}{\text{The population mean of the patients not at goal (mmol/L)}} \times 100$$

The population mean of the patients not at goal (mmol/L)

The results were calculated using the means and not the average of the means. When each individual was calculated separately and then the average of this was calculated, the difference (and percentage) is equivalent.

Statistical and Data Analysis

A descriptive analysis was conducted which included summary measures, frequency tables and cross-tabulations. Means and standard deviations were calculated for the following: age, gender, race, blood pressures, glycated haemoglobins and fasting lipids. The percentage of previous CAD, stroke, nephropathy, neuropathy and retinopathy history in patients were also calculated including frequency of usage of chronic medication for the treatment of glucose, hypertension, lipids as well as receiving anti-platelet treatment. The percentage of patients reaching SEMDSA, ADA, IDF and ESC/EASD treatment goals for different clinical parameters was also tabulated.

Cross-tabulations of summary measures by gender were done to investigate gender differences, if any. Chi-square test was used to investigate whether there were any statistically significant associations of these measures with gender. Where necessary, unpaired Student's *t*-test was used to compare mean differences. Shapiro-Wilk W test was performed to determine normality. If data was not normally distributed, the median and interquartile range (IQR) was reported. A linear regression model was fitted to look at gender differences adjusted for age. A significance level of 5% was used for all the statistical tests conducted.

Microsoft Office Excel 2007 was utilised for the study's databases and statistical analysis was done using STATISTICA version 8.0.

Ethical Considerations

Data from the CRF was entered into a secure database at the University Of Witwatersrand, Faculty of Health Science.

Prior to the study, the Human Research Ethics Committee (HREC) granted ethical approval of the study. Ethics protocol number: M080409 (Figure 49).

RESULTS

This observational study was conducted at the Charlotte Maxeke Johannesburg Academic Hospital between January 2008 and January 2010. In total, the records of 785 patients were captured for the study. After applying study criteria to the captured data, the final cohort consisted of 666 patients. Exclusion criteria included having one or more of the following: patients having a positive diagnosis for type 1 diabetes mellitus, having gestational diabetes, steroid-induced diabetes or triglyceride levels > 5 mmol/L. The cohort consisted of 666 patients of whom 369 (55%) were women. Ages ranged from 29 to 94 years, the mean age for the cohort was 63 (SD: 11.84) years.

Demographics

Using patient records at the Charlotte Maxeke Johannesburg Academic Hospital, CRF were completed. The ethnicity of the participants enrolled are shown in Table 2 and Figure 1.

	n	%
African	285	42.79
Caucasian	196	29.43
Asian	130	19.52
Coloured	39	5.86
Unknown	16	2.40
Total	666	100.00

Table 2 Ethnicity of type 2 diabetic study population

One aim of the study was to document how well T2DM patients were being treated in a South African, public sector setting. The cohort comprised of patients initially

referred from their primary local clinics to a tertiary public sector clinic. This reflects the quality of care the state can provide, especially to those in the lower socio-economic class who cannot afford private health care.

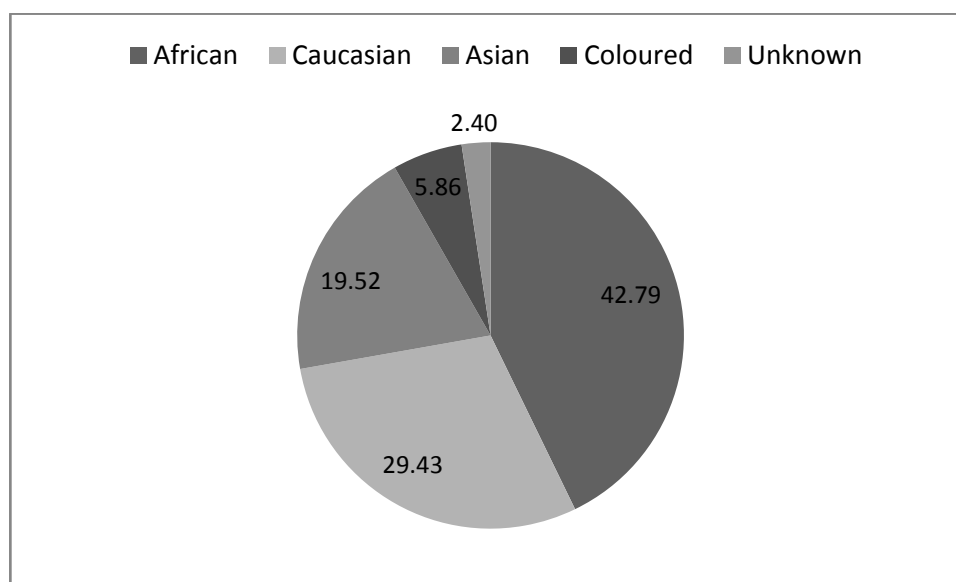


Figure 1 Ethnicity of study type 2 diabetic population

The total study cohort consisted of nearly half African population (42.79%). This study aimed to determine the level of care patients receive in South Africa, it may be said that the cohort breakdown is fairly representative of not only of patients receiving treatment in the public sector, but also that of the country's overall population.

Ages

The mean age for the cohort was 63 (SD: 11.86) years. The age range for the entire cohort was between 29 to 94 years and does not follow a Gaussian distribution ($p < 0.05$), a median of 63 years (IQR = 54.00 – 70.00) was found. (Figure 2)

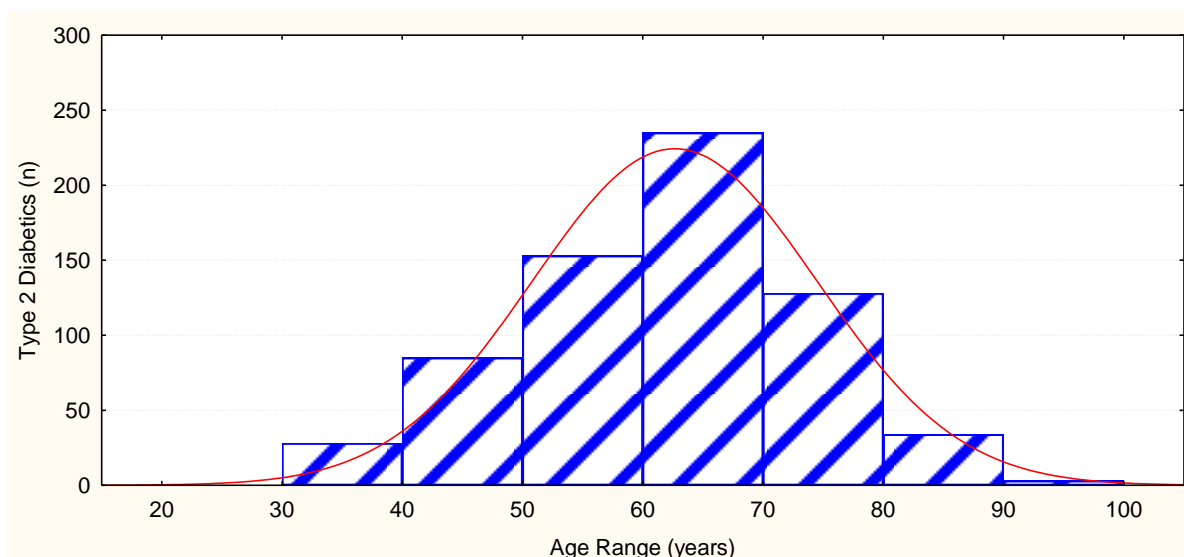


Figure 2 Age distribution of type 2 diabetic study cohort

Mean ages by gender was almost identical, 62 (SD: 11.95) and 63 (SD 11.79) for men and women, respectively.

Previously Established Cardiovascular Equivalent Conditions

Events / Disease	Occurrence
Angina	17
Angioplasty	3
CABG	13
CAD	9
IHD	30
Myocardial Infarct	13
NSTEMI	1
PVD	20
Stent	2
Stroke	16
TIA	4
Triple Bypass	1
TOTAL	129

Table 3 Total CVD-related events or disease amongst study type 2 diabetics; Coronary Artery Bypass Graft (CABG), Coronary Artery Disease (CAD), Ischaemic Heart Disease (IHD), Non-ST Segment Myocardial Infarction (NSTEMI), Peripheral Vascular Disease (PVD), Transient Ischemic Attack (TIA)

In total, there were 129 events or cardiovascular disease equivalent conditions.

103/666 patients (15.5%) had macrovascular disease as some patients had multiple cardiovascular events/strokes. (Figure 3)

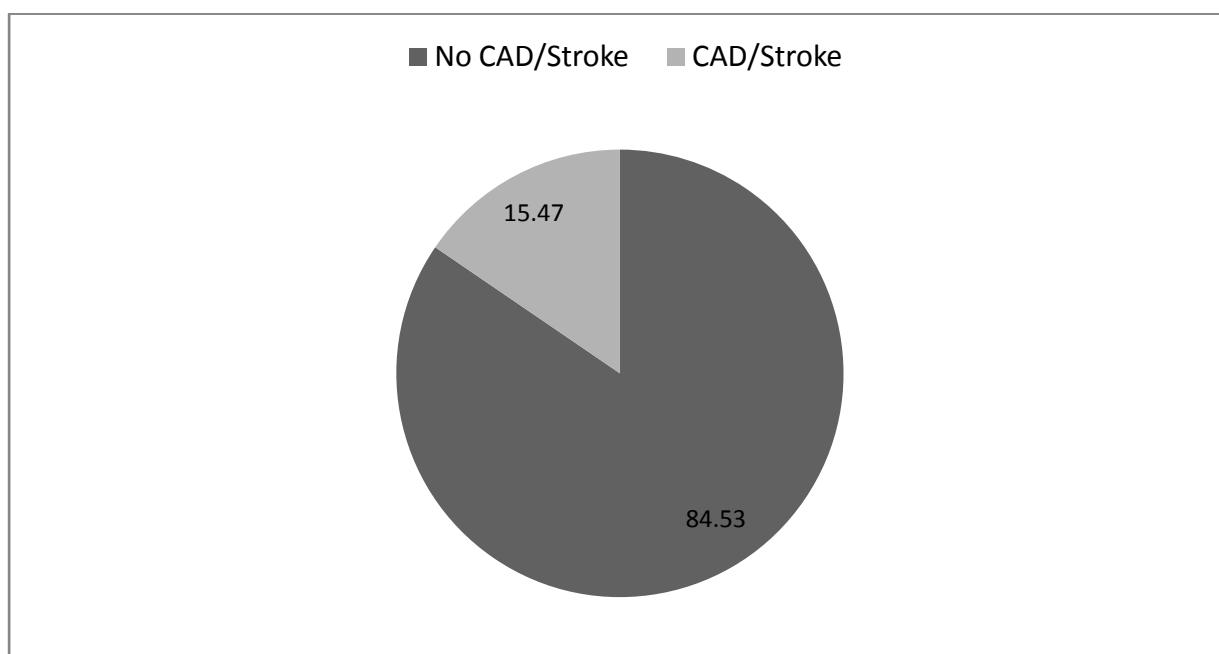


Figure 3 % type 2 diabetics with previously established vascular disease; Coronary Artery Disease (CAD)

In Figure 4, a statistically significant association between ethnicity and prevalence of cardiovascular disease was found ($p < 0.05$). The Asian population had the highest rate of cardiovascular disease, in comparison, the Caucasian population had the second highest rate, but this was not statistically significant (Asian 25.38% vs. Caucasian 23.98%, $p = 0.774$). Despite having the highest count ($n = 285$, comprising 42.79% of the total cohort), the African population had the lowest rate of cardiovascular disease (5.00%). With only 39 patients comprising the Coloured population, 10.26% had some form of cardiovascular disease.

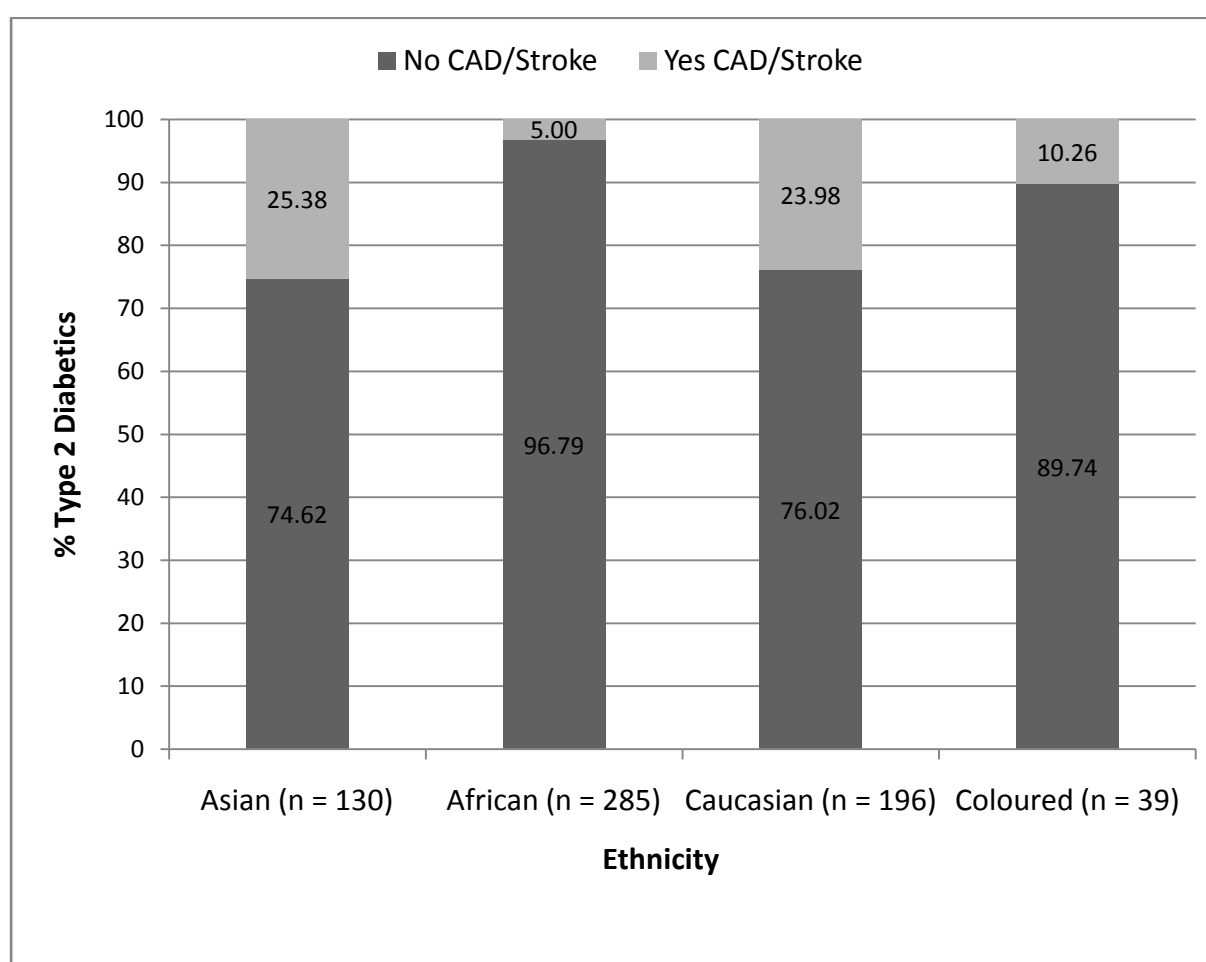


Figure 4 Cardiovascular disease of study type 2 diabetics by ethnicity

Amongst the patients who had microvascular complications, nephropathy was the most common, affecting 78 patients (11.8%) of the cohort. This was followed by 47 patients (7.1%) having neuropathy and 42 patients (6.4%) having retinopathy. Males had an apparently higher prevalence of both macro and microvascular complications, except retinopathy, but this was not statistically significant (male 5.4% vs. female 7.1%, $p = 0.382$). By gender, there was no statistically significant differences for any of the other complications namely, CAD (male 17.2% vs. 11.9% female, $p = 0.054$), stroke (male 3.7% vs. 2.4% female, $p = 0.343$), nephropathy (male 12.5% vs. female 11.1%, $p = 0.592$) and neuropathy (male 7.4% vs. female 6.8%, $p = 0.752$) (Figure 5).

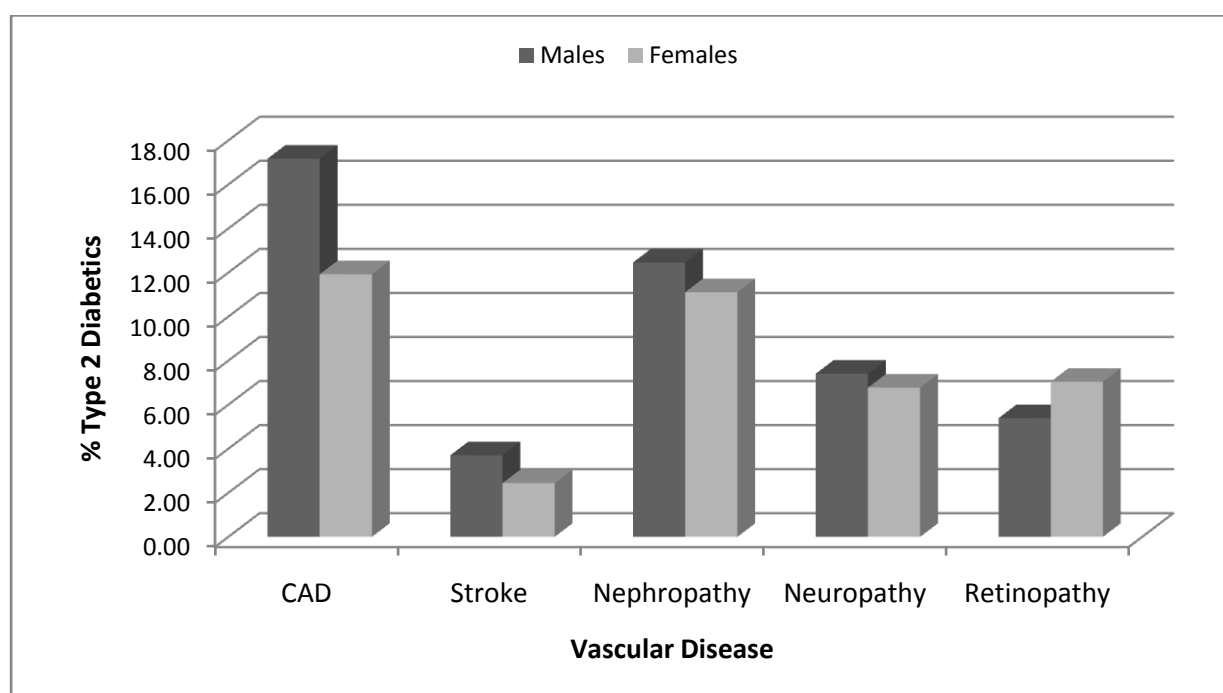


Figure 5 Microvascular and macrovascular disease across genders in type 2 diabetic study population; Coronary Artery Disease (CAD), females (F), males (M)

There were 73 patients (11%) receiving thyroid medication and 47 patients (7.1%) were receiving medication for hyperuricemia.

Blood Pressure Control

From the total cohort (666 patients), 569 (85.44%) were hypertensive and 97 (14.56%) were normotensive. The mean SBP and DBP readings for the cohort were 134 mmHg (SD: 20.0) and 79 mmHg (SD: 11.7), respectively.

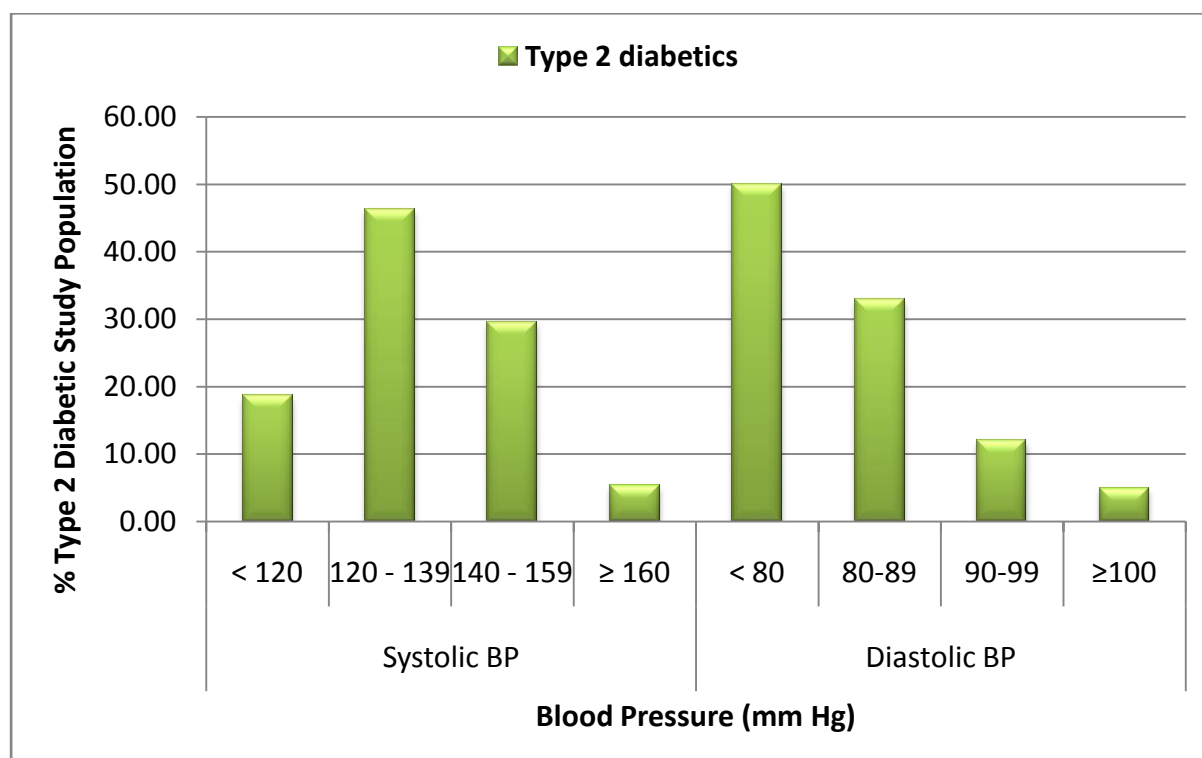


Figure 6 Total blood pressure readings of type 2 diabetic study population; Blood Pressure (BP)

Five hundred and sixty nine patients (85.43% of the total 666 study population) were being treated for hypertension. From these, a portion had a positive history for diabetic nephropathy (which will ultimately affect their recommended BP targets).

	n	%
Hypertensive without diabetic nephropathy	495	74.32
Hypertensive with diabetic nephropathy	74	11.11
Total Hypertensive Population	569	85.43

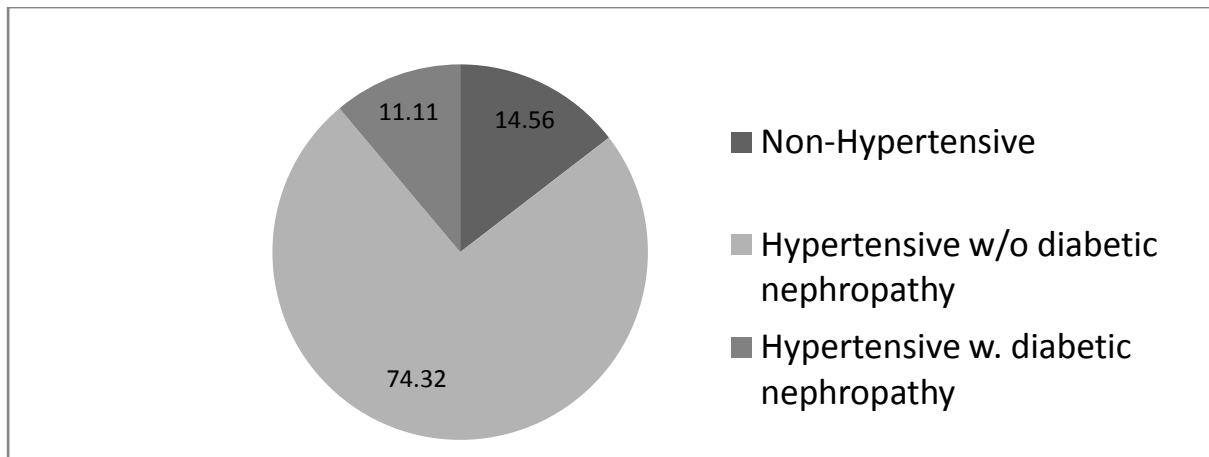


Figure 7 % hypertension amongst type 2 diabetic study population

The normotensive patients in the cohort had a mean SBP of 124 mmHg (SD: 13.0) and DBP of 75 mmHg (SD: 9.7). The hypertensive patients in the cohort had a mean SBP of 135 mmHg (SD: 20.5) and DBP of 78 mmHg (SD: 11.9). In comparison, there was a statistically significant difference between SBP (hypertensive 135 mmHg vs. normotensive 124 mmHg, $p < 0.01$) and no statistically significant difference between DBP (hypertensive 78 mmHg vs. normotensive 75 mmHg, $p = 0.070$).

The hypertensive T2DM patients were receiving different numbers of antihypertensive drug classes as follows: 117 patients (17.57%), 177 patients (26.58%) and 275 patients (41.29%) were being treated with 1, 2 and ≥ 3 antihypertensive drug classes, respectively (Figure 8).

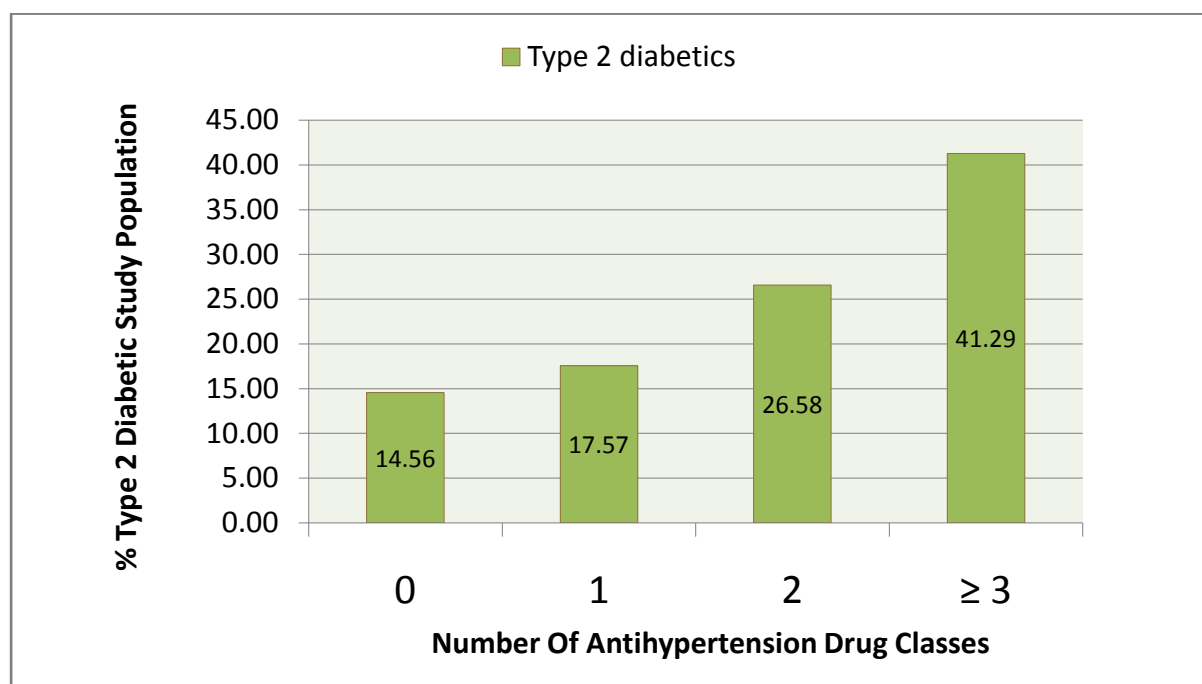


Figure 8 Number of antihypertensive medication classes taken by study type 2 diabetic population

Most of the patients were on an ACE Inhibitor (79.96%). Diuretics were prescribed to 397 patients (69.77%). Two hundred and sixty five patients (46.57%) were receiving calcium channel blockers and one-hundred patients (17.57%) were receiving β -blockers. Especially with the two most frequently prescribed anti-hypertensive classes (ACE Inhibitors and Diuretics), it can be seen how combination therapy is prevalent amongst diabetics in the cohort (Figure 9).

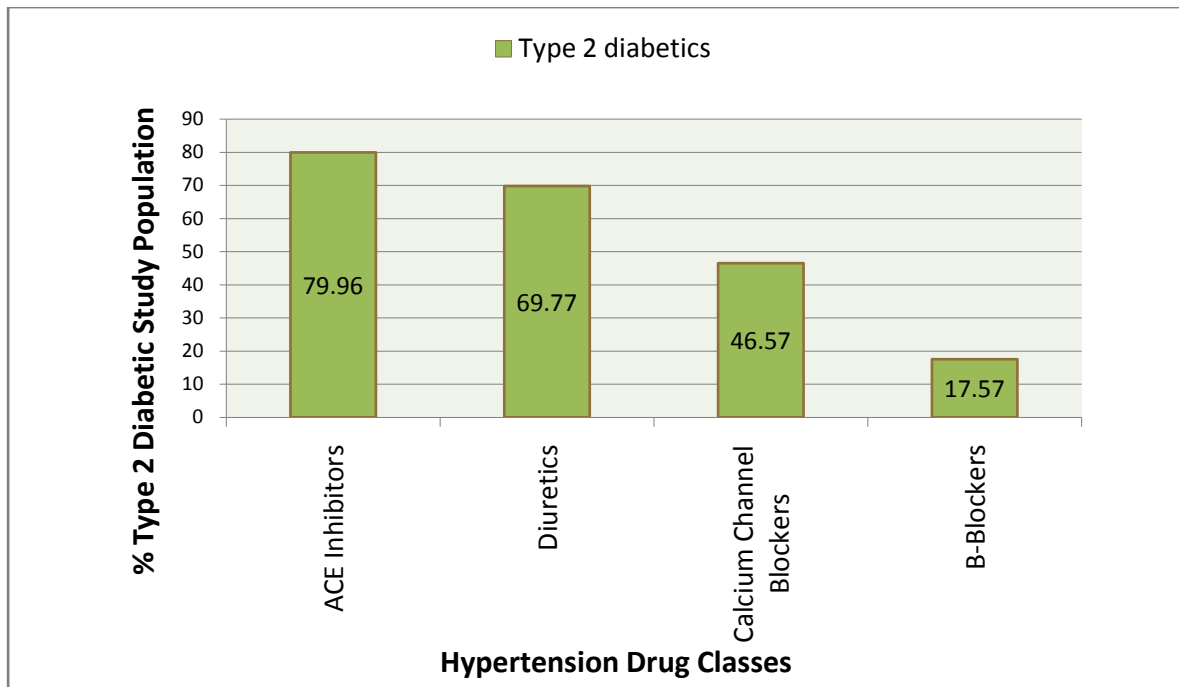


Figure 9 % type 2 diabetic study population receiving different classes of antihypertensives

In the cohort, females had slightly higher systolic blood pressure readings than males (female SBP 136 mmHg (SD: 19.4) vs. male SBP 132 mmHg (SD: 20.6)), $p = 0.028$). More females were being treated for hypertension (88.4% females vs. 81.9% males, $p = 0.018$) (Table 4).

Age Ranges	Mean BP-SYS		Mean BP-DIAS	
	M	F	M	F
30-39	125.60	127.83	75.00	79.83
40-49	135.70	126.56	84.60	78.94
50-59	135.36	134.78	81.13	79.70
60-69	130.25	136.81	77.44	78.23
70-79	133.82	139.63	75.36	77.26
80-89	134.00	144.24	76.50	80.67
90-99	130.00	155.00	80.00	70.00

Table 4 blood pressure comparison amongst study type 2 diabetics; females (F), males (M)

For patients without documented diabetic nephropathy, the recommended SEMDSA/IDF treatment targets (SBP ≤ 130 mmHg; DBP ≤ 80 mmHg) were reached far more easily for DBP than SBP (DBP 69.1% vs. SBP 54.6%, $p < 0.01$). Only 222 (45.8%) reached the goals for both (Figure 10).

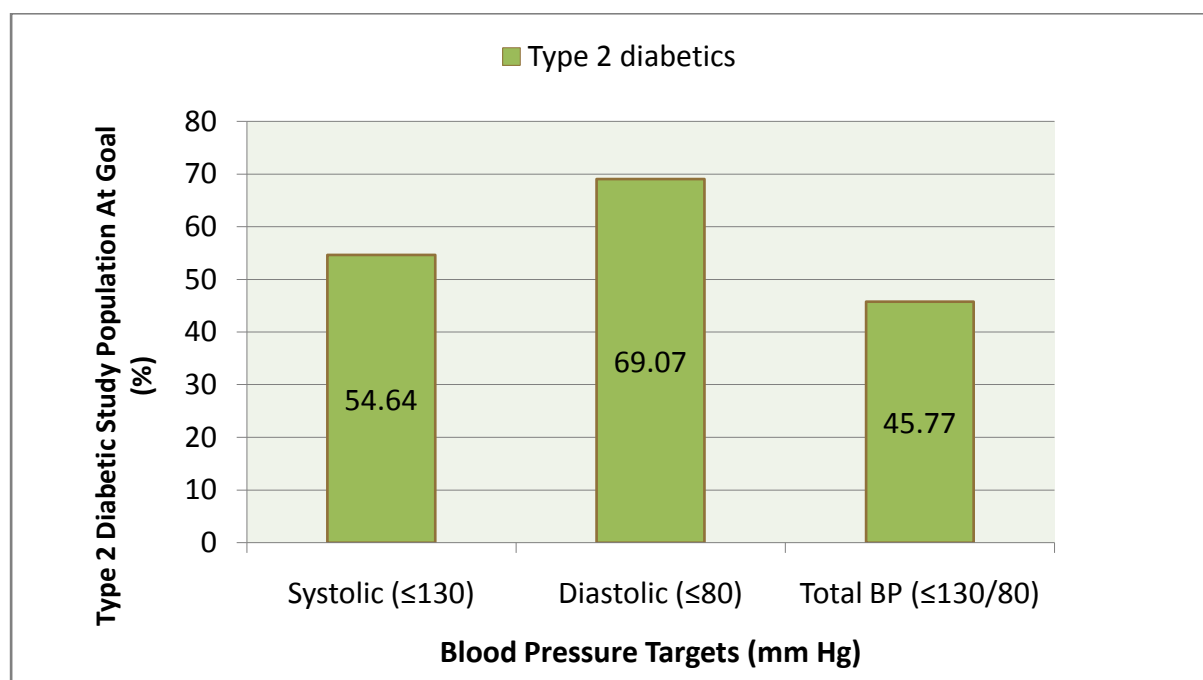


Figure 10% type 2 diabetic study population without diabetic nephropathy achieving SEMDSA blood pressure goals

In the study sample, seventy-four patients (11.11%) had documented nephropathy. These patients have stricter SEMDASA/IDF treatment targets (SBP ≤ 120 mmHg; DBP ≤ 70 mmHg). Only 25.5% of these patients achieved the SBP goal and 32.7% patients achieved the DBP goal (DBP 32.7% vs. SBP 25.5%, $p = 0.013$). Both SBP and DBP were achieved by 16.4% (Figure 11).

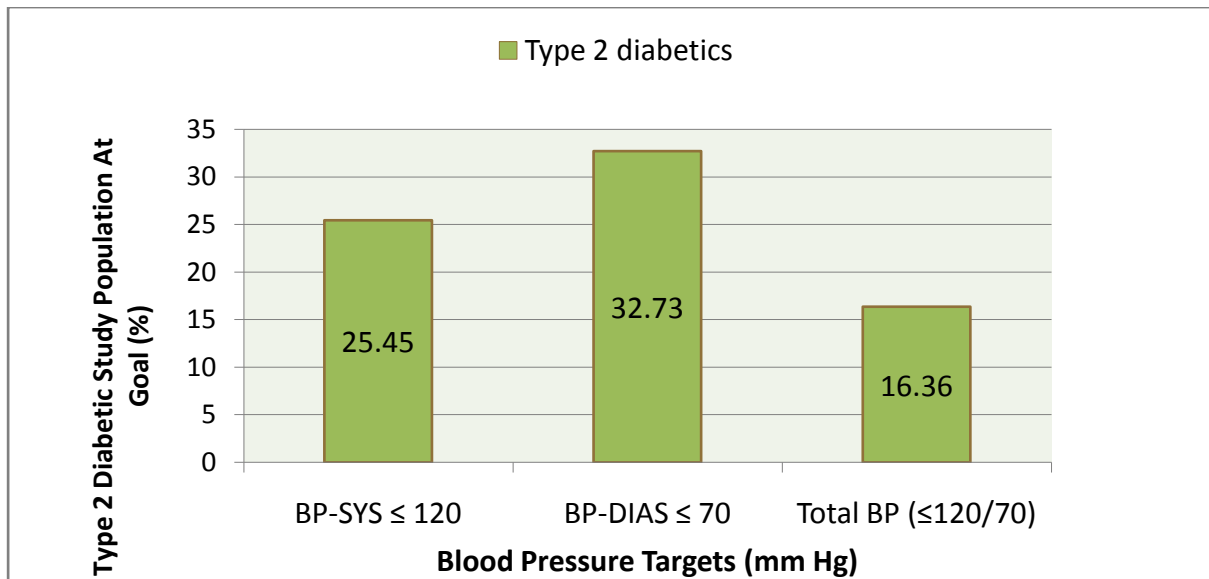


Figure 11 % type 2 diabetic study population with diabetic nephropathy achieving SEMDSA blood pressure goals; Systolic Blood Pressure (BP-SYS), Diastolic Blood Pressure (BP-DIAS), Blood Pressure (BP)

Blood pressure goal achievement by number of antihypertensive classes taken (in patients without nephropathy) revealed that patients on monotherapy (i.e. one class of antihypertensive class) apparently achieved blood pressure goals more easily than those on antihypertensive combination therapy (Figure 12).

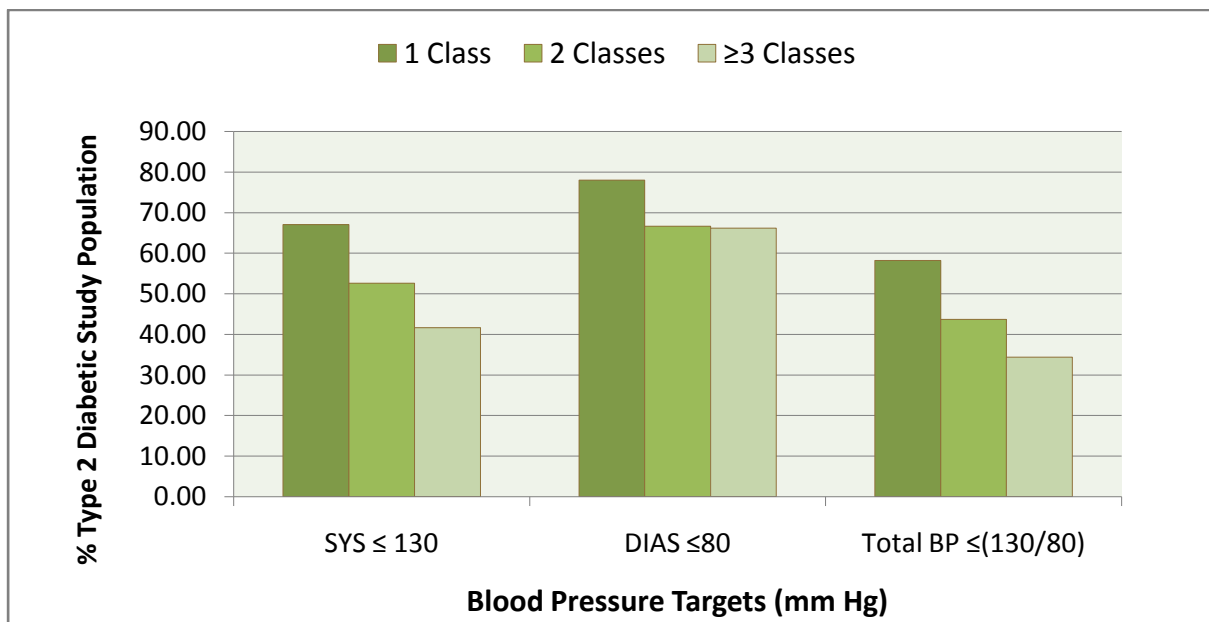


Figure 12 % type 2 diabetic study population without nephropathy achieving SEMDSA blood pressure goals by number of drug classes; Systolic Blood (SYS), Diastolic Blood Pressure (DIAS), Blood Pressure (BP)

Goal attainment by number of antihypertensive drug classes in patients with nephropathy was not possible due to limitations in patient numbers.

Patients without documented diabetic nephropathy who did not reach blood pressure SEMDSA target ($\leq 130/80$ mmHg) were analysed for the level at which they were not at goal (NAG). In Figure 10, it was apparent that fewer patients achieved target SBP than DBP. Further analysis of patients without nephropathy not reaching the SEMDSA blood pressure targets revealed that patients with uncontrolled SBP apparently were more uncontrolled by the first 10 mmHg more than any other range (SBP 47.3% (≤ 10 mmHg range) vs. SBP 27.8% (10-20 mmHg range), $p < 0.01$) and (SBP 47.3% (≤ 10 mmHg range) vs. SBP 25.5% (≥ 20 mmHg range), $p < 0.01$) (Figure 13). Comparing uncontrolled levels of SBP and DBP, patients generally appear to follow a more balanced/equally distributed spread for SBP over all the ranges compared with DBP.

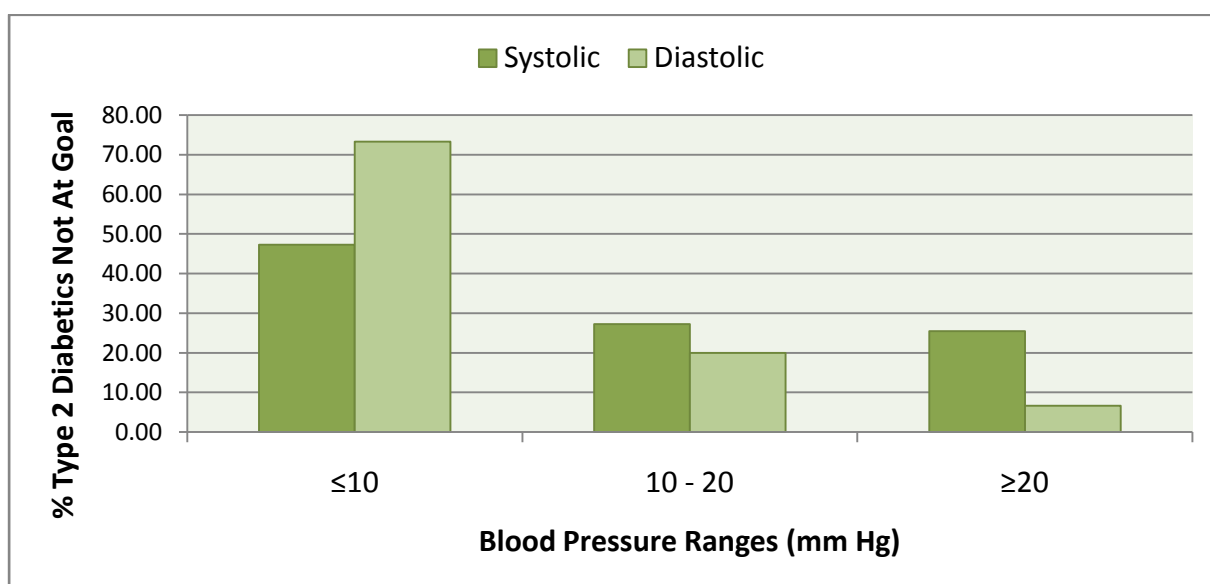


Figure 13 % type 2 diabetic study population without nephropathy not at goal (130/80 mm Hg) by blood pressure ranges

Patients with documented diabetic nephropathy which did not reach SEMDSA goal for blood pressure ($\leq 120/70$ mmHg) were analysed for the level at which they were off goal (Figure 14). There were 48.65% of patients not reaching the 70 mmHg DBP target by ≤ 10 mmHg. A further 40.54% of patients had uncontrolled DBP by 10 – 20 mmHg, whilst 10.81% of patients in the study were away from the DBP target of 70 mmHg by ≥ 20 mmHg. There were equal numbers of patients in the study with uncontrolled levels of SBP in both the ≤ 10 mmHg and 10-20 mmHg ranges. There were 46.34% of patients with uncontrolled levels of SBP by ≥ 20 mmHg away from the desired SBP target of 120 mmHg.

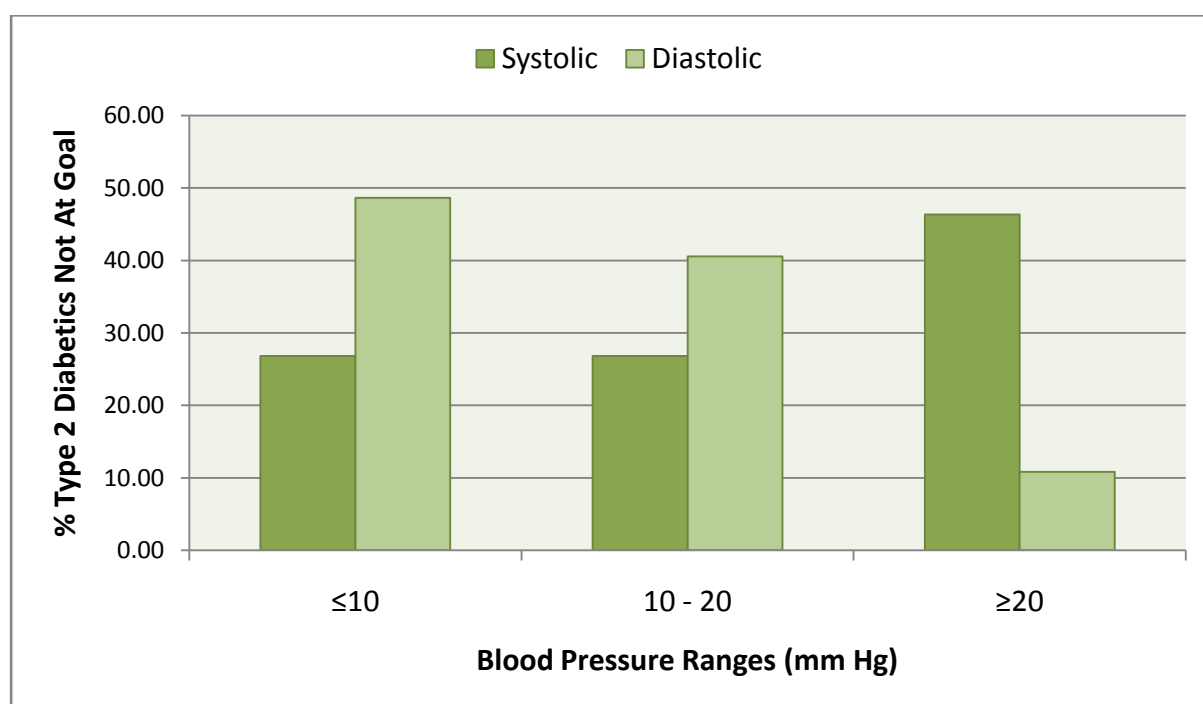


Figure 14 % type 2 diabetic study population with nephropathy not at goal (120/70 mm Hg) by blood pressure ranges

From the total cohort, 12 patients (2.59%) did not meet either blood pressure targets and were not receiving anti-hypertensive treatment for this risk factor.

Glycaemic Control

The mean HbA_{1c} for the cohort was 8.8% (SD: 2.5). The HbA_{1c} range was from 4.8% to 24.2%. HbA_{1c} was not normally distributed ($p < 0.05$) and the median was 8.1% (IQR = 7.00 – 10.10) (Figure 15).

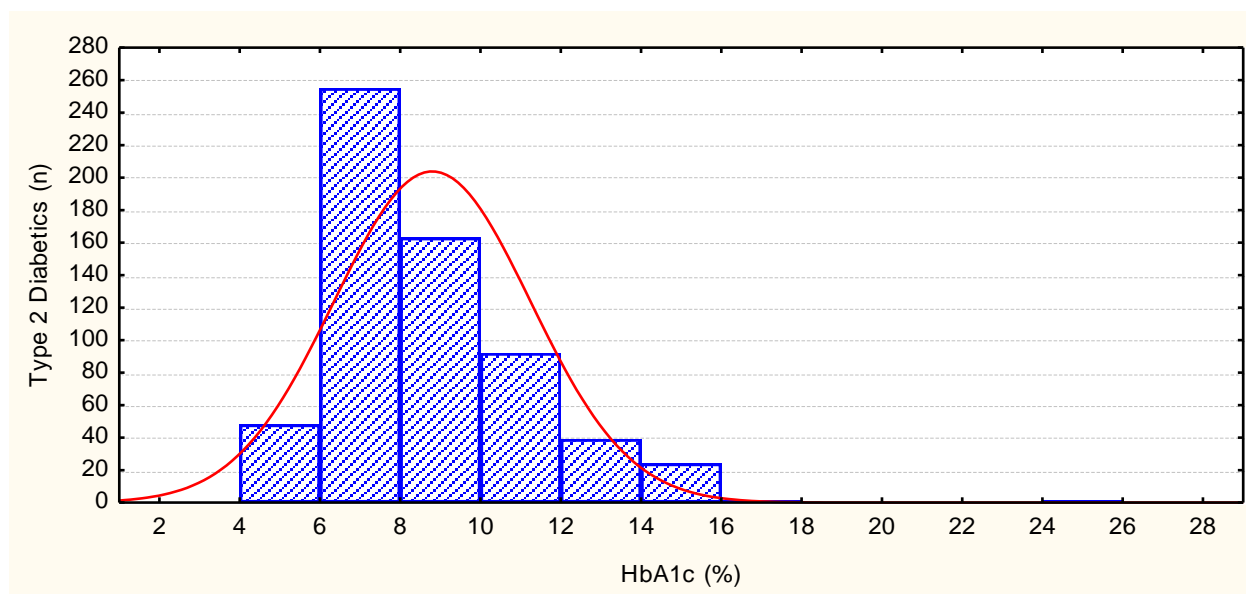


Figure 15 HbA_{1c} of study type 2 diabetic population; Glycated Haemoglobin (HbA_{1c})

Ninety-nine patients (15.9%) had HbA_{1c} of <6.5% in comparison to one-hundred and ninety three (31.0 %) which had HbA_{1c} of 6.5%-8.0% (HbA_{1c} <6.5% range vs. HbA_{1c} 6.5% - 8.0% range, $p < 0.01$). Three hundred and thirty one patients (53.1%) had an HbA_{1c} of >8% (HbA_{1c} >8% range vs. HbA_{1c} <6.5% range and HbA_{1c} 6.5% - 8.0%, $p < 0.01$ and $p < 0.01$, respectively) (Figure 16).

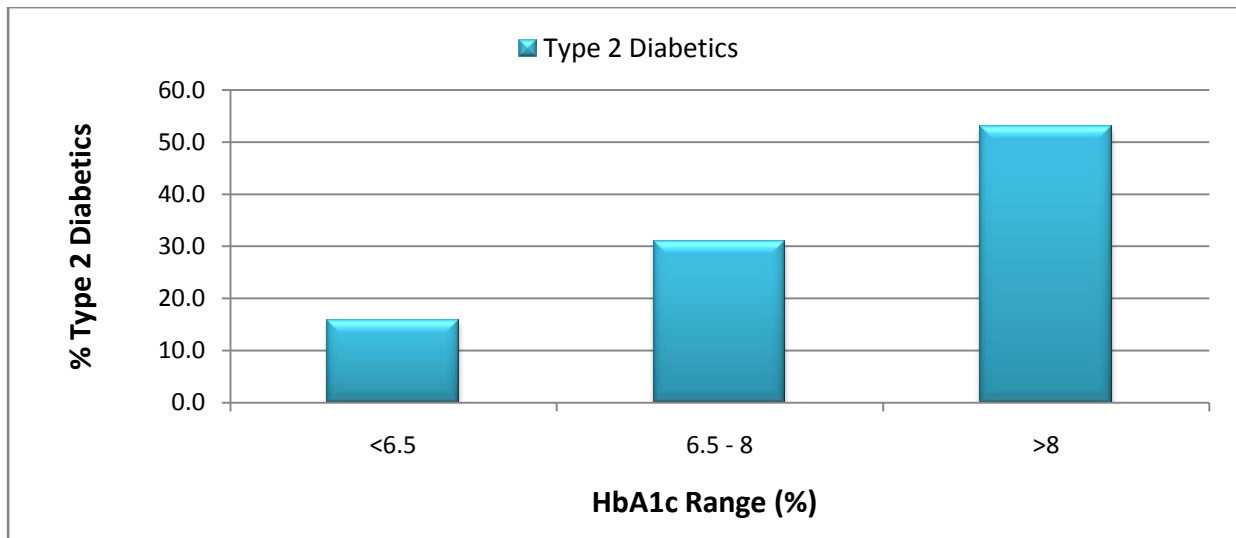


Figure 16 HbA_{1c} of study type 2 diabetic population; Glycated Haemoglobin (HbA_{1c})

One hundred and forty five patients (23.3%) had a HbA_{1c} of less than 7%. One hundred and forty six patients (23.4%) had an acceptable 7% - 8% range. Three hundred and thirty two patients (53.3%) had an HbA_{1c} of >8% (where additional treatment needs to be initiated). There was no statistical difference between HbA_{1c} <7% range vs. HbA_{1c} 7-8% range, ($p = 0.947$), but there was a statistical difference between HbA_{1c} >8 range vs. HbA_{1c} <7% range and HbA_{1c} 7-8% range ($p < 0.01$ and $p < 0.01$, respectively) (Figure 17).

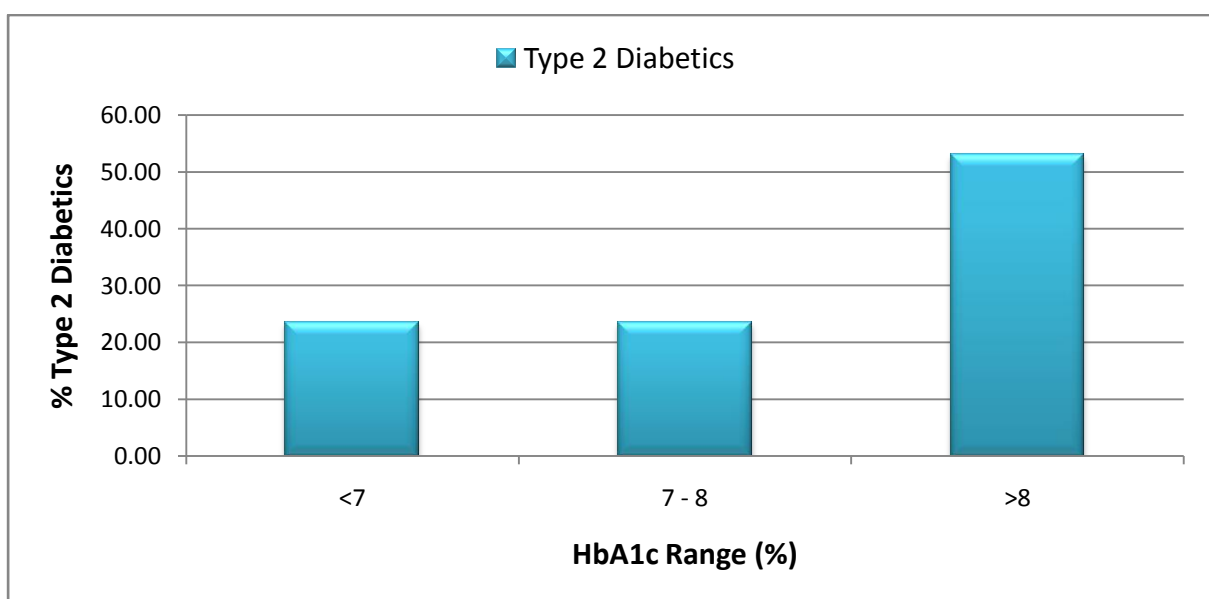


Figure 17 HbA_{1c} of study type 2 diabetic population; Glycated Haemoglobin (HbA_{1c})

Females had slightly higher mean HbA_{1c} than males (female 8.9% (SD: 2.6) vs. male 8.5% (SD: 2.3)), but this was not statistically significant (p= 0.053) (Figure 18).

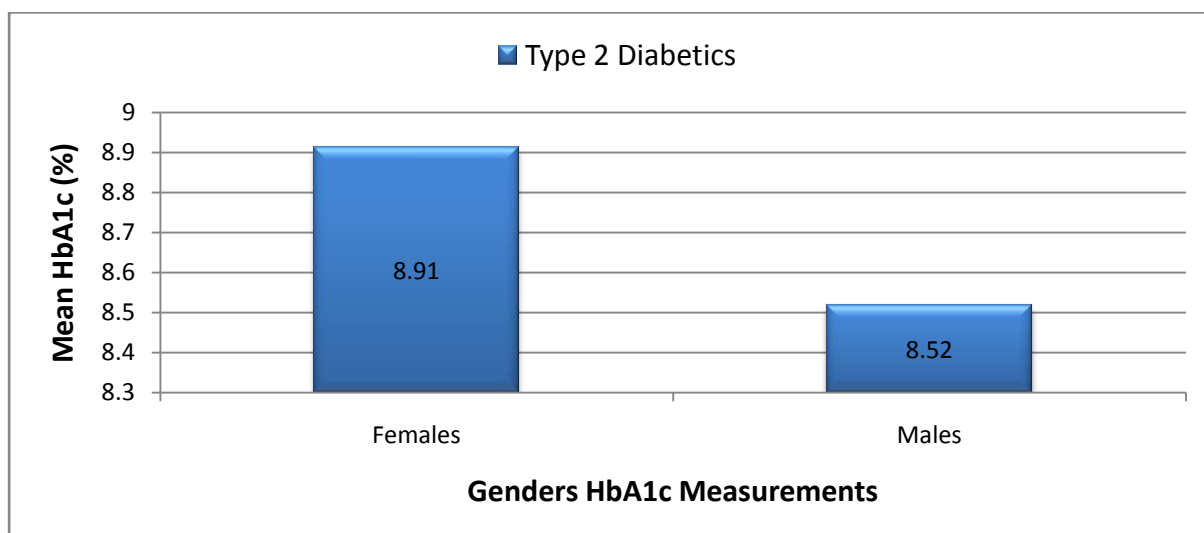


Figure 18 Mean gender HbA_{1c} comparison amongst study type 2 diabetics; Glycated Haemoglobin (HbA_{1c})

Diet alone was used in 16 patients (2.4%). 196 patients (29.4%) were receiving oral hypoglycaemic therapy alone, 229 (34.4%) were on a combination of both oral hypoglycaemic and insulin therapy. 225 patients (33.8%) were receiving insulin alone (Figure 19).

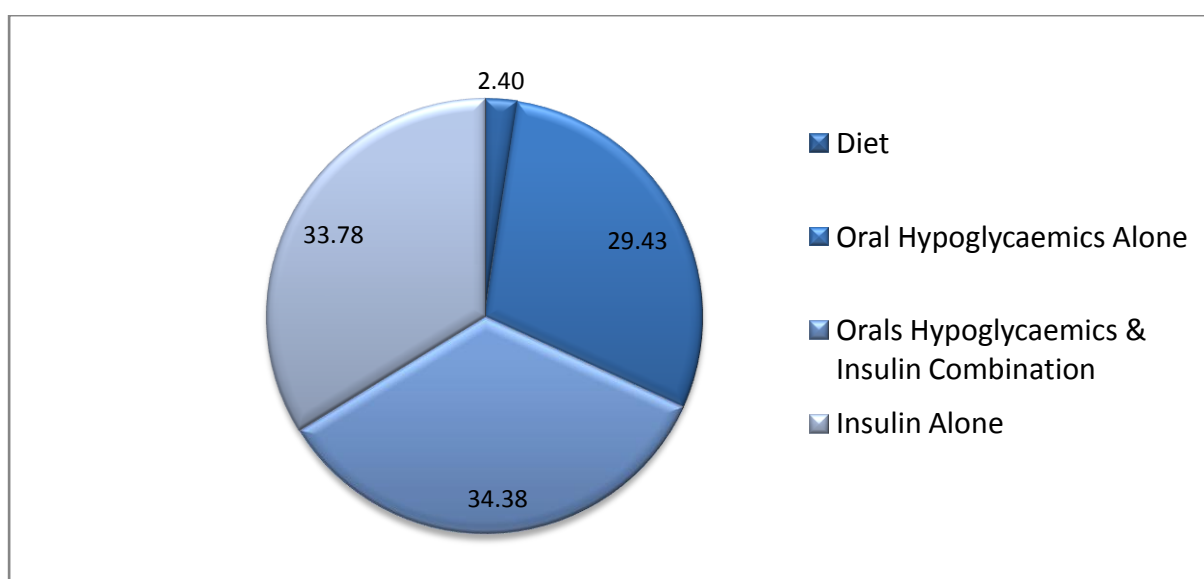


Figure 19 % type 2 diabetic study population receiving different hypoglycaemic therapy

Males apparently received more oral hypoglycaemic monotherapy (male 30.6% vs. female 28.5%, $p = 0.591$) and insulin monotherapy (male 36.7% vs. female 31.4%, $p = 0.455$), both not statistically significant. Females were more frequently on a combination of oral hypoglycaemic and insulin (female 37.9% vs. male 29.9%, $p = 0.031$), which was statistically significant (Figure 20).

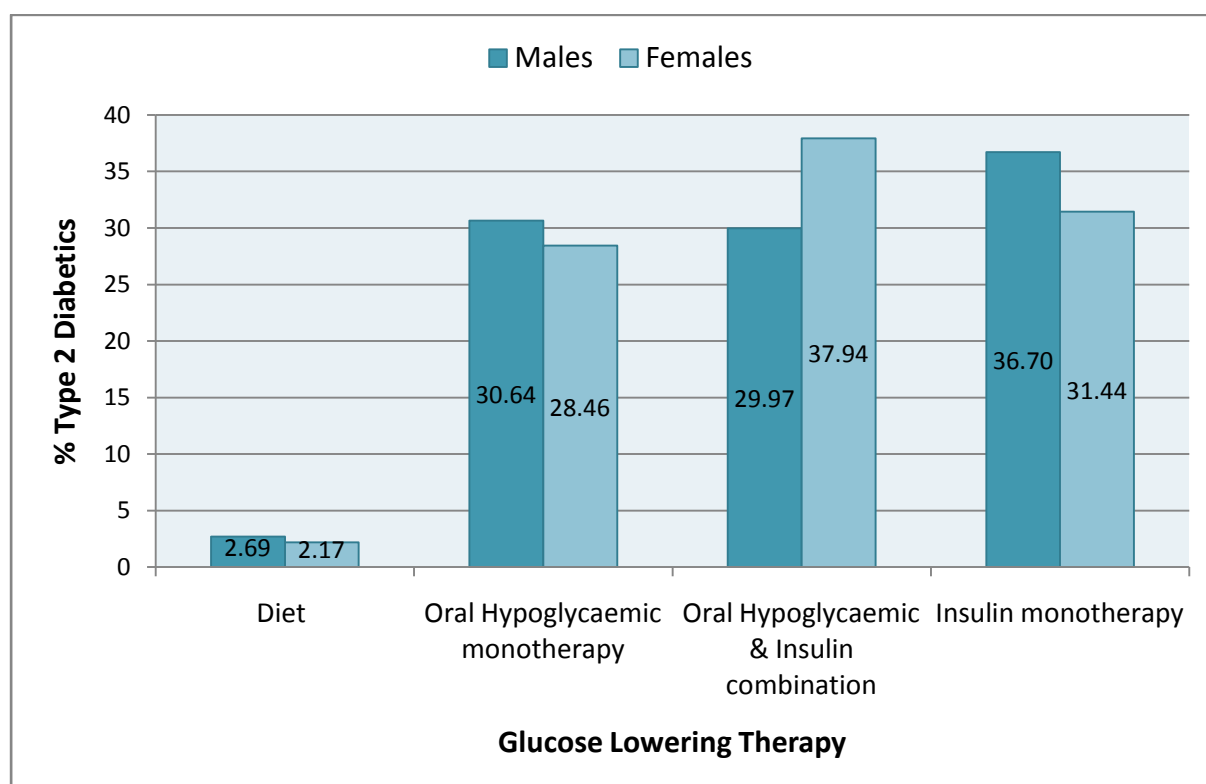


Figure 20 Gender glucose therapy comparison amongst study type 2 diabetics

Patients receiving insulin monotherapy had the highest HbA_{1c} 9.40% (SD: 2.6) whilst patients on insulin and hypoglycaemic combination therapy had an HbA_{1c} of 9.11% (SD: 2.3), (HbA_{1c} insulin monotherapy 9.40% vs. HbA_{1c} combination therapy 9.11%, $p = 0.097$). Patients being treated with oral hypoglycaemics alone had an HbA_{1c} of 7.67% (SD: 2.0), whilst, the lowest HbA_{1c} of 6.25% (SD: 1.0) was present in patients on diet alone (HbA_{1c} oral hypoglycaemics 7.67% vs. HbA_{1c} diet alone 6.25, $p = 0.007$) (Figure 21).

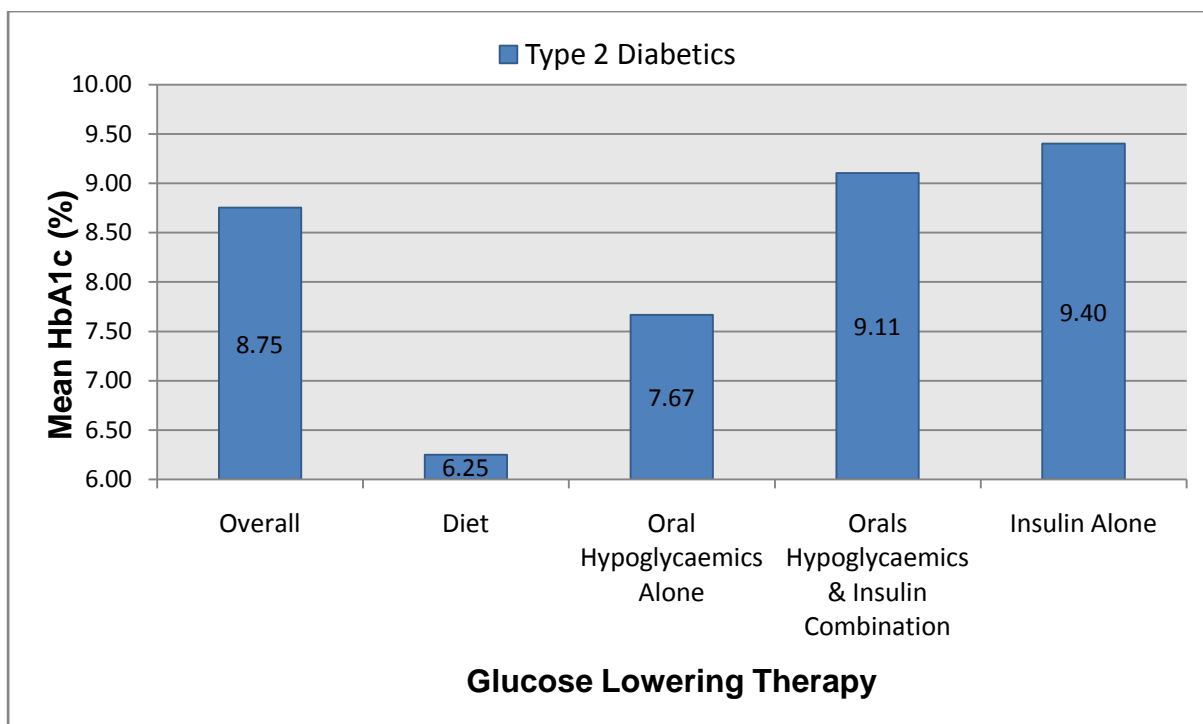


Figure 21 Mean HbA1c of type 2 diabetic study population by glucose-lowering therapy; Glycated Haemoglobin (HbA1c)

The study population used three classes of oral hypoglycaemics, namely Biguanides, Sulphonylureas and Thiazolidinediones. Three hundred and ninety seven patients (70%) were receiving Biguanides, one hundred and sixty two patients (29%) were receiving Sulphonylureas whilst four patients were on Thiazolidinediones (1%) (Figure 22).

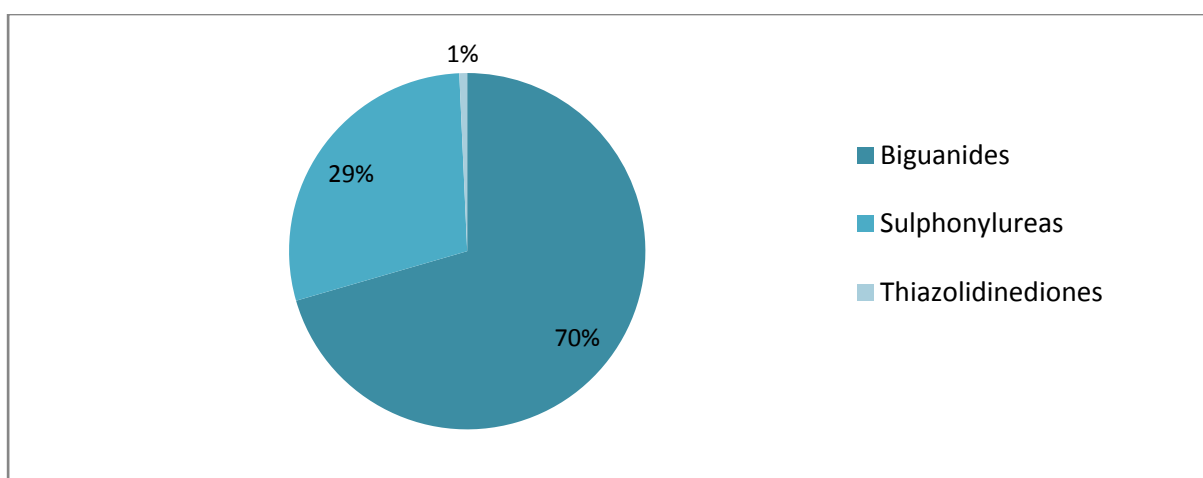


Figure 22 Type 2 diabetic study population receiving different oral hypoglycaemic therapy

The number of oral hypoglycaemics classes taken by study patients varied: 284 (66.8%) received one class, 139 (32.7%) received two classes and 2 patients (0,5%) received three classes (Figure 23).

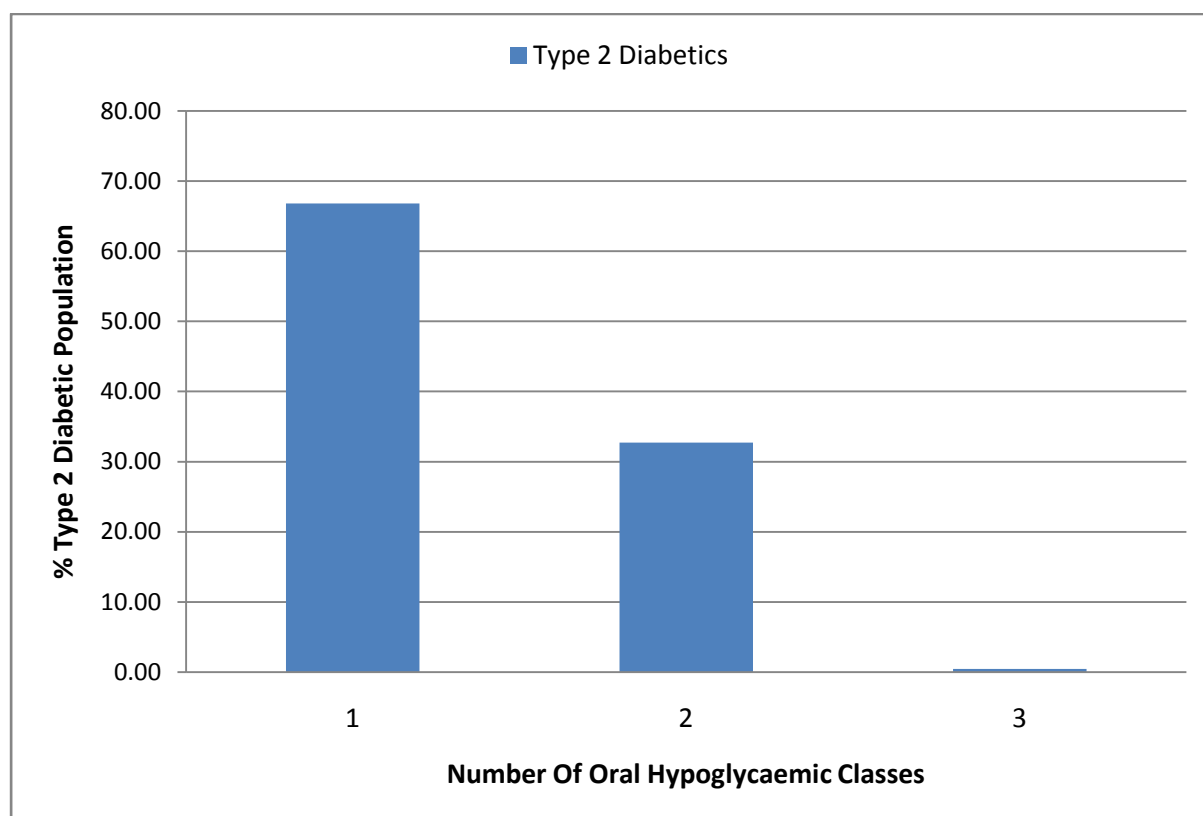


Figure 23 Number of oral hypoglycaemic medication classes taken by study type 2 diabetic population

Further analysis revealed that monotherapy with Biguanides (namely Metformin 850mg) were the most common form of oral hypoglycaemic taken, as they were taken by 261 patients (61.5%) (Biguanides vs. Biguanides / Sulphonylurea combination and Sulphonylurea monotherapy, $p < 0.01$ and $p < 0.01$, respectively). Biguanides / Sulphonylurea combination was taken by 134 patients (31.6%). Sulphonylurea monotherapy was taken by 25 patients (5.9%). There were 5 patients (1%) taking a Thiazolidinedione (either Pioglitazone or Rosiglitazone) (Figure 24).

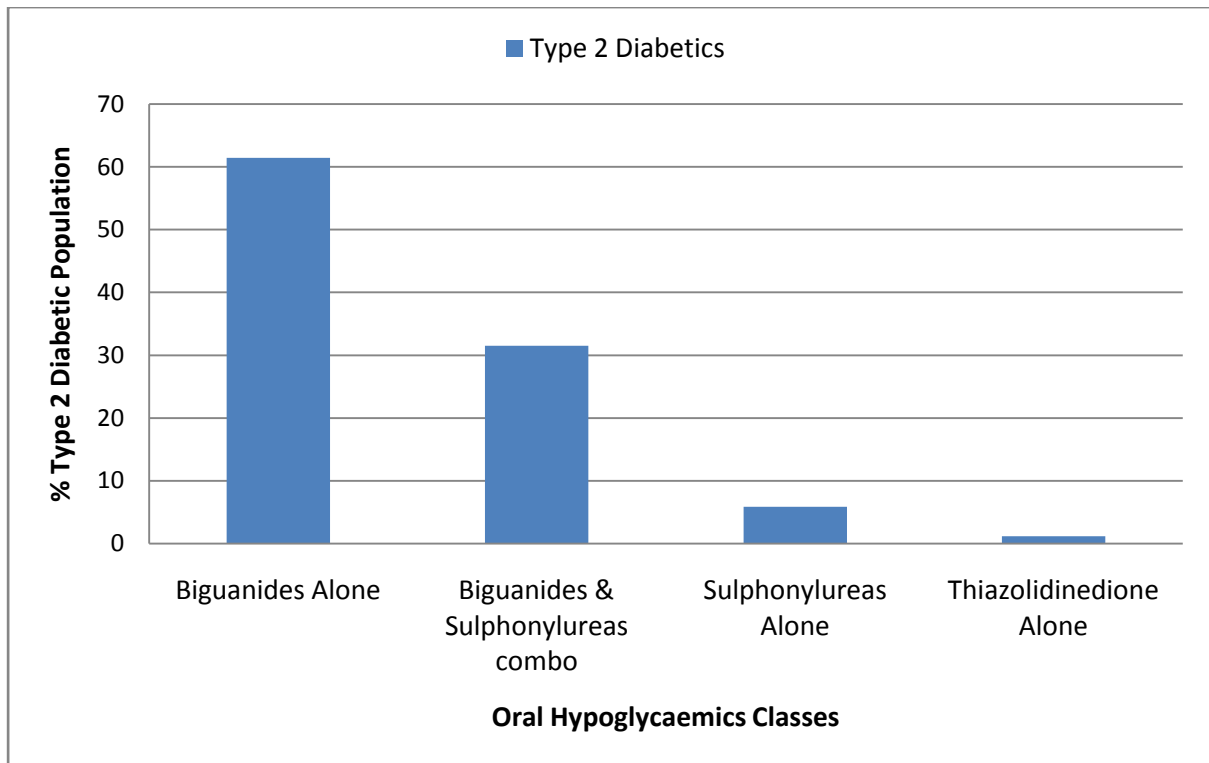


Figure 24 Classes of oral hypoglycaemic medication taken by study type 2 diabetic population

From the 454 patients (68.17%) receiving insulin, 390 patients were receiving one class of insulin, whilst 64 patients were on a combination of two insulins, (one class of insulin vs. combination insulin, $p < 0.01$) (Figure 25).

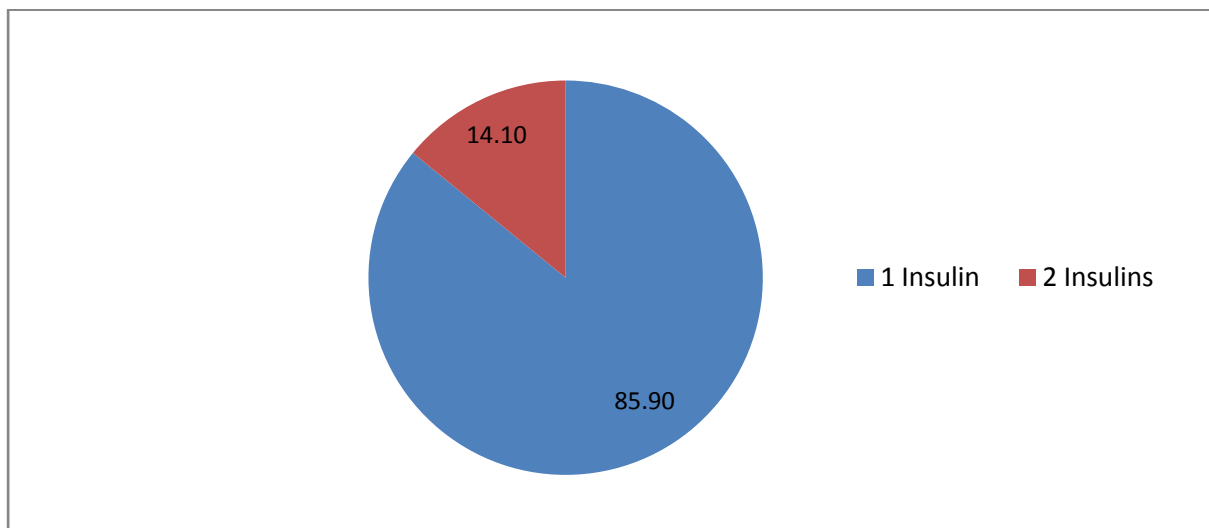


Figure 25 Number of insulins used by study type 2 diabetic population

Of the total number of patients receiving insulin (be it mono- or combination therapy), 317 patients were receiving intermediate-acting (Actraphane ® and Humulin ®), 122 patients were receiving long-acting (Protaphane ®), 75 patients were receiving short-acting (Actrapid ®) whilst 4 patients were receiving rapid acting insulin (Humalog ® and Novorapid ®)(Figure 26).

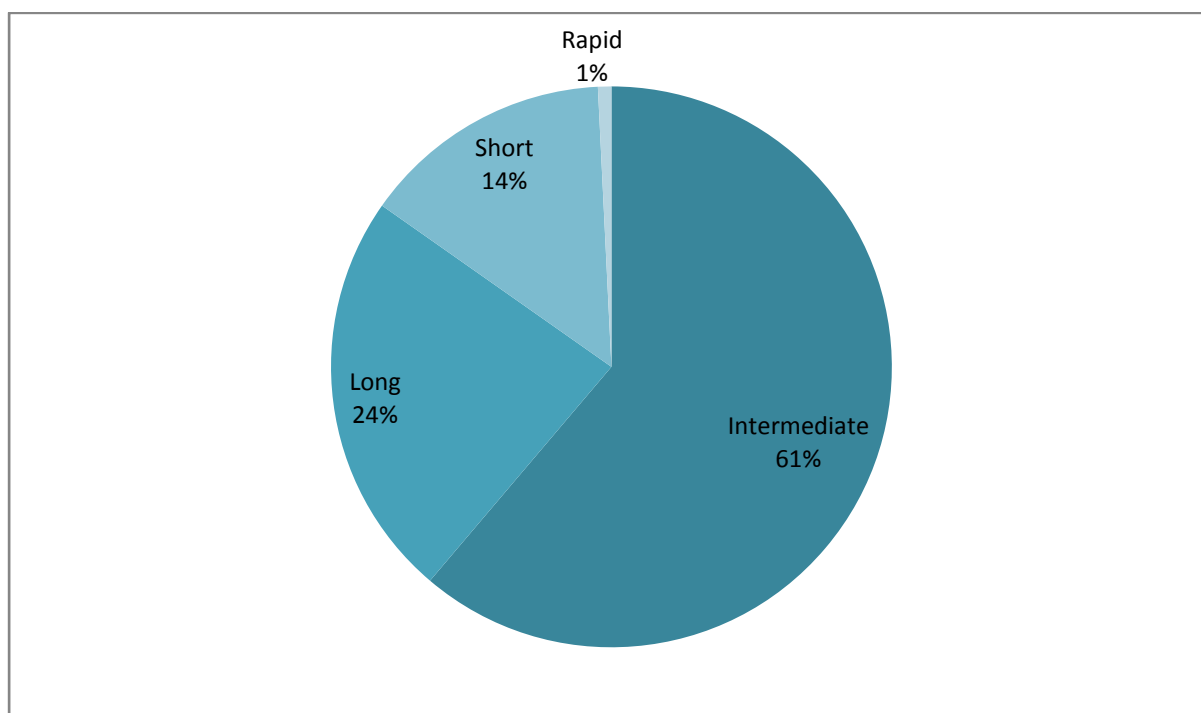


Figure 26 Types of insulin used by study type 2 diabetic population

In the cohort, 163 patients (26.2%) reached the SEMDSA/ADA treatment target ($\text{HbA}_{1c} \leq 7\%$) in comparison to the 107 patients (17.2%) which reached the EASD/ESC/IDF treatment target ($\text{HbA}_{1c} \leq 6.5\%$). SEMDSA/ADA treatment target $\text{HbA}_{1c} \leq 7\%$ vs. EASD/ESC/IDF treatment target $\text{HbA}_{1c} \leq 6.5\%$, $p < 0.05$ (Figure 27).

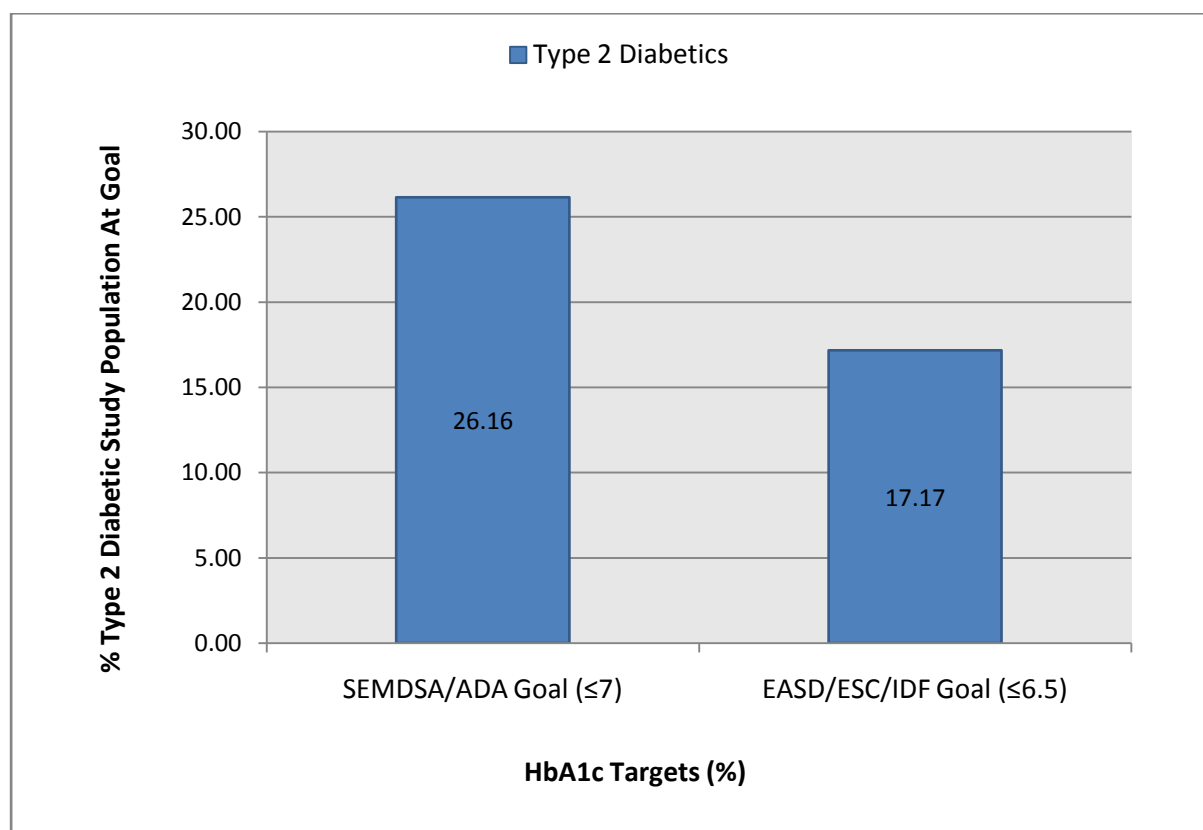


Figure 27 % type 2 diabetic study population achieving HbA_{1c} goals by various guidelines; Society for Endocrinology, Metabolism and Diabetes of South Africa (SEMDSA), American Diabetes Association (ADA), International Diabetes Federation (IDF) and European Society of Cardiology / European Association for the Study of Diabetes (ESC/EASD), Glycated Haemoglobin (HbA_{1c})

Patients who did not reach SEMDSA goal for HbA_{1c} ($\leq 7\%$) were analysed for the level at which they were off goal. One hundred and sixty patients (33.5%) were off goal by $\geq 3\%$, making it slightly higher than the one hundred and forty-seven patients (30.6%) which were off target by $\geq 1\%$, ($\geq 3\%$ range vs. $\geq 1\%$ range, $p < 0.01$).

Combining the two middle ranges (patients that off goal by 1-3%) would yield a new majority (35.9%) of patients off goal (Figure 28).

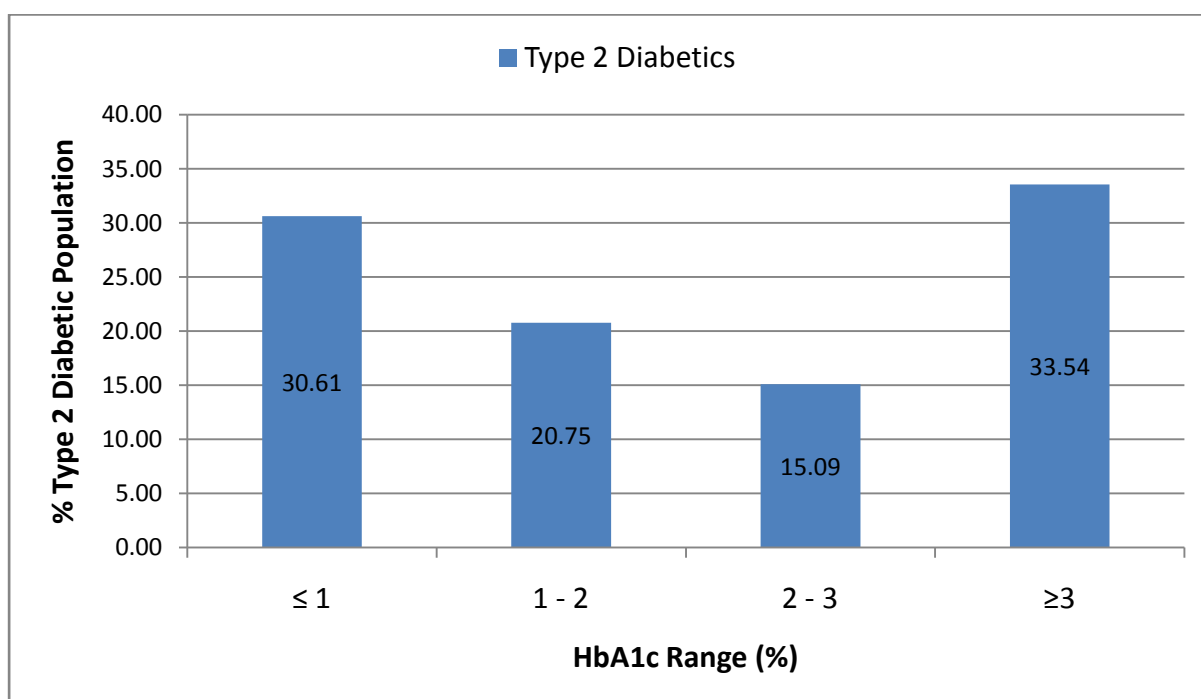


Figure 28 % type 2 diabetic study population not at goal (7%) by HbA_{1c} ranges; Glycated Haemoglobin (HbA_{1c})

A gender comparison of patients off SEMDSA HbA_{1c} target revealed that males were apparently more off target than the females in the $\leq 1\%$ and 2-3% range (male 32.7% vs. female 29.0%, not statistically significant, $p = 0.634$) and (male 16.1% vs. female 14.3%, not statistically significant, $p = 0.605$), respectively. Females were more apparently off target in the 1-2% and $\geq 3\%$ range (male 19.0% vs. female 22.1%, not statistically significant, $p = 0.259$) and (male 32.2% vs. female 34.6%, not statistically significant, $p = 0.823$), respectively (Figure 29).

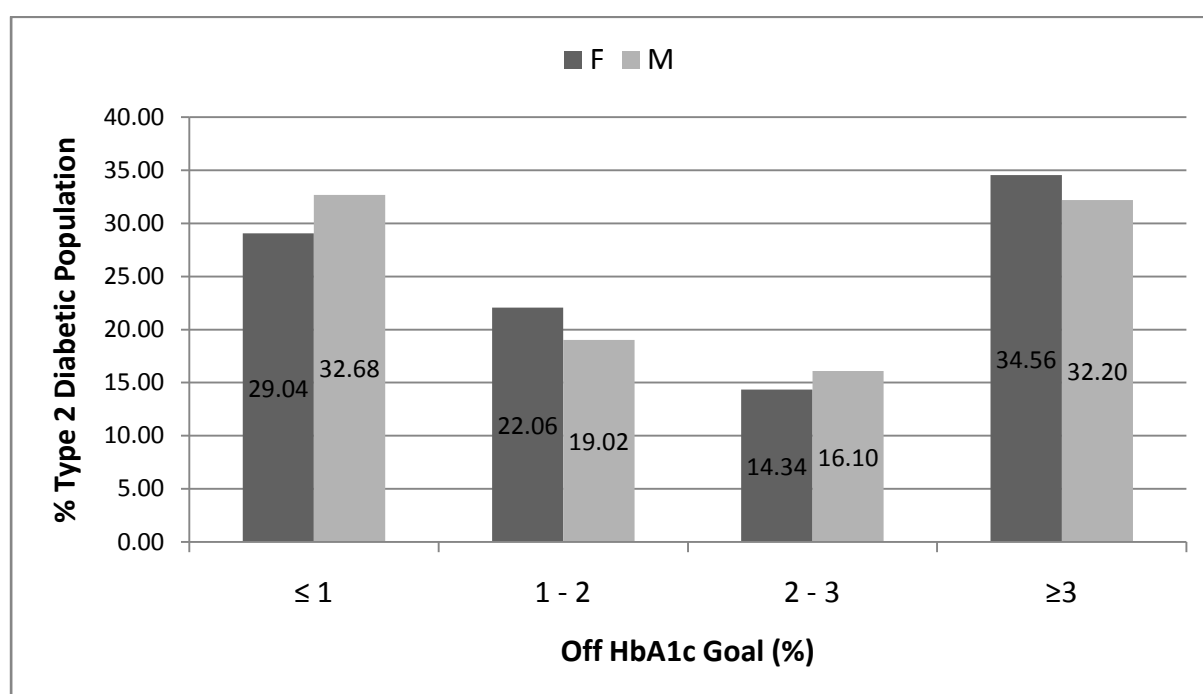


Figure 29 % type 2 diabetic study population not at goal (7%) by gender-HbA_{1c} ranges; females (F), males (M), Glycated Haemoglobin (HbA_{1c})

A gender-age comparison of patients off SEMDSA HbA_{1c} target (>7%) demonstrates that 50.8% and 43.8% of the youngest males and female patients (≤55 years) were apparently off target by HbA_{1c} ≥3%, respectively. Most trends follow an apparently similar pattern except for the youngest males (≤55 years) in the 1-2% off target range (Figure 30).

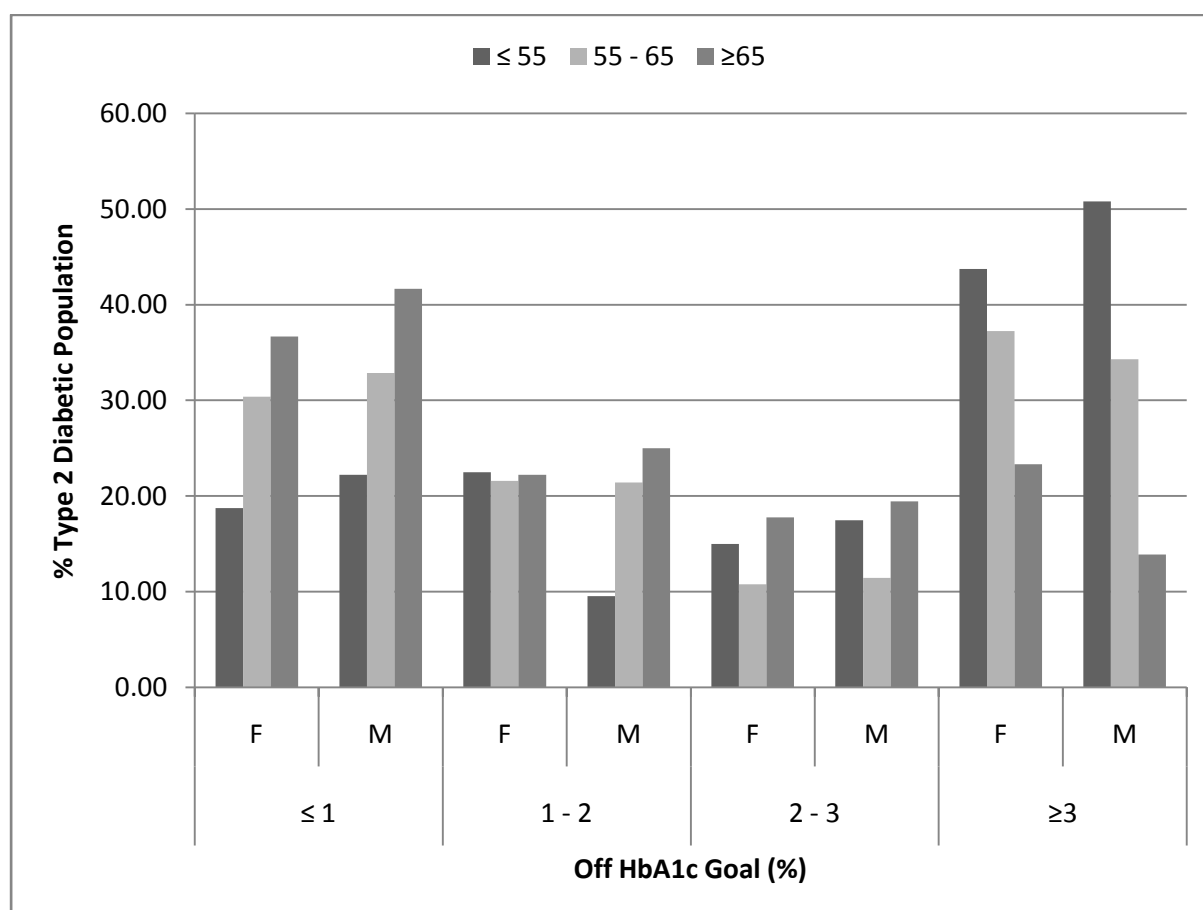


Figure 30 Comparison showing type 2 diabetics off SEMDSA HbA_{1c} target (7%) using gender-age (years) groupings; females (F), males (M)

Lipid Control

The lipid readings for the entire population were 4.6 mmol/L (SD: 1.2), 1.8 mmol/L (SD: 1.0), 1.2mmol/L (SD: 0.4) and 2.6 mmol/L (SD: 0.9) for TC, TG, HDL-C and LDL-C respectively.

Females had slightly higher TC than males (female 4.8 mmol/L (SD: 1.11) vs. male 4.5 mmol/L (SD: 1.2), $p < 0.05$) as well as higher HDL-C (female 1.3 mmol/L (SD: 0.4) vs. male 1.1 mmol/L (SD: 0.4), $p < 0.05$). Males had similar TG to the females, whilst females had higher LDL-C, both not significant (Figure 31).

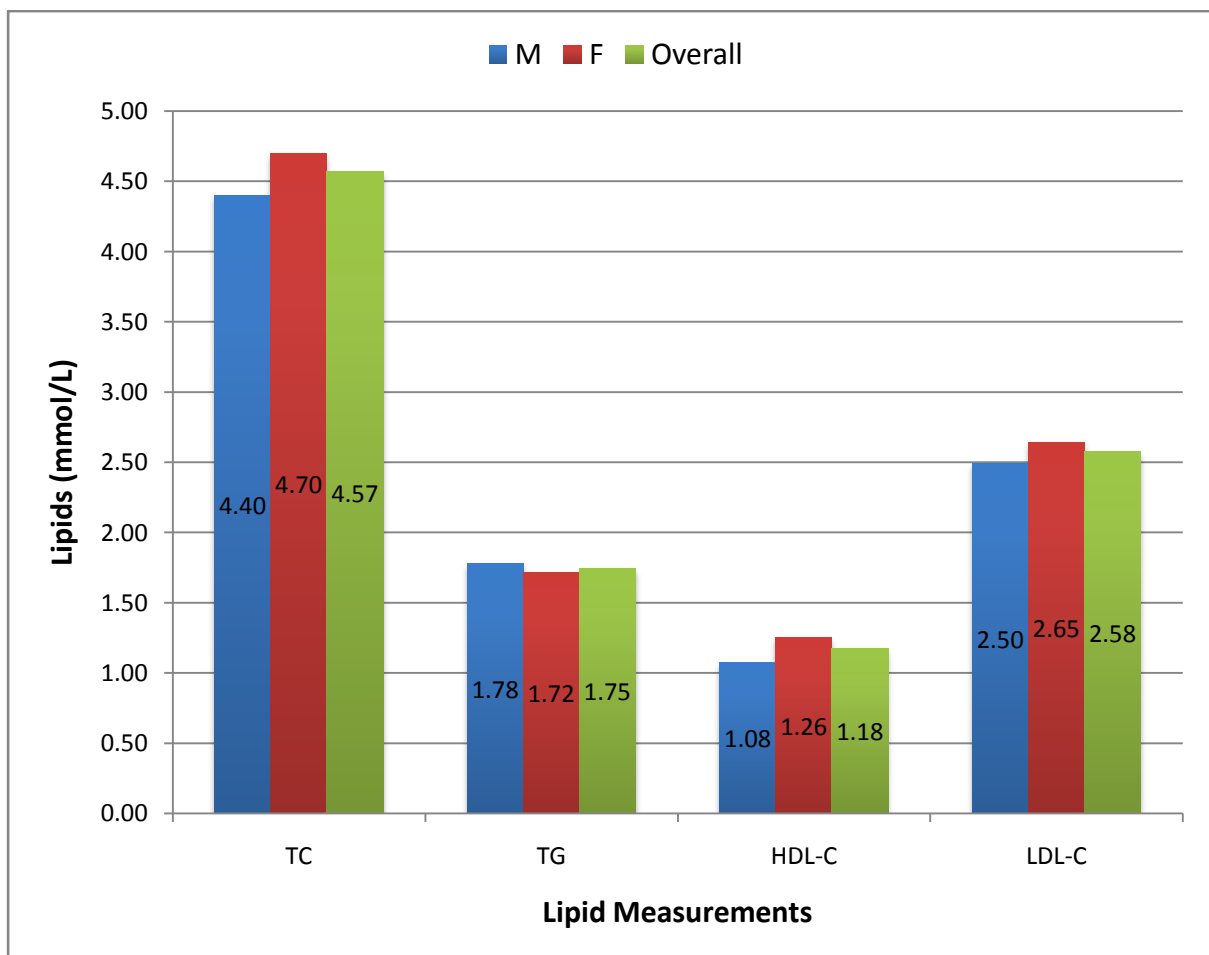


Figure 31 Lipid mean comparison of type 2 diabetic study population by gender; total cholesterol (TC), triglycerides (TG), High Density Lipoprotein Cholesterol (HDL-C), Low Density Lipoprotein Cholesterol (LDL-C), females (F), males (M)

The analysis of mean LDL-C reduction needed (from 2.5 mmol/L) by gender-age groups for patients without previous CAD/Stroke revealed some interesting results. Males required a larger reduction than the females in both the ≤ 55 year (male 0.99 mmol/L vs. female 0.92 mmol/L, not statistically significant, $p = 0.928$) as well as in the 55 – 65 year group (male 0.84 mmol/L vs. female 0.72 mmol/L, not statistically significant, $p = 0.794$). The females in the ≥ 65 year group required a larger reduction than the males (female 0.75 mmol/L vs. male 0.64 mmol/L, not statistically significant, $p = 0.556$) (Figure 32).

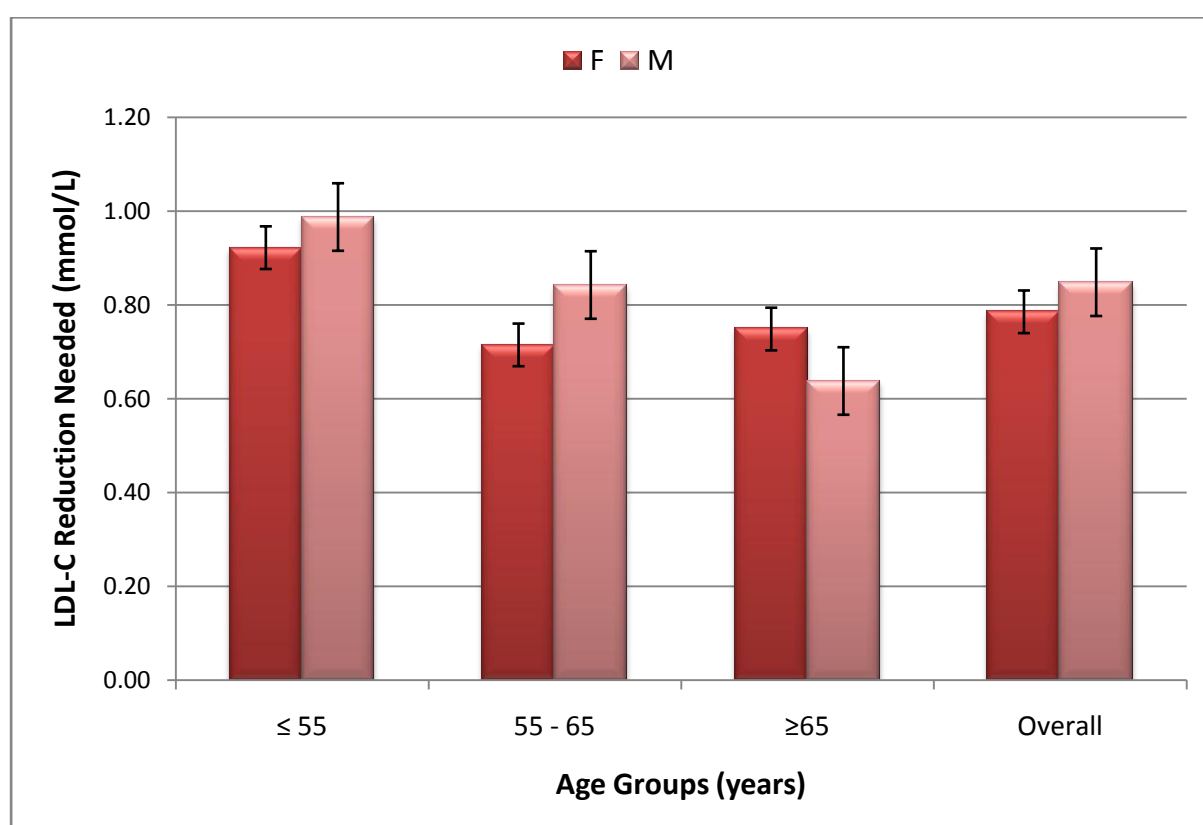


Figure 32 LDL-C reduction needed for study type 2 diabetics without previous CAD/stroke (2.5 mmol/L) by gender-age grouping; Coronary Artery Disease (CAD), females (F), males (M), Low Density Lipoprotein Cholesterol (LDL-C)

An analysis of mean LDL-C reduction (from 1.8 mmol/L) needed by gender-age groups for patients with previous CAD/Stroke was conducted. Females in the ≤ 55 age group required a larger reduction in LDL-C than the males (female 1.52 mmol/L vs. 1.39 mmol/L, not statistically significant $p = 0.869$). Males required a greater reduction in the 55-65 age group (male 1.22 mmol/L vs. female 0.86 mmol/L, statistically significant, $p = 0.023$) as well as in the ≥ 65 age group (male 1.05 mmol/L vs. female 1.02 mmol/L, not statistically significant, $p = 0.992$) than the females (Figure 33).

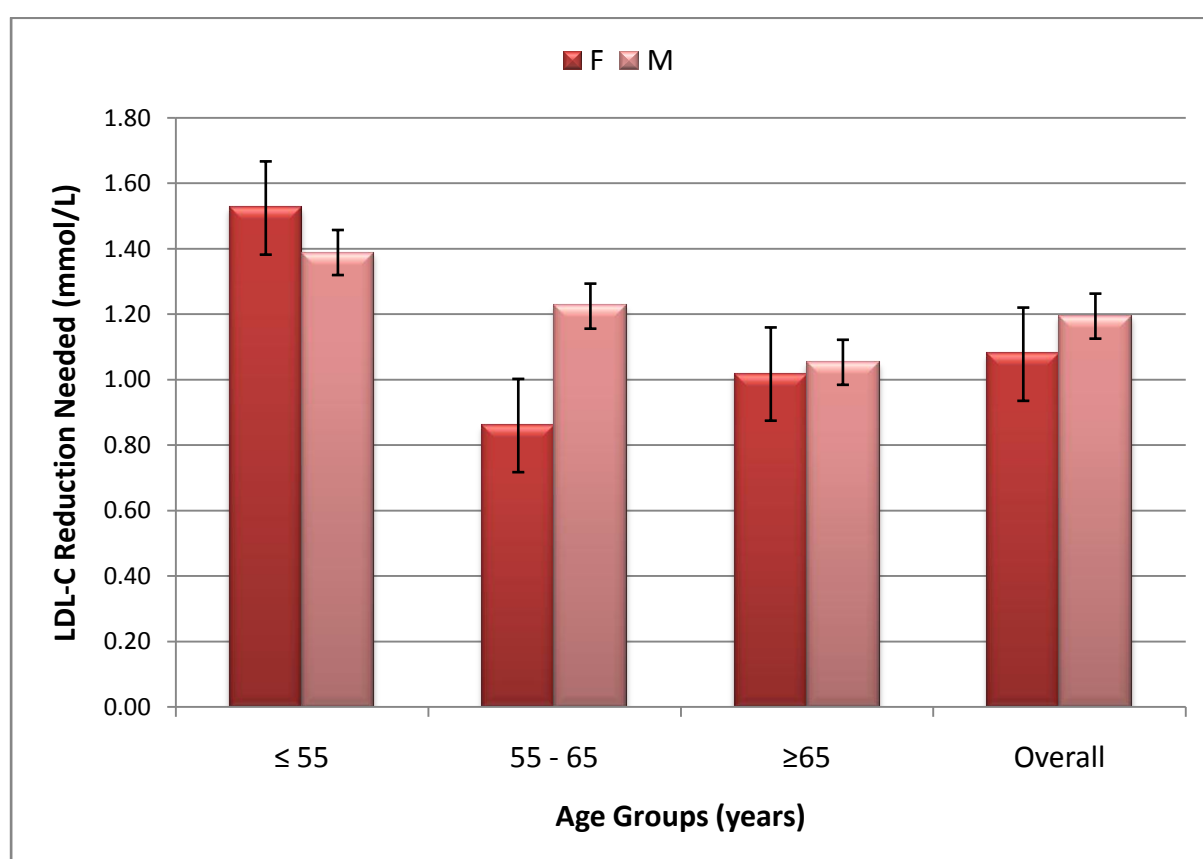


Figure 33 LDL-C reduction needed for study type 2 diabetics with previous CAD/stroke (1.8 mmol/L) by gender-age grouping; Coronary Artery Disease (CAD), females (F), males (M), Low Density Lipoprotein Cholesterol (LDL-C)

TC target was reached by 320 patients (53.8%) (≤ 4.5 mmol/L SEMDSA/ADA), 348 patients (60.2%) reached the TG target (≤ 1.7 mmol/L SEMDSA / ADA goal). 150 males (58.6%) reached the male SEMDSA/ADA HDL-C targets (≥ 1 mmol/L) whilst 171 and 141 female patients reached the SEMDSA (≥ 1.2 mmol/L) and ADA (>1.3 mmol/L) HDL-C targets (52.8% vs. 43.5%, $p < 0.05$), respectively. More patients reached ADA LDL-C goal compared with SEMDSA goal (57.6% vs. 53.8%, $p = 0.173$) as the latter target was slightly harder to achieve (ADA goal 2.6mmol/L vs. SEMDSA goal 2.5mmol/L) for patients without previous CAD or stroke. For patients with previous CAD or stroke, 17 patients (17.9%) reached targets (1.8 mmol/L SEMDSA / ADA goal) (Figure 34).

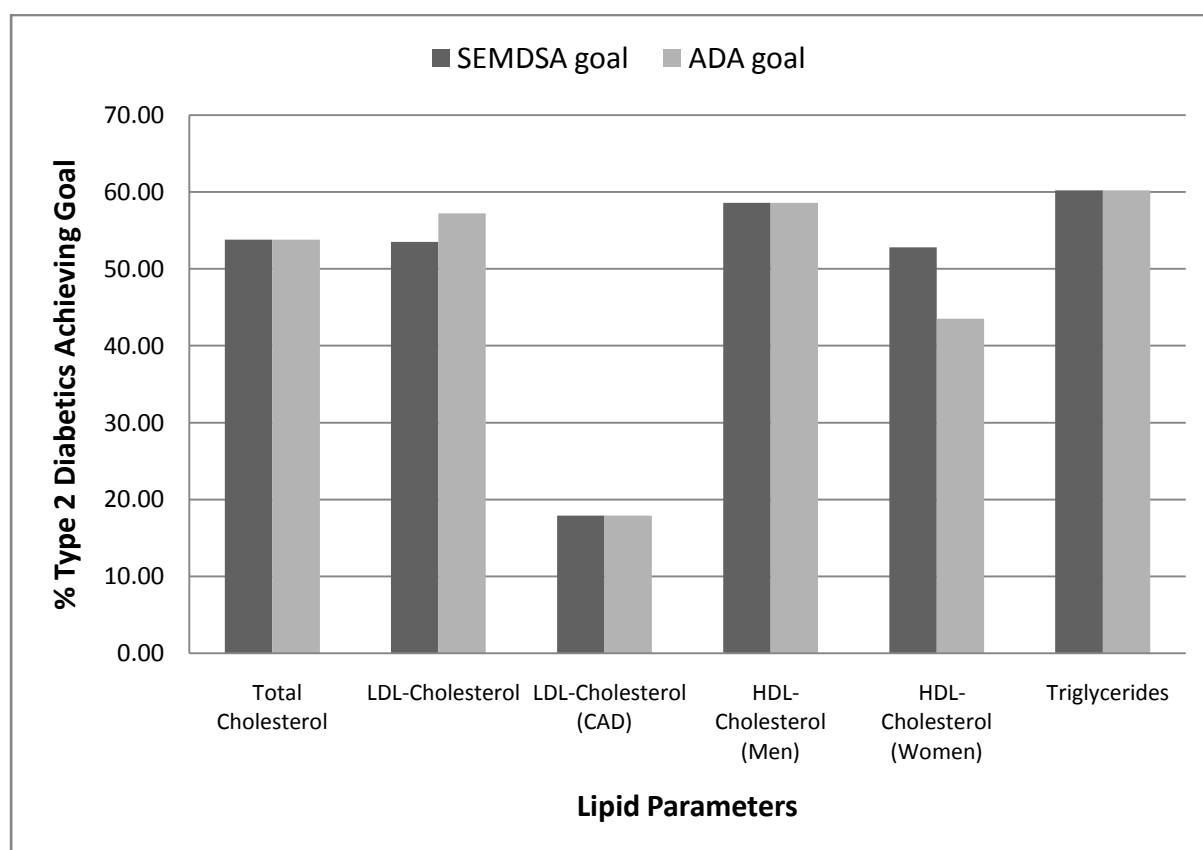


Figure 34 % type 2 diabetic study population achieving lipid goals as set by SEMDSA and ADA guidelines; High Density Lipoprotein Cholesterol (HDL-C), Low Density Lipoprotein Cholesterol (LDL-C), Society for Endocrinology, Metabolism and Diabetes of South Africa (SEMDSA), American Diabetes Association (ADA), Coronary Artery Disease (CAD)

From the total cohort (666 patients), 275 patients (46.2%) had hypercholesterolaemia and 230 patients (39.8%) had hypertriglyceridaemia. Three hundred and forty five patients (51.8%) were being treated with HMG-CoA Reductase Inhibitors (statins) lipid-lowering drugs (Figure 35). More females were being treated with statin lipid-lowering therapy than males (male 56.9% vs. female 61.3%, not statistically significant, $p = 0.449$), whilst the opposite was seen with fibrate therapy (male 15.5% vs. female 9.8%, statistically significant, $p = 0.025$).

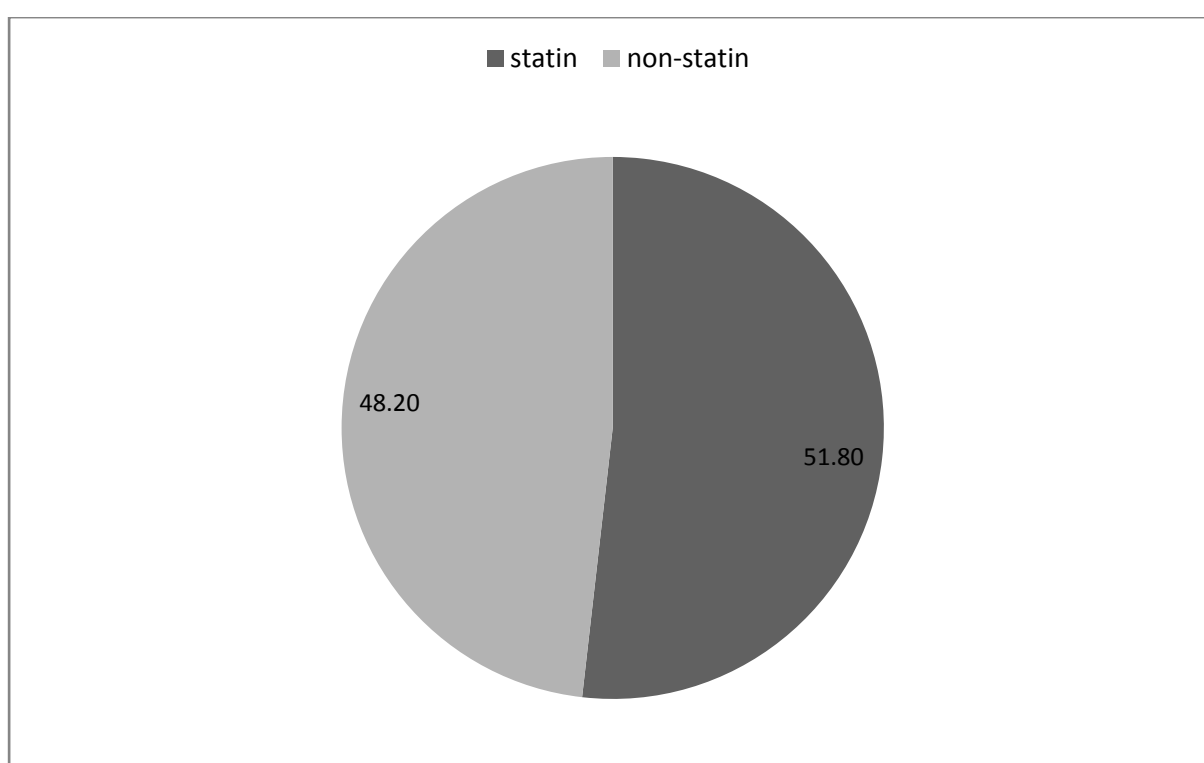


Figure 35 % type 2 diabetics of total study population receiving and not receiving statin lipid-lowering therapy

Analysis of patients with and without CVD revealed that 289 patients (51.3%) without previous CAD/Stroke were not receiving statin lipid-lowering therapy for primary prevention purposes. For patients with previous CVD, 32 patients (31.1%) were not being treated for secondary prevention purposes with statin lipid-lowering therapy (primary prevention 51.3% vs. secondary prevention 31.1%, $p < 0.05$) (Figure 36).

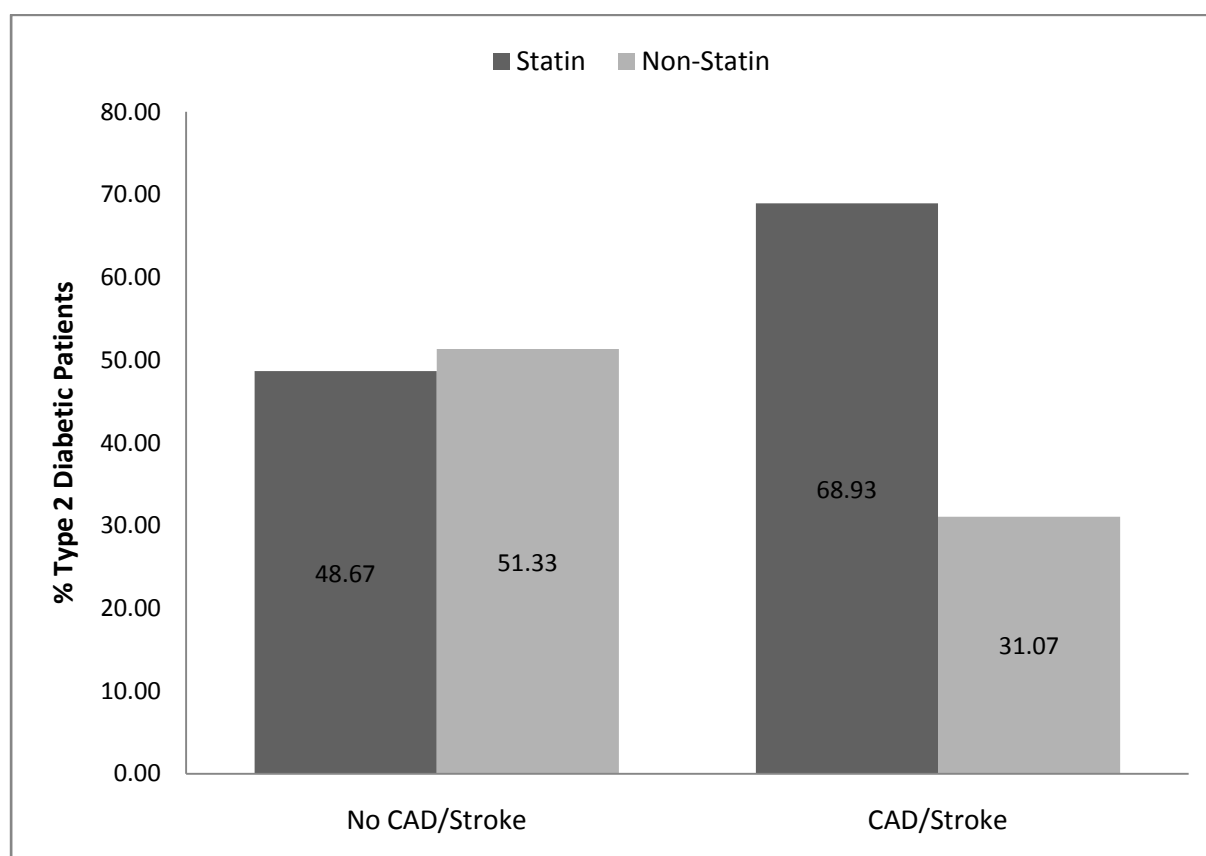


Figure 36 % study type 2 diabetics with or without CAD/stroke receiving or not receiving statin lipid-lowering therapy; Coronary Artery Disease (CAD)

In 481 patients without previously established CAD or stroke, LDL-C target (≤ 2.5 mmol/L SEMDSA/IDF) was reached by 259 (53.9%). In those with previously established CAD or stroke, 17 patients (18.1%) reached goal (≤ 1.8 mmol/L SEMDSA/IDF) (Figure 52 / Appendix VII).

Patients without previous CAD/Stroke receiving statin lipid-lowering therapy had higher mean LDL-C than those not receiving lipid-lowering therapy (2.60 mmol/L (SD: 0.97) vs. 2.53 mmol/L (SD: 0.80), $p = 0.408$), respectively. The same was seen in patients with previous CAD/Stroke (2.71 mmol/L (SD: 0.91) vs. 2.54 mmol/L (SD: 1.09), $p = 0.441$), respectively (Figure 37).

In patients receiving statin lipid-lowering therapy, those with previous CAD/Stroke had higher mean LDL-C than without previous CAD/Stroke (2.71 mmol/L (SD: 0.91) vs. 2.60 mmol/L (SD: 0.97), not statistically significant, $p = 0.415$), respectively. A similar pattern followed with patients not receiving statin lipid-lowering therapy ($p = 0.934$) (Figure 37).

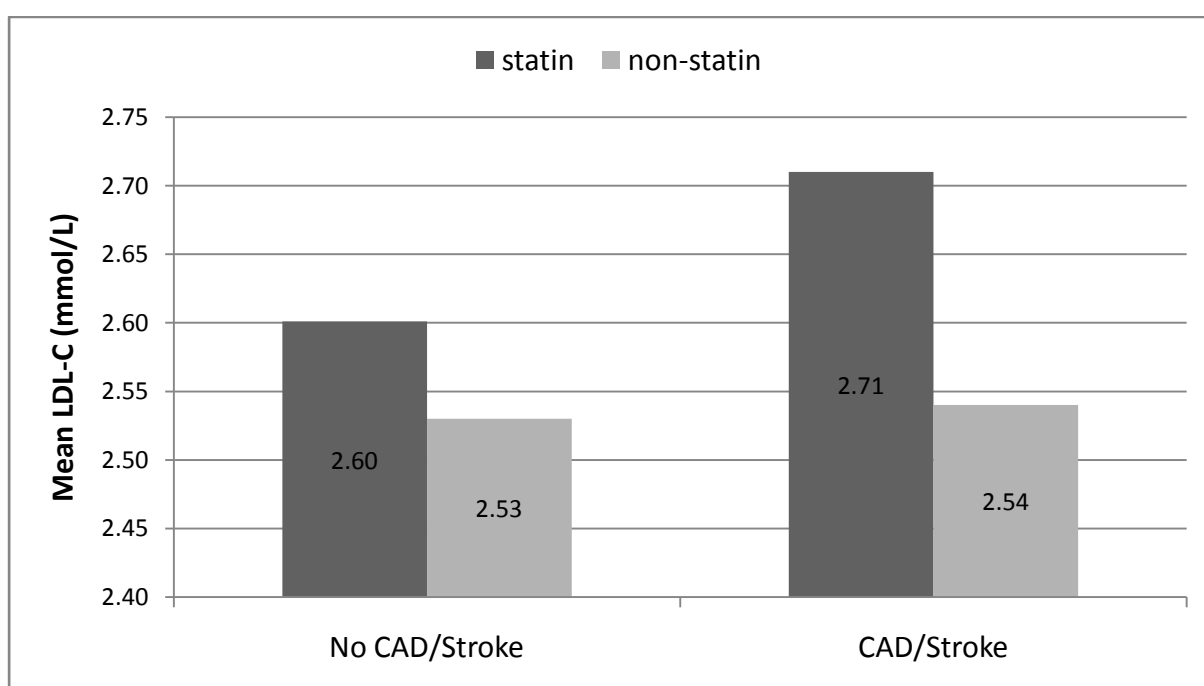


Figure 37 Mean LDL-C of study type 2 diabetics with or without CAD/stroke; Low Density Lipoprotein Cholesterol (LDL-C), Coronary Artery Disease (CAD)

Patients with lower risk (no previous CAD/Stroke, Figure 38) reached SEMDSA LDL-C goal more easily than those patients with higher risk (positive history for CAD/Stroke) (53.9% vs. 18.1%, $p < 0.05$), respectively (Figure 39).

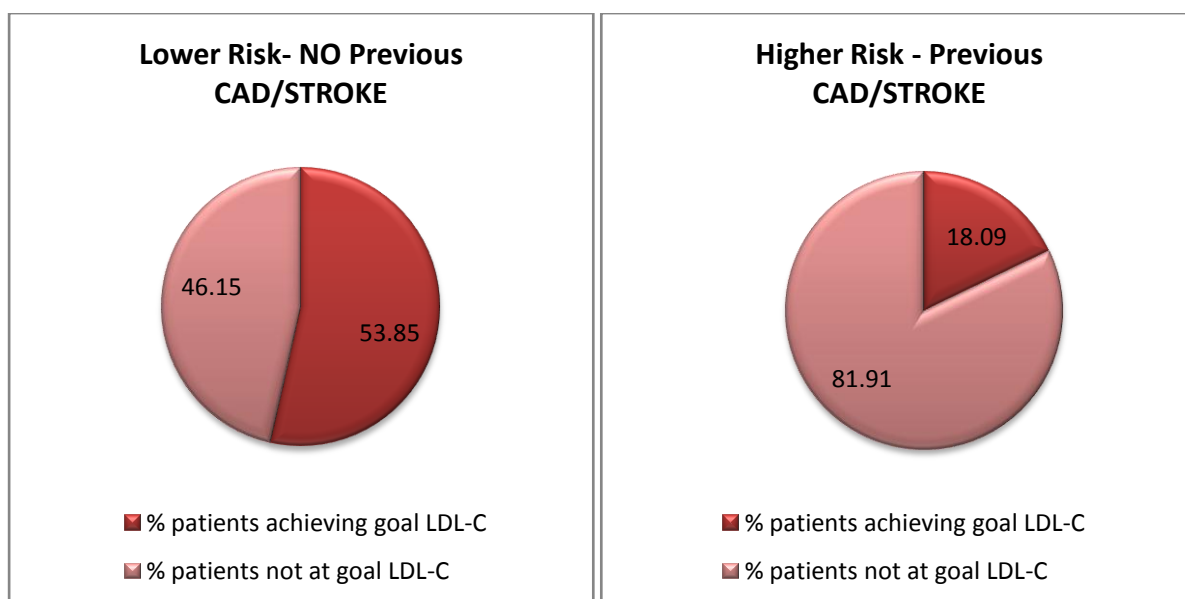


Figure 38 % type 2 diabetics achieving SEMDSA LDL-C goals (2.5mmol/L)

Figure 39 % type 2 diabetics achieving SEMDSA LDL-C goals (1.8 mmol/L)

The mean LDL-C of patients achieving SEMDSA goal without previous CAD/Stroke was 1.49 mmol/L (SD: 0.3) whilst those with previous CAD/Stroke, 1.42 mmol/L (SD: 0.4), (1.49 mmol/L vs. 1.42 mmol/L, not statistically significant, $p = 0.421$). Patients not achieving goal and without previous CAD/Stroke had an LDL-C of 3.31 mmol/L (SD: 0.7), less than the 3.37 mmol/L (SD: 0.7) LDL-C of those patients with previous CAD/Stroke (3.31 mmol/L vs. 3.37 mmol/L, not statistically significant, $p = 0.602$) (Table 5).

	SEMDSA LDL-C Goals (2.5mmol/L) (No Previous CAD/Stroke)	SEMDSA LDL-C Goals (1.8mmol/L) (Previous CAD/Stroke)
	(mmol/L)	(mmol/L)
LDL-C Achieving Goal	1.49 (SD: 0.3)	1.42 (SD: 0.4)
LDL-C NOT Achieving Goal	3.31 (SD: 0.7)	3.37 (SD: 0.7)

Table 5 Mean LDL-C levels of study type 2 diabetic population; Low Density Lipoprotein Cholesterol (LDL-C), Coronary Artery Disease (CAD), Society for Endocrinology, Metabolism and Diabetes of South Africa (SEMDSA)

Patients without previous CAD/Stroke were off LDL-C target (2.5mmol/L) by an average of 0.81 mmol/L. Patients with previous CAD/Stroke were off LDL-C target (1.8mmol/L) by an average of 1.13 mmol/L, (patients without previous CAD/Stroke 0.81 mmol/L vs. patients with previous CAD/Stroke 1.13 mmol/L, $p<0.01$). (Figure 40).

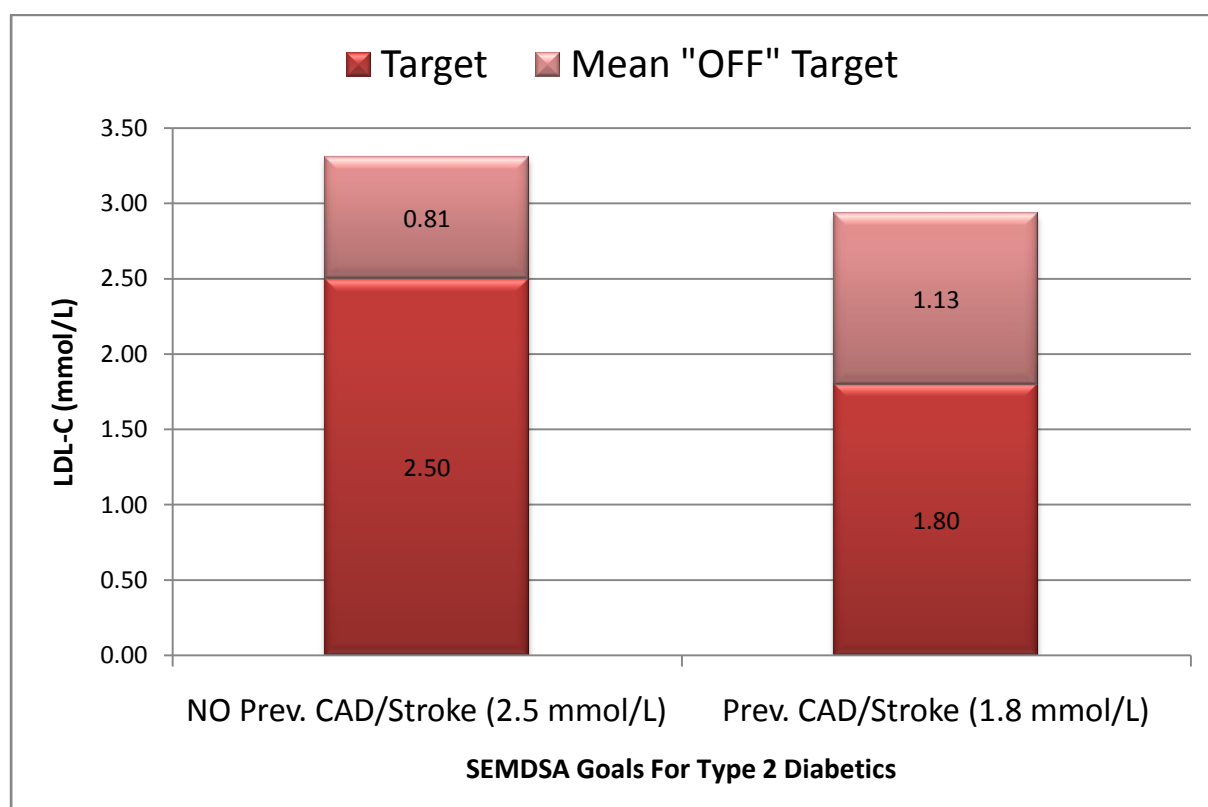


Figure 40 Mean LDL-C Off Target levels for study type 2 diabetic population with and without previous CAD/Stroke; Low Density Lipoprotein Cholesterol (LDL-C), Coronary Artery Disease (CAD), previous (prev), Society for Endocrinology, Metabolism and Diabetes of South Africa (SEMDSA)

Figure 41 demonstrates the comparison of patients achieving SEMDSA targets by either receiving or not receiving statin lipid lowering therapy. Patients without previous CAD/Stroke reached LDL-C targets (2.5 mmol/L) more frequently using statin lipid lowering therapy (statin 53.28% vs. non-statin 46.72%, not statistically significant, $p = 0.620$) and the same was seen in patients with previous CAD/Stroke (statin 52.94% vs. non-statin 47.06%, not statistically significant $p = 0.059$) for LDL-C targets (1.8 mmol/L).

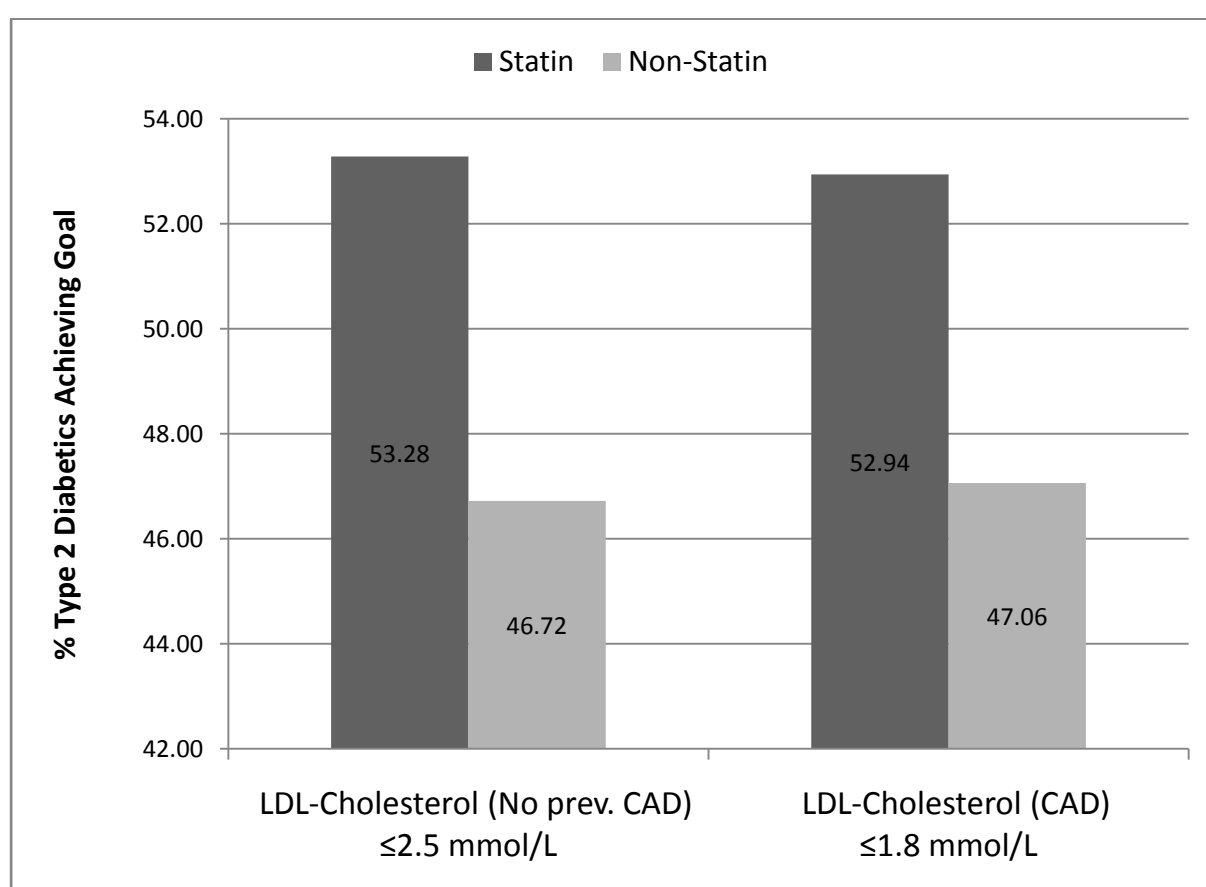


Figure 41 % type 2 diabetics achieving SEMDSA LDL-C goals by lipid-lowering therapy; previous (prev), Low Density Lipoprotein Cholesterol (LDL-C), Coronary Artery Disease (CAD), Society for Endocrinology, Metabolism and Diabetes of South Africa (SEMDSA)

Patients which did not achieve LDL-C targets were analysed (Figure 42). Those who had no previous CAD/Stroke followed a consistent pattern; most count of patients (n=69) were off target by $\leq 10\%$ and the least count of patients (n=9) were off by $\geq 51\%$ from target LDL-C (2.5 mmol/L) ($\leq 10\%$ group vs. $\geq 51\%$ group, $P < 0.01$).

Patients with previous CAD/Stroke were most off target by 21-30% and 41-50% equally (both 23.38%), whilst least off target by $\leq 10\%$ (21-30% and 41-50% group 23.38% vs. $\leq 10\%$ group 6.49%, $p < 0.01$).

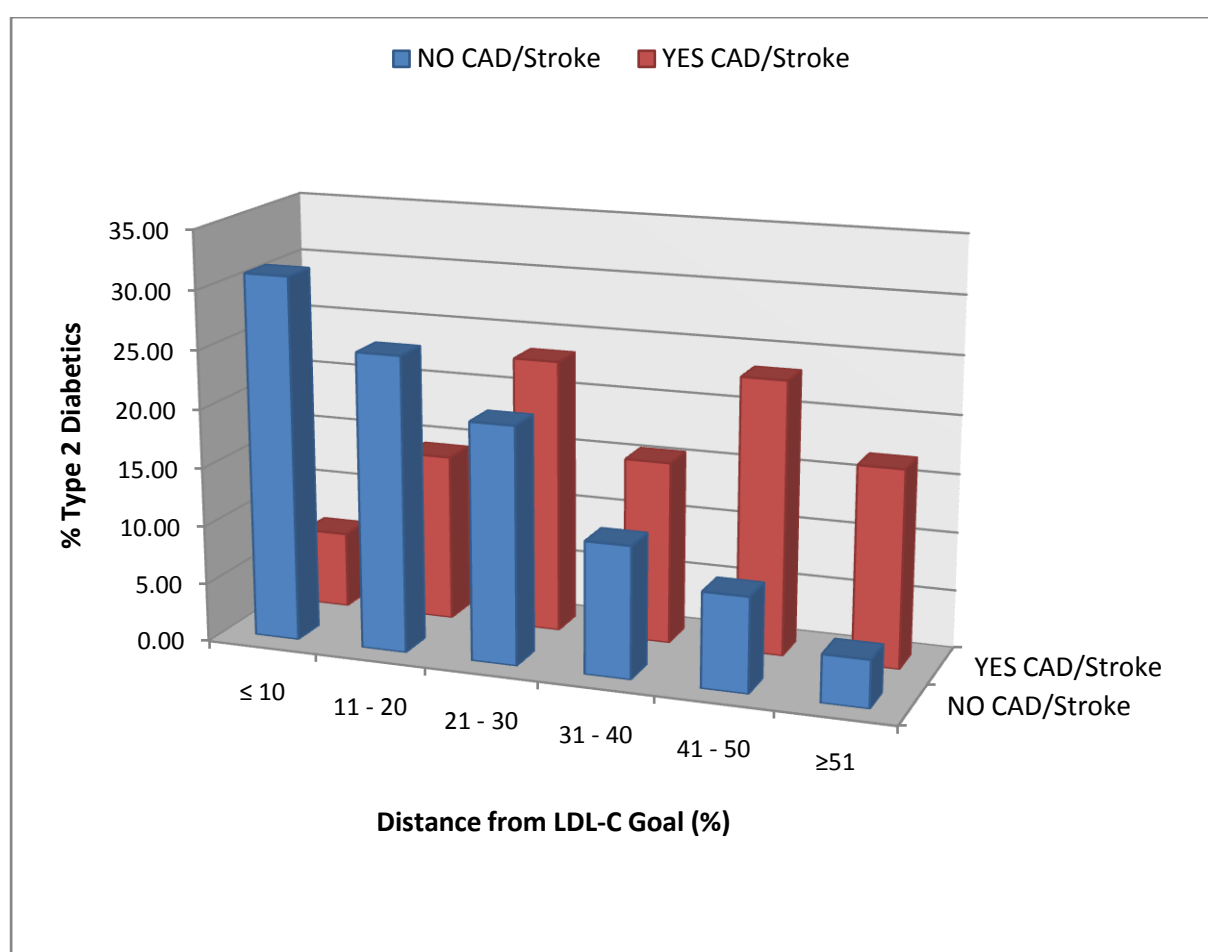


Figure 42 % type 2 diabetic patients away from LDL-C goal; Low Density Lipoprotein Cholesterol (LDL-C), Coronary Artery Disease (CAD), Society for Endocrinology, Metabolism and Diabetes of South Africa (SEMDSA)

From the 345 patients (51.8%) being treated with statin lipid-lowering drugs, 45 patients (13.0%) were receiving 10mg Simvastatin, 204 patients (59.1%) were receiving 20mg Simvastatin, 77 patients (22.3%) were receiving 40mg Simvastatin and 8 patients (2.3%) were receiving 40mg Atorvastatin (simvastatin 20mg vs. simvastatin 10mg, simvastatin 40mg and atorvastatin 40mg, $p<0.01$, $p<0.01$ and $p<0.01$, respectively) . 11 patients (3.2%) were receiving other tailored doses of Simvastatin and Atorvastatin (Figure 43).

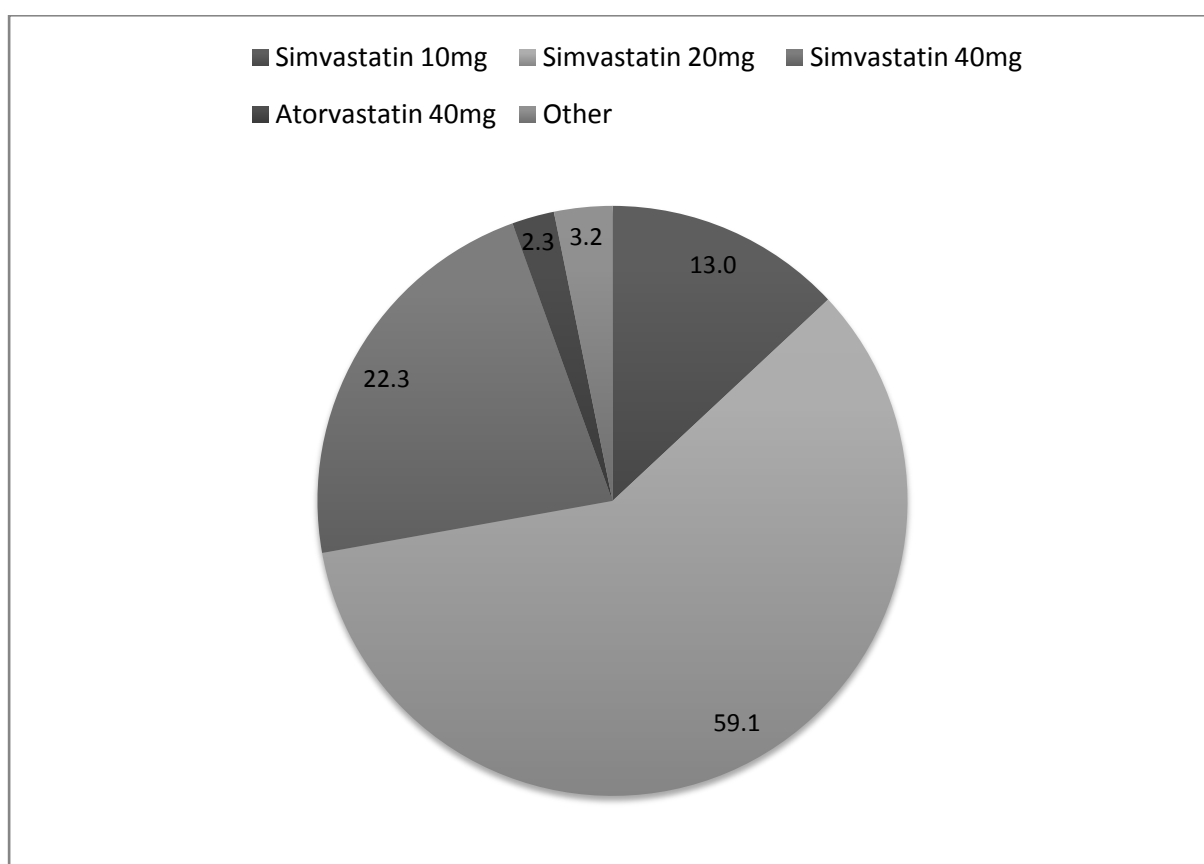


Figure 43 Type and dosage of statin therapy in study type 2 diabetic population; milligrams (mg)

In the following, patients either achieving or not achieving LDL-C SEMDSA targets by statin classes and dosages were analysed. Study patients were classified by either lower-risk (Figure 44) or higher-risk (Figure 45).

Patients without previous CAD/Stroke (lower-risk) were analysed to see if they were achieving SEMDSA LDL-C target (2.5 mmol/L). There were more counts of patients (n = 54) off target (LDL-C 2.5 mmol/L) using 20mg Simvastatin than any other statin (simvastatin 20mg 54 patients vs. simvastatin 10mg 16 patients, simvastatin 40mg 31 patients and atorvastatin 40mg 3 patients, $p < 0.01$, $p < 0.01$ and $p < 0.01$, respectively). The highest % of patients off target (LDL-C 2.5 mmol/L) by statin dosage were those using 40mg Simvastatin (64.6%) followed by those using Atorvastatin 40mg (60.0%), but this was not statistically significant ($p = 0.076$) (Figure 44).

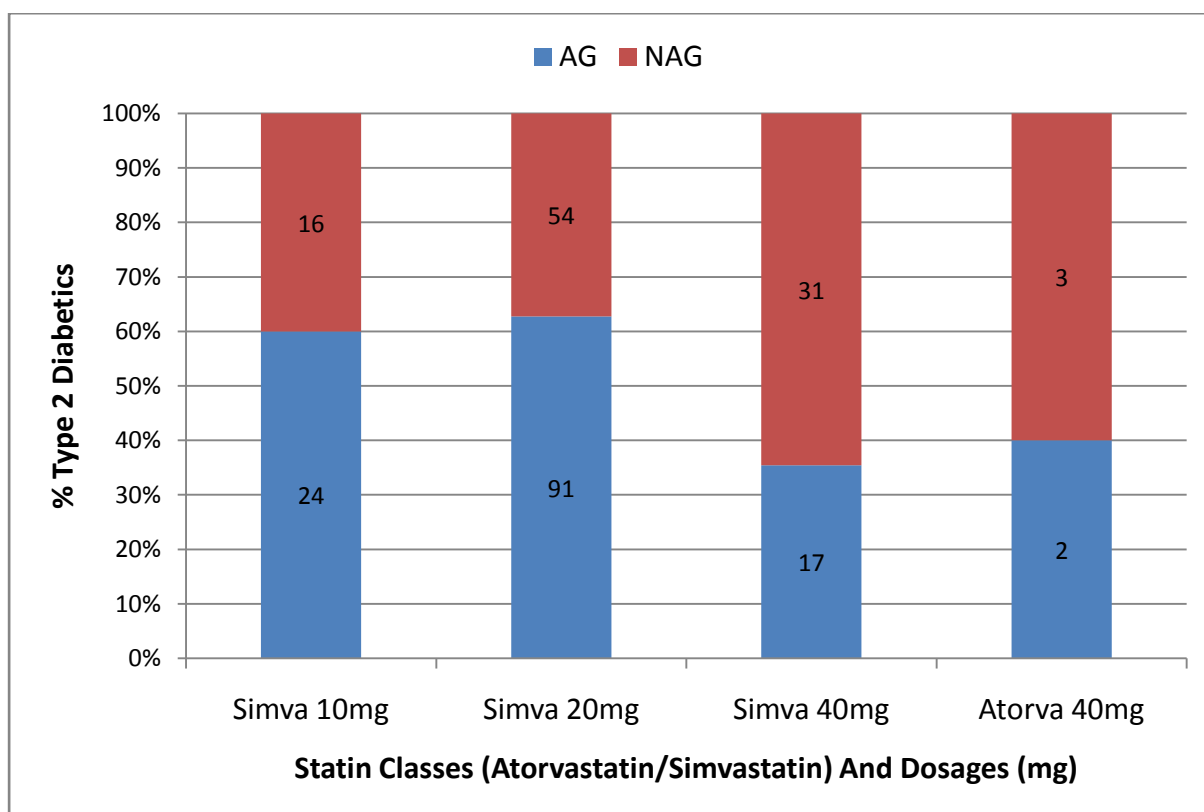


Figure 44 % type 2 diabetics without previous CAD/stroke reaching SEMDSA goal (2.5mmol/L) using different statin classes and dosages; Not At Goal (NAG), At Goal (AG), Atorvastatin

For patients with previous CAD/Stroke (higher-risk), most patients were off target across all statin classes and dosages (Figure 45). By count, more patients were off target (LDL-C 1.8 mmol/L) using 20mg Simvastatin than any other class or dosage of statin (n = 29) (simvastatin 20mg 29 patients vs. simvastatin 10mg 1 patient, simvastatin 40mg 23 patients and atorvastatin 40mg 1 patient, $p < 0.01$, $p < 0.01$ and $p < 0.01$, respectively). In Figure 45, all patients receiving 40mg Atorvastatin and 10mg Simvastatin were off LDL-C target (LDL-C 1.8 mmol/L).

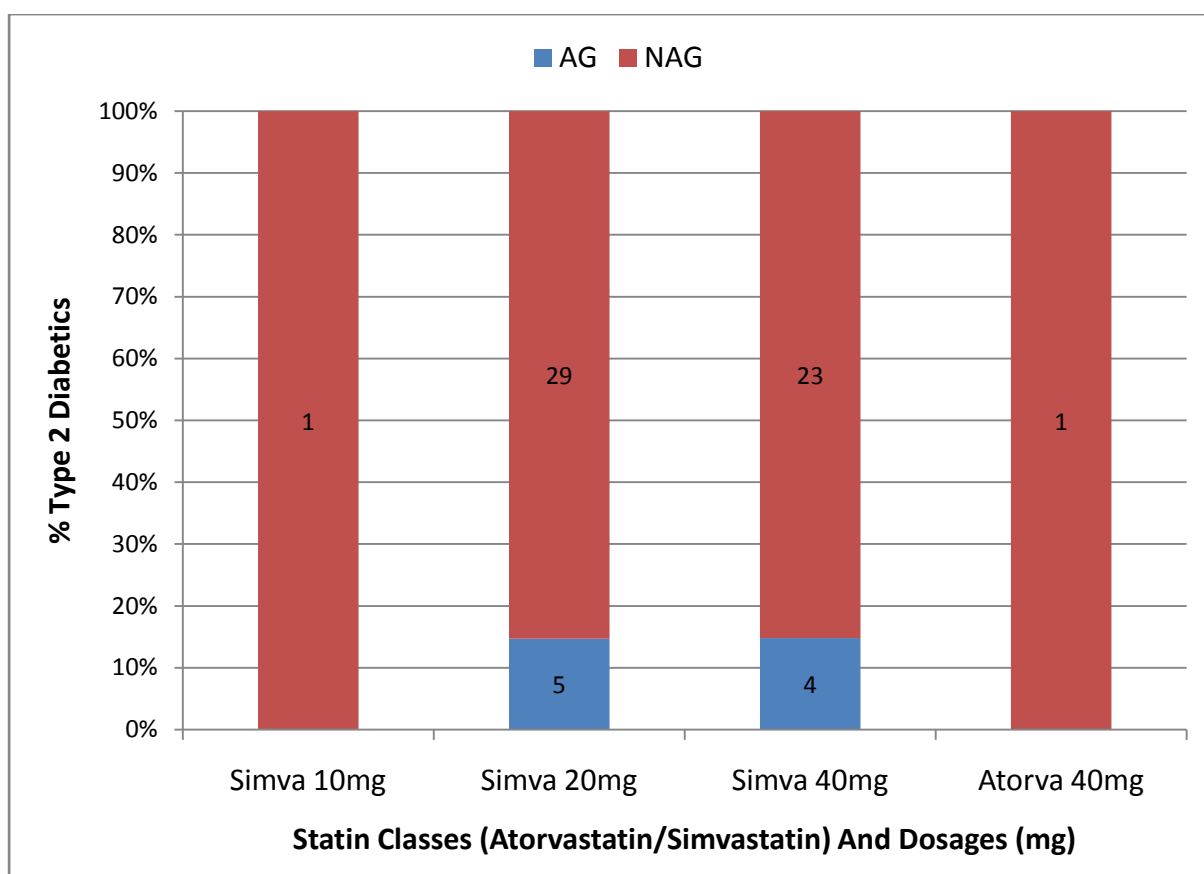


Figure 45 % type 2 diabetics with previous CAD/stroke reaching SEMDSA goal (1.8 mmol/L) using different statin classes and dosages; Not At Goal (NAG), At Goal (AG), Atorvastatin (Atorva), Simvastatin (Simva), Not At Goal (NAG), milligrams (mg), Society for Endocrinology, Metabolism and Diabetes of South Africa (SEMDSA)

An analysis of patients NAG for both SEMDSA LDL-C targets (1.8 mmol/L and 2.5 mmol/L for patients with and without CAD/stroke, respectively) demonstrated the overall average LDL-C for patients receiving statin lipid-lowering therapy by class and dosage (Figure 46). Patients on 40mg atorvastatin (without previous CAD/Stroke) apparently had the highest LDL-C (4.07 mmol/L), whilst those on simvastatin 10mg (with previous CAD/Stroke) apparently had the lowest LDL-C (1.90 mmol/L), (40mg atorvastatin LDL-C 4.07 mmol/L vs. 10mg simvastatin LDL-C 1.90 mmol/L, $p < 0.01$).

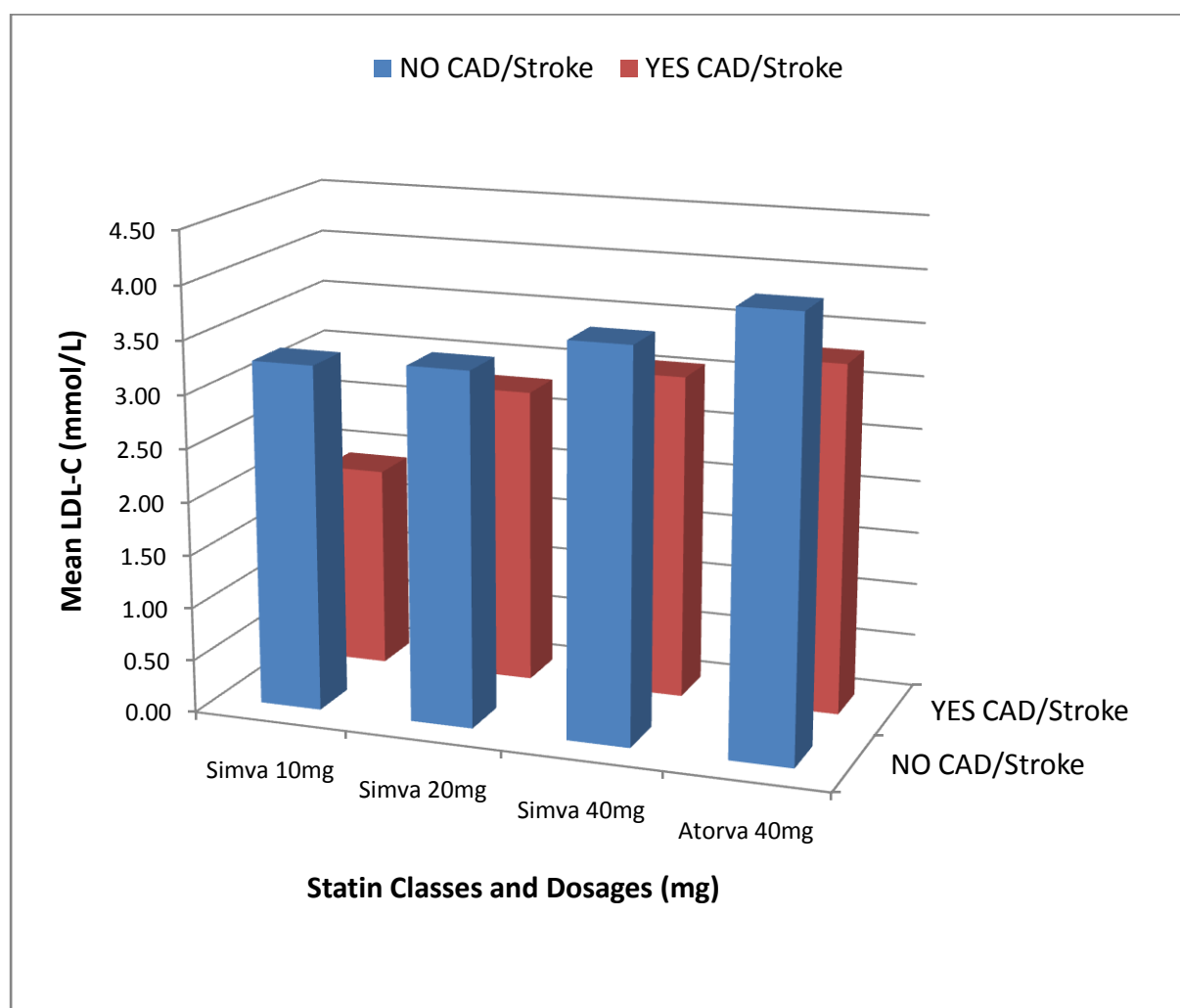


Figure 46 Mean LDL-C for study type 2 diabetic patients NAG for SEMDSA targets using different statin lipid lowering therapy; Atorvastatin (Atorva), Simvastatin (Simva), Not At Goal (NAG), Coronary Artery Disease (CAD), milligrams (mg), Society for Endocrinology, Metabolism and Diabetes of South Africa (SEMDSA)

Patients with or without cardiovascular disease have different LDL-C goals to reach as set by both national and international guidelines. Patients in the study receiving statin lipid-lowering therapy and not at SEMDSA LDL-C goal were analysed. Using the “rule of six” where there is a further 6% LDL-C reduction for every doubling of statin dosage, we hypothetically calculated how many patients in the cohort off target would require their current statin dosage increased in order to achieve goal. The “rule of six” can be applied to doubling, tripling or even possibly doubling the statin dosage twice in order to achieve a 6%, 6-12% or 12-18% LDL-C reduction, respectively.

Patients further off goal (>18%) may require adding Ezetimibe to their current statin. When combining 10mg Ezetimibe to a statin (at any dosage), there is an approximate 20-25% LDL-C reduction. Similarly as done with the “rule of six”, we hypothetically calculated how many patients in the cohort off target would require Ezetimibe added to their current statin in order to achieve goal. In order to achieve LDL-C, certain patients would require a change of statin class all together, thereby necessitating the much-needed greater reduction in LDL-C. Table 6 shows the number of patients who are eligible for either a dosage increase, addition of Ezetimibe or both.

Away From LDL-C Goal (%)	NO CAD/Stroke n (%)	CAD/Stroke n (%)	Action Required
≤6	7 (6.5%)	2 (3.5%)	Double Statin Dose
6 - 12	26 (24.1%)	2 (3.5%)	Triple Statin Dose
12 - 18	13 (12.0%)	7 (12.3%)	Double Statin Dose (twice)
18 - 25	14 (13.0%)	10 (17.5%)	Add Ezetimibe
≥25	48 (44.4%)	36 (63.2%)	Add Ezetimibe and Double Statin Dose

Table 6 Study type 2 diabetics not achieving goal and receiving statin lipid-lowering therapy; Coronary Artery Disease (CAD), Low Density Lipoprotein Cholesterol (LDL-C)

Without the use of lipid-lowering therapy, results from the data indicate that 114 patients (51.4%) without previous CAD/Stroke, as well as 20 patients (26.0%) with previous CAD/Stroke were off LDL-C target (≤ 2.5 mmol/L and ≤ 1.8 mmol/L, respectively). In order for patients to reach LDL-C goal, it may be necessary to commence lipid-lowering therapy. Table 7 demonstrates the % reduction needed for patients off LDL-C goal by recommended class and dosage of different statins currently available on the market. This of course is a hypothetical exercise and can only be used to indicate which possible statin would be ideal for patients only based on their LDL-C. Patients off LDL-C target should be placed on suitable lipid-lowering therapy subject to many factors such as and (not limited to) tolerance of side-effects and possible drug interactions with other concurrent therapy.

Away From LDL-C Goal (%)	NO CAD/Stroke n (%)	CAD/Stroke n (%)	Recommended Statin	Dosage (mg)	LDL-C Reduction Expected (%)
≤ 10	23 (20.2%)	1 (5.0%)	Same as for 10 – 20% away from LDL-C goal group (below)	-	-
10 - 20	52 (45.6%)	2 (10.0%)	Pravastatin	10	18-25
20 - 30	19 (16.7%)	4 (20.0%)	Lovastatin	10	21
			Fluvastatin	20	22
			Fluvastatin	40	25
			Pravastatin	10	18-25
			Lovastatin	20	24-27
			Pravastatin	20	23-29
			Simvastatin	10	26-33
			Pravastatin	40	26-34
30 - 40	13 (11.4%)	1 (5.0%)	Fluvastatin	80	35
			Pravastatin	80	30-37
			Atorvastatin	10	34-38
			Simvastatin	20	30-40
40 - 50	4 (3.5%)	8 (40.0%)	Ezetimibe/Simvastatin	10/10	45
			Simvastatin	40	35-45
			Rosuvastatin	5	39-46
			Atorvastatin	20	42-46
			Lovastatin	80	39-48
			Simvastatin	80	40-50
			Rosuvastatin	10	43-50
50 - 60	3 (2.6%)	3 (15.0%)	Atorvastatin	40	47-51
			Ezetimibe/Simvastatin	10/20	52
			Atorvastatin	80	46-54
			Ezetimibe/Simvastatin	10/40	55
			Rosuvastatin	20	52-55
			Ezetimibe/Atorvastatin	10/10	53

			Ezetimibe/Atorvastatin	10/20	54
			Ezetimibe/Atorvastatin	10/40	56
≥ 60	0 (0.0%)	1 (5.0%)	Ezetimibe/Simvastatin	10/80	≥60
			Ezetimibe/Atorvastatin	10/80	≥60
			Ezetimibe/Rosuvastatin	10/All	≥60

Table 7 Current statin therapy lipid-lowering therapy available to study type 2 diabetics off LDL-C target; Low Density Lipoprotein Cholesterol (LDL-C), Coronary Artery Disease (CAD), milligram (Mg)

Blood Pressure, Glycaemic Control and Lipids Targets

The combination of all three targets - HbA_{1c} ($\leq 7\%$), Blood Pressure ($\leq 130/80$ mmHg) and LDL-C (≤ 2.5 mmol/L) revealed that 27/362 patients (7.5%) were at goal for the above mentioned targets. Furthermore, a comparison of the results with other international guideline studies produced some interesting results. (Table 8)

Study (No)	Guideline Applied	Glycaemic Control (HbA _{1c}) (%)	Blood Pressure (SBP/DBP) (%)	Lipids (LDL-C or TC) (%)	All Targets (%)
Current	SEMDSA 2009	26.2	45.8*	53.8**	7.5
1	SEMDSA 2003	30.7	21.3 (SBP) 40.2 (DBP)	50.7	-
2	SID 2002 ADA 2007 ESC/EASD 2007	37.0	10.3	16.5	5.0
3	IDF 1999	35.0	52.0	32.0	6.0
4	ADA 2003	41.0	27.0 (SBP) 72.0 (DBP)	41.0	0.0
5	ADA 2003	39.0	14.0	27.0	1.0

Table 8 % patients achieving goals in other studies; Glycated Haemoglobin (HbA_{1c}), Systolic Blood Pressure (SBP), Diastolic Blood Pressure (DBP), Low Density Lipoprotein Cholesterol (LDL-C), Total Cholesterol (TC)

*Diabetics without nephropathy achieving SEMDSA goal ($\leq 130/80$ mmHg) ** Diabetics without previous CAD/Stroke achieving SEMDSA goal (≤ 2.5 mmol/L)

Guideline Study

Current: The Implementation Of Current Guidelines Regarding The Treatment Of Cardiovascular Risk In Type 2 Diabetics

1. Sub-Optimal Management Of Type 2 Diabetes Mellitus - A Local Audit.⁵⁵
2. The clinical reality of guidelines for primary prevention of cardiovascular disease in type 2 diabetes in Italy.⁴⁹

3. The gap between guidelines and practice in the treatment of type 2 diabetes – A nationwide survey in Norway.⁵¹
4. Cardiovascular risk factors in patients with type 2 diabetes – Do we follow the guidelines? ⁵²
5. Can the atherosclerosis prevention targets be achieved in type 2 diabetes? ⁵³

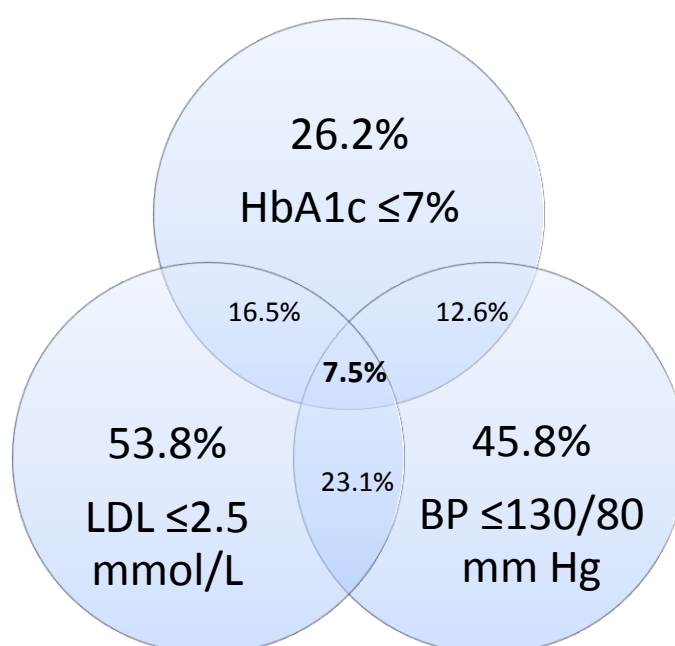


Figure 47 % study type 2 diabetics at SEMDSA goal for glycaemia, blood pressure and lipids; Glycated Haemoglobin (HbA_{1c}), Low Density Lipoprotein Cholesterol (LDL-C), Blood Pressure (BP)

There were 229/563 patients receiving anti-platelet therapy for primary prevention purposes whilst 56/103 patients were receiving for secondary prevention (primary prevention 40.7% vs. secondary prevention 54.4%, $p=0.013$) (Figure 48).

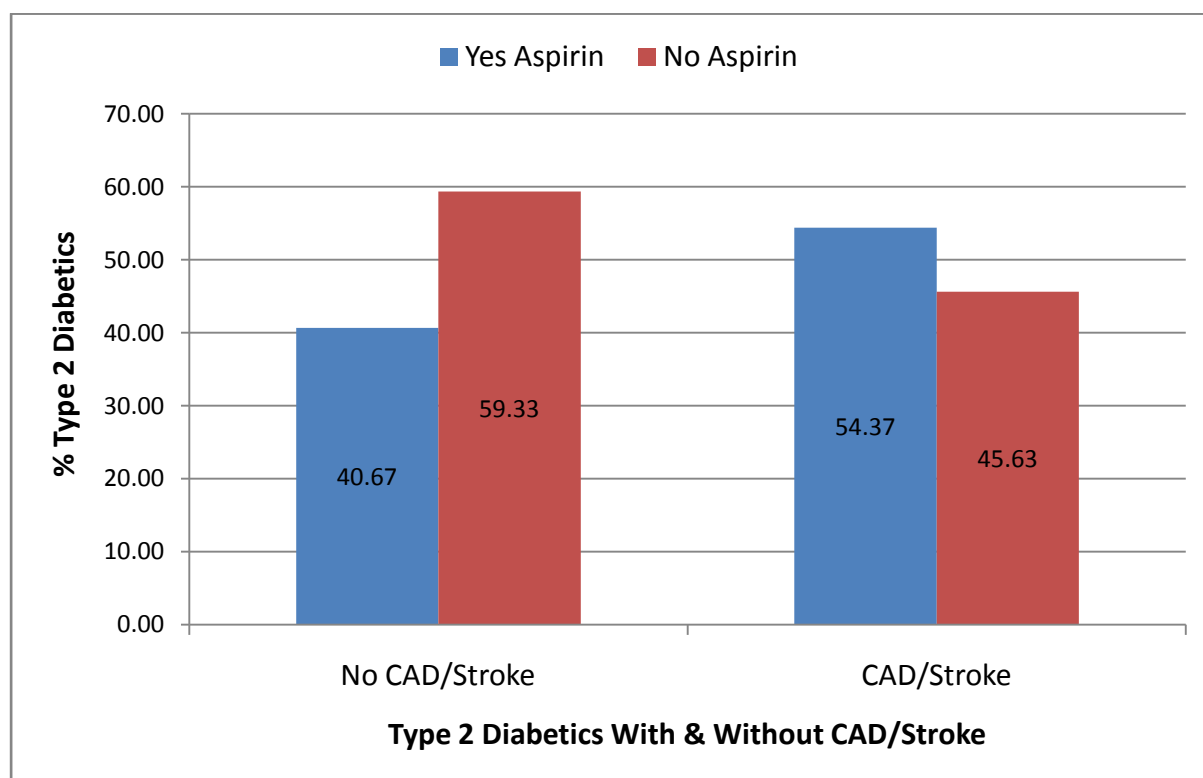


Figure 48 Antiplatelet therapy in study type 2 diabetic population with & without CAD/stroke; Coronary Artery Disease (CAD)

DISCUSSION

Type 2 Diabetes Mellitus is frequently accompanied by obesity.⁶⁶ A 2003 South African epidemiological study revealed that as much as 29% of men and 56% of women were classified as overweight or obese.⁶⁷ As the South African population becomes urbanised and more affluent, diseases of lifestyle such as T2DM have proliferated in a similar fashion. The most recent South African mortality patterns reveal a 41% increase due to non-communicable diseases such as CVD.⁶⁸ Evidence linking CVD and T2DM is strong, CVD being the primary cause of mortality in these patients.⁶⁹ According to the Framingham Heart study, diabetics have a 2-3 times higher risk of cardiovascular events than non-diabetics.⁶³ Clearly South Africa faces many threats on the health care front, but T2DM is growing alarmingly.

Although hyperglycaemia is undoubtedly a risk factor for microvascular complications, intensive glycaemic management has delivered only modest improvements in macrovascular endpoints thus far. A multidisciplinary approach addressing all the components of the dysmetabolic syndrome, including insulin resistance, dyslipidaemia, hypertension, obesity and impaired fibrinolysis, will be required to protect the cardiovascular system more effectively.⁷⁰

In T2DM, treatment needs be multidimensional. The landmark UKPDS trial demonstrated that glycaemic control alone was not enough to reduce the fatal consequences of CVD.⁹ Only through the implementation of guidelines that target additional cardiovascular risk factors such as blood pressure and lipids that significant reduction in mortality in these patients can be achieved.

In 1996, Raal et al. conducted an audit in the Johannesburg Academic Hospital with 82 diabetic patients.⁵⁴ The objectives were to measure the management of cardiovascular risk factors in T2DM patients. Outcomes revealed that diabetic management was primarily aimed at glycaemic control alone. In 2006, 50 patients were audited for similar parameters at the same location.⁷¹ Results from this study revealed that not much had changed over ten years and that a significant gap in the management of cardiovascular risk factors in T2DM still existed.

Using the latest SEMDSA, IDF, ESC/EASD and ADA T2DM guidelines, the present study aimed to further investigate management of South African T2DM patients in a public sector setting.

Blood Pressure

Hypertension is common amongst T2DM patients.⁷² The present study had 569 hypertensive patients (85.4%). Importance of management of blood pressure in T2DM has been recognised by national⁵⁶ and international^{48 57 58} guidelines; yet reaching these targets remains difficult.⁷³ Almost half the cohort (45.8%) reached SEMDSA $\leq 130/80$ mmHg targets (no nephropathy), less patients with nephropathy (16.4%) reached targets of $\leq 120/70$ mmHg.

The current study, where almost half the patients (45.8%) without nephropathy reached SEMDSA $\leq 130/80$ mmHg targets is comparable to the 52.0% of patients which reached targets of $< 140/85$ mmHg as set by the previous IDF 1999 guidelines in a separate Norwegian study.⁵¹ Had patients in the current study been measured against “less stricter” blood pressure targets of $140/85$ mmHg as those set by the

previous guidelines, then certainly more patients would at goal. Only 14.0% and 10.3% of patients achieved blood pressure targets of $\leq 130/80$ in a Czech and an Italian study, respectively.^{53 49} With so few patients reaching blood pressure targets, perhaps patients comprising the cohorts of the Czech and Italian studies were more complicated or further burdened with disease in comparison with the current and Norwegian study.

The benefits of tight blood pressure are comparable with the benefits of tight glycaemic control in T2DM. In the landmark United Kingdom Prospective Diabetes Study (UKPDS) where 1148 hypertensive T2DM patients were assigned to either captopril or atenolol, there was a significant reduction in the risk of both fatal and non-fatal macrovascular and microvascular complications.⁴² In the same year, using felodipine, there were similar findings in the Hypertension Optimal Treatment (HOT) study.⁷⁴ Both trials demonstrated the benefits of blood pressure reduction in T2DM patients and the suggestion of “the lower the better” became unmistakable.

For both patients with and without documented diabetic nephropathy in the cohort, DBP goal was reached more easily than SBP. DBP was once seen as the chief parameter for hypertension diagnosis, staging and as the antihypertensive drug efficacy index. Data from the latest trials suggests that “both SBP and pulse pressure are better predictors of CVD than DBP” as “increased SBP and pulse pressure are closely related and usually represent increased stiffness of large arteries, which is associated with increased prevalence of CVD and increased cardiac mortality.”⁷⁵ Also, it has been documented that raised SBP is indicative of stroke mortality.⁷⁶

In the current cohort, the majority of hypertensive patients (without nephropathy) were receiving ≥ 3 anti-hypertensive drug classes. Goal attainment was more prevalent in patients using mono therapy (58.2% vs. 43.7% vs. 34.4% achieved targets using 1, 2 and ≥ 3 anti-hypertensive drug classes, respectively). Similar outcomes were seen in a 2009 Canadian study.⁷² It is possible that the monotherapy group achieved targets more easily as in the likely case of patients with less severe hypertension or a shorter duration of diabetes (less burdened with disease).⁷⁷ One study advocates that an average of 2.9 medicines per patient is necessary in order to achieve BP targets.⁷⁸ In the intensive treatment arm of the UKPDS study, 29% of patients greatly benefited from treatment with at least 3 classes of antihypertensives.⁴² Dosage adjustments will affect BP reduction levels and drug side-effects may impact patient compliance. An analysis of 354 randomized trials demonstrated that combination therapy using half the standard dose produces an additive BP lowering effect with the benefit of side-effect reduction.⁷⁹ Perhaps dosage reductions in addition to combination therapy are the way forward in order to achieve the best blood pressure goals.

The UKPDS demonstrated that adequate blood pressure control can lower incidence of developing microvascular complications such as nephropathy.⁴² The most commonly prescribed antihypertensive drug class in the study were ACE-Inhibitors (79.96%) followed by diuretics (69.8%). As per the SEMDSA guidelines, ACE-I are recommended as first line therapy for hypertensive diabetics, especially in those patients with microalbuminuria or pre-existing CVD.⁵⁶ With almost 30% of patients with diabetic nephropathy progressing to ESRF,⁸⁰ the use of ACE-Inhibitors in T2DM has significant benefit. ACE-I are particularly useful over other antihypertensive drug

classes through delay of the onset or progression of nephropathy and reduction in the progression from micro to macroalbuminuria.^{81 82 83}

Diuretics were the second most commonly prescribed drug class in the cohort and this mainly comprised of thiazide diuretics. There has been data which has suggested the role of thiazide diuretics in the cause diabetes. In the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) study,⁸⁴ patients receiving chlorthalidone had a higher incidence of diabetes onset compared with amlodipine and lisinopril (11.6% vs. 9.8% vs. 8.1%, respectively). However, no hypertension drug study to date has used diabetes onset as a primary end point, leaving the question open until proven otherwise with more definitive evidence. The use of β -blockers in T2DM has many benefits, yet familiar concerns such as hypoglycaemia masking brings about hesitance in using this therapy in this population. β -blockade is particularly useful in improving outcomes in T2DM patients with previous CVD.⁸⁵ In the Diabetes Insulin-Glucose in Acute Myocardial Infarction (DIGAMI) study where diabetics post myocardial infarction were given β -blockers, there was a 50% reduction in mortality.⁸⁶ In the cohort, one-hundred patients (17.6%) were receiving β -blockers.

Females in the study had slighter higher blood pressures than the males, despite receiving more treatment. Women with T2DM have a significantly increased CVD risk compared with women without diabetes.⁸⁷ In a US-based survey where heart disease related mortality had declined in non-diabetic women over time, the opposite was seen in diabetic women.⁸⁸

In this study, most patients were off target by the first 10 mmHg for both SBP and DBP. Perhaps given the cross-sectional limitations of this study and the short proximity by which targets are missed, patients are being managed in line with the prescribed national guidelines. This points out the challenges of treating patients to goal. Nonetheless, the hypertension treatment gap in T2DM has been well recognized and needs to be addressed far more aggressively in order to improve outcomes.⁸⁹

Glucose

The management of hyperglycaemia is often considered the primary focus of diabetes care. Maintaining or improving glucose control may prevent or even delay the onset of microvascular complications in T2DM patients.⁶ There is also a modest reduction in macrovascular complications with tighter HbA_{1c}. In the landmark UKPDS study, it was shown that for every 1% reduction in HbA_{1c}, there is a 14% reduction in all cause-mortality, a 21% reduction in diabetes-related death, a 14% reduction in fatal and non-fatal MI, and a 16% reduction in the risk of heart failure.⁹⁰

There have been correlations between CVD and elevated postprandial glucose levels in patients with T2DM.⁹¹ However, evidence from newer clinical trials does not support this contention.⁹²

The latest guidelines urge practitioners to treat patients to targets more difficult to reach and evidence suggests intensive HbA_{1c} targeting is not the solution. Meta-analysis⁹³ and randomized trials⁴⁶ demonstrated that overall mortality has not been impacted by massive reductions in HbA_{1c} and treating to HbA_{1c} of $\leq 6.5\%$ has shown

no incremental benefit. In fact, the latest evidence suggests that further reductions in HbA_{1c} increase the chance of hypoglycaemia which negatively impact patient outcomes.⁹⁴ It is no wonder that it has been proposed that HbA_{1c} targets should be measured in terms of upper limits (e.g. 9%) as opposed to the current lower limits.⁹⁵ Glycated haemoglobin targets should remain 7%, but where appropriate, patients which require further reductions should have additional clinical attention given as they stand the added risk of hypoglycaemia, CVD or mortality.

In the present study, HbA_{1c} of $\leq 7\%$ was achieved by over a quarter of the cohort, whilst the harder to reach IDF goal (HbA_{1c} $\leq 6.5\%$) was reached by less. Just about as many which reached the HbA_{1c} of $\leq 7\%$ target were between the acceptable 7% - 8% range. More than half had an HbA_{1c} of $>8\%$, which would require additional action to be taken as recommended by the ADA guidelines.⁴⁸

In the current study, 26.2% of patients reached HbA_{1c} $\leq 7\%$. This result is poor in comparison to the 37.0%, 41.0% and 39.0% of patients achieving those same targets in studies conducted in Italy, Spain and the Czech Republic, respectively.^{49 52 53} A separate Norwegian study showed that 35.0% of their patients were at goal for HbA_{1c} $\leq 6.5\%$, almost double the amount of patients to be at goal for HbA_{1c} in comparison to the current study (17.2%).⁵¹ The South African 2006 had demonstrated a slightly better HbA_{1c} of 30.7% in comparison to the current study. Results from the current study show that out of all the risk factors (blood pressure and serum lipids), HbA_{1c} is being managed worse and in addition, far poorer compared to the other studies reviewed. Perhaps more attention is needed in order to achieve those desired HbA_{1c} levels and as much as guidelines now recommend

more aggressive cardiovascular risk factor management, the treatment of HbA_{1c} should not be left forgotten.

Even though almost the entire cohort received glucose-lowering therapy, the failure to reach these targets remains disappointing. Patients on less intensive glucose lowering therapy (oral hypoglycaemics alone) had lower mean HbA_{1c} levels than those receiving insulin alone. This may reflect the progressive nature of the diabetes mellitus condition or perhaps practitioners are substituting poor glucose control with more intensive treatment.

In this study, patients with higher HbA_{1c} levels tended to present with higher mean LDL-C levels. This may not necessarily signify that T2DM patients with raised HbA_{1c} levels will have higher LDL-C levels. It may however point out that poor control of one risk factor is often accompanied by other poorly controlled risk factors.

Biguanides (metformin) was used by 70% of patients as monotherapy or in combination with other treatment. Metformin, in the 850mg dosage form was the most commonly prescribed oral hypoglycaemic. There is evidence to suggest that metformin has vascular protective effects. In the UKPDS study, patients on combination metformin/sulphonylurea suffered more myocardial infarcts, strokes and cardiovascular mortality than those receiving metformin monotherapy.⁹⁶ In addition, metformin's weight neutral properties helped stabilize blood pressure levels in obese patients. Given the predisposition to cardiovascular disease and the frequent association of T2DM with obesity, metformin may in fact be the drug of first choice in these patients.

As previously mentioned, patients which present at this particular hospital are most often referral patients. There were 454 (68.17%) patients receiving insulin as either mono or combination therapy. With so many insulin users comprising the cohort, it may be said that the study population was comprised of patients with an advanced stage of diabetes. On the other hand, perhaps practitioners are opting for insulin usage over oral hypoglycaemic therapy in an attempt to achieve better glycaemic control. Or perhaps insulin was favoured over oral hypoglycaemics as first line therapy? The missing data on diabetes duration as well as the cross-sectional nature of this study limits the understanding of this. Indeed, future studies should opt to include this parameter as it may shed some light on the greater use of insulin in T2DM patients.

Lipids

“From an initial perception that a disorder of glucose metabolism was the primary event in the pathogenesis of T2DM, there is now a growing appreciation that chronic elevation of free fatty acid (FFA) levels is an early event that contributes to the development of this disease. “⁹⁷

Despite having cholesterol levels similar to that of the general population, T2DM patients have lipid abnormalities which place them at high risk for cardiovascular disease and stroke. An epidemiological study demonstrated that T2DM patients have a 2 to 6 fold increased risk of cardiovascular disease and death.⁹⁸ T2DM management should routinely be considered secondary prevention, rather than primary prevention. The National Cholesterol Education Program (NCEP) recognizes

T2DM as “CVD-equivalent.”⁹⁹ Outcomes from the Framingham study set secondary prevention treatment for T2DM patients, similar to patients with a $\geq 20\%$ risk of sustaining a cardiac event over the next ten years. Other patients classed into the same category as T2DM patients are those who have established CVD.⁶³

Lipid management in T2DM patients remains poor. In a study conducted by Mehler et al, there was a consistent non-adherence trend to lipid guidelines for over 5 years.¹⁰⁰ In the current study, there were 275 patients (46.2%) with hypercholesterolaemia and 230 patients (39.8%) with hypertriglyceridaemia. Only half the cohort (53.85%) in the low risk category reached LDL-C SEMDSA targets (2.5 mmol/L) whilst much fewer (18.09%) reached targets in the high risk category (1.8 mmol/L). Patients not at goal for LDL-C were off by 0.81 mmol/L (2.5 mmol/L target) and 1.13 mmol/L (1.8 mmol/L target) on average. By lowering lipids in T2DM, vascular events and mortality can be drastically reduced. Clearly there needs to be an effective intervention in order to improve outcomes in T2DM patients.

In comparison to the 53.8% of patients which reached the LDL-C target of 2.5 mmol/L in the current study, 41.0% and 23.0% of patients achieved 2.6 mmol/L LDL-C targets in two separate Spanish and Czech Republic studies, respectively.^{52 53} Despite an easier target to reach, 16.5% and 32.0% of patients in separate Italian and Norwegian studies reached LDL-C of 3.0 mmol/L targets, respectively.^{49 51} The results from the current study demonstrated that patients are achieving LDL-C targets far better than the other studies compared, including the previous 2006 study where 50.7% reached the LDL-C target of 2.5 mmol/L.⁵⁵ Perhaps patients in the current study are being better managed for serum lipids through use of lipid-lowering

therapy or have a better knowledge of dietary modifications. One could argue that patients selected for the current study are being treated on a tertiary level, however, the Italian study had the poorest results, despite being conducted over 10 large hospital-based out-patient diabetes clinics. Outcomes from the Spanish study are most comparable to those obtained from the current study, both having similar LDL-C targets, similar level of patients achieving LDL-C targets and both study sites consisting of public referral hospitals. It is not clear why the last two last studies with targets of 3.0 mmol/L had such poor outcomes.

Despite the wealth of evidence in favour of aggressive treatment of lipids in T2DM and treatment guideline recommendations, lipid-lowering therapy was only prescribed to just over half the cohort. The normal to slightly raised LDL cholesterol levels often makes lipid-lowering therapy unjustified for the primary prevention of cardiovascular disease in T2DM. However, clinical trials like CARDS²⁹ and others²⁸ support the contention that lipid-lowering treatment in diabetic patients reduces CVD, regardless of baseline LDL-C levels.

Patients in the current study were treated for both primary and secondary prevention on different levels; 317/563 patients (56.3%) and 78/103 patients (75.7%) were being treated for primary and secondary prevention, respectively.

T2DM patients are at an increased risk of sustaining a cardiovascular event, especially those which should be treated for secondary prevention. Haffner et al. found that T2DM patients which previously had an MI, the risk of a recurrent event is nearly 50%.¹⁴ Poor guideline adherence and the lack of adequate therapy will lead to

costly surgical interventions and/or mortality if aggressive lipid-lowering treatment is not commenced.

The high prevalence of CVD associated with T2DM is not unique to men, in fact, in the developed world it is the primary cause of death in females.¹⁰¹ In the present study, more females were being treated with statin lipid-lowering therapy (male 56.9% vs. female 61.3%, not statistically significant, $p = 0.449$), yet had higher mean LDL-C levels (male 2.5 mmol/L (SD: 0.9) vs. female 2.7 mmol/L (SD: 0.9), not statistically significant, $p = 0.052$).

T2DM patients tend to have small, dense and atherogenic LDL which may in fact be deceptive of the actual risk.⁴⁵ Even if patients are achieving goal, statin therapy should be encouraged to lower the absolute risk of developing CVD.²⁸ In the current study, patients (without previous CVD) receiving lipid-lowering therapy tended to have slightly higher mean LDL-C than those not receiving lipid-lowering therapy. With the disadvantages of cross-sectional studies, we can only assume that patients with higher LDL-C were only recently (just before the time of data collection) placed on lipid-lowering therapy and that levels were still to adjust. This reasoning can also be applied to where patients on lipid-lowering therapy tended to have higher prevalence of cardiovascular disease or stroke. The presence of cardiovascular history or a previous event may have encouraged the treating practitioner(s) to prescribe lipid-lowering therapy for secondary treatment. Conceivably, due to the limited duration of therapy usage or poor patient compliance, those undeniable risk reductions offered by lipid-lowering therapy had yet to be realized. Perhaps the statin dosage was inappropriate and could have been adjusted. Simvastatin, particularly in the

20mg/day dosage was the most frequently prescribed. A comparison of target achievement by either receiving or not receiving lipid-lowering therapy favoured those on therapy to be more at goal.

The use of statins in T2DM patients is beneficial. A study of 18 686 diabetic participants demonstrated that major vascular events (coronary events, stroke and coronary revascularisations) were reduced by a fifth for every mmol/L LDL-C reduced over 5 years.¹⁰² With newer evidence available, there has been a progressive demand to lower LDL-C targets.¹⁰³ Especially in high risk groups such as T2DM, lower LDL-C will lead to less cardiovascular disease and better patient outcomes. With newer and more potent agents available, future studies are needed to define what LDL-C levels are optimal and safe, as cholesterol forms a “core component in cellular membranes” of the body.¹⁰⁴

Until now, with the major impact statins have had on reducing CVD, their safety in the development of diabetes may have not been fully investigated. In a recent meta-analysis, it was shown that with statin usage, there is a 9% increased risk in diabetes development.¹⁰⁵ The authors of the study recommended that statins be prescribed by doctors accordingly and that patients receiving statins should be screened for diabetes, particularly older patients. It was also mentioned that the slight risk of diabetes incidence is “favourably balanced by cardiovascular benefit.” Hence, although there is a slight risk of developing diabetes in patients using statins, the benefits of statins shouldn’t be disregarded. Guidelines pertaining to statin use should still be followed, especially in those individuals that are high-risk of CVD.

Anti-platelet therapy

The benefit of anti-platelet therapy in T2DM secondary prevention is well established.¹⁰⁶ The prescribing of low-dose aspirin in the secondary treatment of CVD for T2DM is suggested in all the latest guidelines and has been “standard practice” for decades, not just in T2DM patients, but also for other high-risk populations. Despite T2DM patients having high risk for CVD, the use of aspirin for primary prevention remains controversial. T2DM patients with multiple risk factors should undoubtedly be treated for secondary prevention with aspirin anti-platelet therapy as they stand a far greater risk of sustaining coronary events. However, aspirin in primary prevention may not always outweigh its risks and the only evidence to suggest its use is based on “extrapolations from data from other high-risk populations.”¹⁰⁷ In a recent meta-analysis, the use of aspirin in diabetics for the primary prevention of major cardiovascular events showed no significant benefit.¹⁰⁸ The lack of conclusive beneficial evidence that this therapy has had in the primary prevention of diabetics warrants the need for more studies to be conducted. Two studies currently under way are: A Study of Cardiovascular Events in Diabetes (ASCEND ISRCTN60635500) and the Aspirin and Simvastatin Combination for Cardiovascular Events Prevention Trial in Diabetes (ACCEPT-D).¹⁰⁹ In the present study, 40.7% and 54.4% of patients were being treated for primary and secondary prevention, respectively. Poor guideline adherence is clear, especially in those patients which should be treated with anti-platelet therapy for secondary prevention.

All Cardiovascular Risk Factors

The use of aspirin and a statin in addition to targeted lowering of glucose and blood pressure is associated with reduction in cardiovascular risk in patients with T2DM. When these reductions are achieved all together, there may even be a greater benefit.⁴³ Patients in the current study achieved LDL-C goals easier than blood pressure or glycaemic control (53.8% vs. 45.8% vs. 26.2% reached LDL-C, blood pressure and HbA_{1c} targets, respectively). Less than 10% of the study population achieved the combined treatment goals for all three risk factors. The poor achievement of targets is in line with other studies. In an Italian study, where 2465 patients were recruited, only 5% achieved the recommended goals for LDL-C, BP, glycated haemoglobin and smoking habits.⁴⁹ Similarly, a Czech study concluded that 1% of their patients achieved goals, whilst a Norwegian study consisting of 975 patients had 6% of their total cohort at goal for the combined targets of glucose, BP and cholesterol control.^{51 53} This may also demonstrate how challenging it is to control all risk factors in T2DM.

Newer guidelines often set targets more difficult to achieve. However, the level of guideline adherence is often based on glycaemic control alone. The T2DM condition requires treatment which is multifactorial. It is no wonder so many patients are left undertreated. Lifestyle or dietary modification should also be stressed in addition to any pharmacotherapy. With the present challenges in treating T2DM patients, practitioners need to target all risk factors more aggressively.

Resources

“The changing prevalence and incidence of DM is a major public health and economic problem.”¹¹⁰ In 2002, the US economy spent \$132 billion on diabetes.¹¹¹ South Africa’s resource limitations in the state sector are a constant reality. The number of doctors available to treat patients is limited. The selection of medications is subject to governmental formulary and may not always be the most effective available treatment. Short routine consultations, coupled with communication barriers lead to a major compromise in patient education. Improper lifestyle intervention, poor technique training leading to incorrect storage or administration of medicine such as insulin will surely result in poor diabetic control. The SEMDSA guidelines acknowledge patient education to be “cornerstone in effective diabetes care.”⁵⁶ In the DESMOND study, the benefit of a structured educational program for both new and previously diagnosed diabetics proved to have had a positive impact on weight loss and smoking cessation.¹¹² It is pivotal for T2DM patients to be fully aware of their risk factors and know how to manage these effectively.¹¹³ Patients must also understand the chronic nature of the disease and their need to continue therapy for the rest of their lives. Better diabetes management is associated with better outcomes.¹¹⁴ As much as patient compliance is important, practitioner’s convictions will also impact patient outcomes.¹¹⁵

On the positive, T2DM treatment gaps don’t necessarily affect developing countries but also those with greater resources available. Despite the resource shortfalls of South Africa, the treatment gaps are in line with that of resource rich developed countries. Generally, further efforts in resource allocations and practitioner-patient communication are undoubtedly necessary to address disease management issues.

Limitations

It could be said that data obtained from only one hospital may not entirely reflect the state of healthcare in the country. However, this study serves a very useful purpose and that is of, the value of auditing the level of care T2DM patients are receiving in a diabetes clinic at a major public sector academic hospital. Given the size and ethnicity ratios of the study cohort, the results may be a good representation of the South African population and may further be applicable to other major public hospitals across the country.

The national SEMDSA guidelines are adapted from both US and European guidelines (ADA and ESC/EASD, respectively). This may limit their application in the South African setting and may not be appropriate to benchmark the levels achieved (in the study) against international targets. With the South African population being a minority Caucasian, local future research will aid the development of guidelines that are better applicable to the South African population as whole.

The current study was cross-sectional in design and may not have reflected the patients which prematurely passed away before the commencement of the study (i.e. those patients having the poorest control of risk factors). It was not an objective of the study, but future studies could be aimed at determining outcomes using longitudinal data.

Data collected was done retrospectively. Due to the referral nature of the diabetic clinic, there were instances where patients had incomplete history. Some patients presented at the clinic whilst already controlled on therapy and did not require further

laboratory tests to be carried out. Some data may have been lost within the clinic. With details of weight, height, waist measurement, diet details and smoking status not found in the majority of patient files, calculations and classifications such as BMI and classification of the MS were omitted. Blood pressure readings were left out in some of the patient files and this is a large limitation to the study. Since hypertension and T2DM are components of the MS, it would have been worthwhile to determine the status of the cohort. Future studies should opt to include all necessary laboratory levels as well as other measurement parameters.

There were also too few patients (5.86%) recruited in the Coloured population. It may be useful to recruit more Coloured patients in a future study.

At the time of collection (July 2008-July 2009), practitioners may have used the previous SEMDSA 2003 guidelines to manage their patients. In this study, the latest SEMDSA 2009 guidelines were applied to the cohort. Despite this, practitioners, especially those working in an academic environment would have enough opportunities to revise or be updated (using circulations, meetings, seminars, literature etc) as to the latest treatment goals advised both nationally and locally.

Conclusion

“It has been shown that 85-95% of all diabetes cases are of type 2 in developed countries and this percentage is even higher in developing countries.”³

Aggressive targeting of HbA_{1c} as well as blood pressure and dyslipidaemia is suggested by the latest T2DM treatment guidelines.^{48 56 57 58} But are treatment

guidelines being adhered to in clinical practice and are treatment target goals being met? Certainly important, but even more so in developing countries such as South Africa where there less resources are available.

Treating T2DM is challenging, it is no wonder that a large gap exists between practice and recommended treatment targets. Two previous studies conducted at the Charlotte Maxeke Johannesburg General Hospital demonstrated the under treatment of major cardiovascular risk factors in T2DM patients.^{54 55} Using a larger sized cohort and the latest T2DM treatment guidelines, the current study was conducted to further evaluate the treatment gaps in T2DM. This study was not only conducted in order to augment our understanding of the treatment gap in the management of cardiovascular risk factors but indeed also to help influence modern day practice in the complexities of management in the T2DM condition.

Numerous clinical trials have demonstrated the benefits of targeting and reducing blood pressure and lipid levels in T2DM.⁴³ With so much focus centred around glucose control in the T2DM condition it is imperative that more attention is given to the above mentioned risk factors.

There needs to be a more focused multi-factorial approach in managing the cardiovascular risk factors in these patients. Whether improvement lies in the form of therapeutic titration adjustment or an increase in patient education, there needs to be a more aggressive therapeutic approach to treating this high risk group of patients in order to reduce overall morbidity and mortality.

In conclusion, the study aimed to evaluate T2DM patients being treated in a resource-limited public sector setting hospital for CVD risk factors and to see whether they were being treated to goal. The majority of the cohort were treated with the necessary pharmacotherapy, but there still lies a gap in the reaching of treatment goals. Less than 10% of the cohort achieved the combined treatment goals for HbA_{1c}, blood pressure and serum lipids. Indeed this indicates a poor level of goal attainment, however, in comparison to other studies; South Africa may have in fact achieved similar results with fewer resources available.

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APPENDICES

APPENDICES

Ethics Approval Letter

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

Division of the Deputy Registrar (Research)

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

R14/49 Pinchevsky

CLEARANCE CERTIFICATE

PROTOCOL NUMBER M080409

PROJECT

The Implementation of current guidelines regarding the treatment of cardiovascular risk in type 2 diabetics: A retrospective analysis

INVESTIGATORS

Mr Y Pinchevsky

DEPARTMENT

Pharmacy and Pharmacology

DATE CONSIDERED

08.04.25

DECISION OF THE COMMITTEE*

Approved unconditionally

+

Unless otherwise specified this ethical clearance is valid for 5 years and may be renewed upon application.

DATE 08.05.20

CHAIRPERSON.....



(Professor P E Cleaton Jones)

*Guidelines for written 'informed consent' attached where applicable

cc: Supervisor : Dr N Butkow

DECLARATION OF INVESTIGATOR(S)

To be completed in duplicate and ONE COPY returned to the Secretary at Room 10004, 10th Floor, Senate House, University.

I/We fully understand the conditions under which I am/we are authorized to carry out the abovementioned research and I/we guarantee to ensure compliance with these conditions. Should any departure to be contemplated from the research procedure as approved I/we undertake to resubmit the protocol to the Committee. **I agree to a completion of a yearly progress report.**

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

Figure 49 Ethics approval letter

Protocol Approval Letter



Faculty of Health Sciences Medical School, 7 York Road, Parktown, 2193
Fax: (011) 717-2119 / Tel: (011)717-2125

Reference: Ms Helen Selolo

E-mail: monyai.selolo@wits.ac.za
17 June 2008

Person No: 0404881D
PAG

Mr Y Pinchevsky
P O Box 10643
Vorna Valley
1686
South Africa

Master of Science in Medicine: Approval of Title

We have pleasure in advising that your proposal entitled *The implementation of current guidelines regarding the treatment of cardiovascular risk in type 2 diabetic a retrospective analysis* has been approved. Please note that any amendments to this title have to be endorsed by the Faculty's higher degrees committee and formally approved.

Yours sincerely

A handwritten signature in black ink, appearing to read "S Benn".

Mrs Sandra Benn
Faculty Registrar
Faculty of Health Science

Figure 50 Case report form

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Risk Factors For CVD Classified by Risk Group, Gender-Age Groups

Risk Group Age Group (years)	Lower Risk - No CAD/Stroke				Higher Risk - YES CAD/Stroke			
	≤ 55	55 - 65	≥65	Overall	≤ 55	55 - 65	≥65	Overall
Gender								
	Females (n = 322)				Females (n = 47)			
n	101	118	103	322	8	14	25	47
Total Cholesterol (mmol/L)	4.64	4.73	4.67	4.68	5.35	4.45	4.86	4.83
Triglycerides (mmol/L)	1.72	1.73	1.61	1.69	2.21	1.63	1.96	1.92
HDL-C (mmol/L)	1.23	1.23	1.33	1.27	1.01	1.14	1.28	1.20
LDL-C (mmol/L)	2.59	2.70	2.60	2.63	3.33	2.47	2.70	2.75
NAG COUNT (n)	40	53	47	140	8	10	23	41
NAG Average LDL-C (mmol/L)	3.42	3.22	3.25	3.29	3.33	2.66	2.82	2.88
Mean Reduction needed (mmol/L)	0.92	0.72	0.75	0.79	1.53	0.86	1.02	1.08
% from Goal (%)	23.33	19.27	20.97	21.00	40.55	28.13	32.64	33.09
Gender								
	Males (n = 241)				Males (n = 56)			
n	85	74	82	241	12	19	25	56
Total Cholesterol (mmol/L)	4.53	4.38	4.11	4.34	4.75	5.09	4.29	4.67
Triglycerides (mmol/L)	1.84	1.70	1.58	1.71	2.19	2.48	1.69	2.08
HDL-C (mmol/L)	1.04	1.10	1.11	1.09	1.07	1.01	1.02	1.03
LDL-C (mmol/L)	2.71	2.47	2.24	2.48	2.66	2.64	2.49	2.58
NAG COUNT (n)	33	28	21	82	9	12	15	36
NAG Average LDL-C (mmol/L)	3.49	3.34	3.14	3.35	3.19	3.03	2.85	2.99
Mean Reduction needed (mmol/L)	0.99	0.84	0.64	0.85	1.39	1.23	1.05	1.19
% from Goal (%)	25.12	21.67	19.40	22.48	39.85	37.56	32.72	36.12

Table 9 Risk factors for CVD classified by risk group, gender and age group for study type 2 diabetic patients; Low Density Lipoprotein Cholesterol (LDL-C), High Density Lipoprotein Cholesterol (HDL-C), Coronary Artery Disease (CAD), Cardiovascular Disease (CVD), Not At Goal (NAG)

Exclusion of Participants in Type 2 Diabetes Study

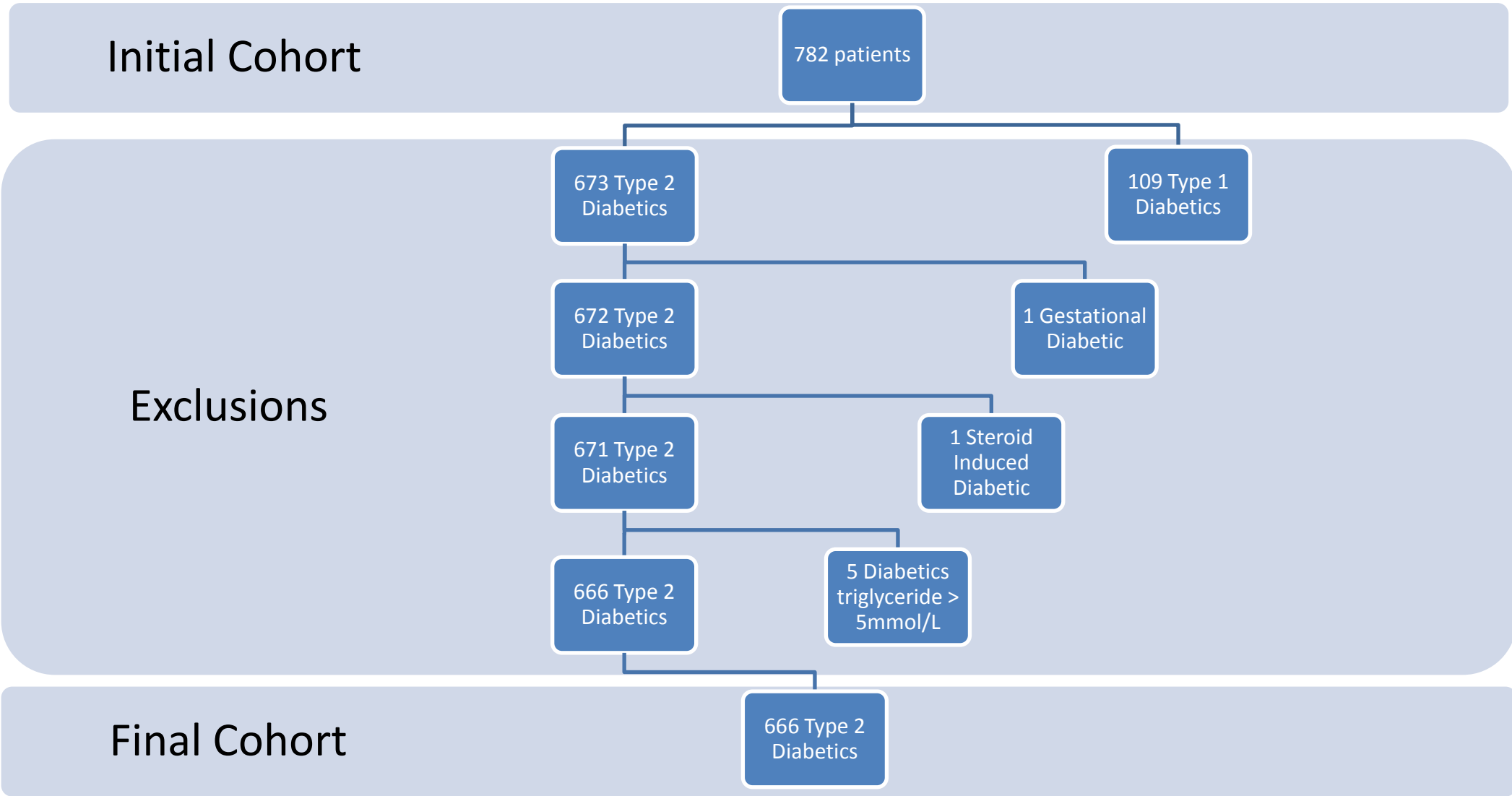


Figure 51 Exclusion of participants in type 2 diabetic study

The Use Of Statin Lipid-Lowering Therapy In Type 2 Diabetic Study Population

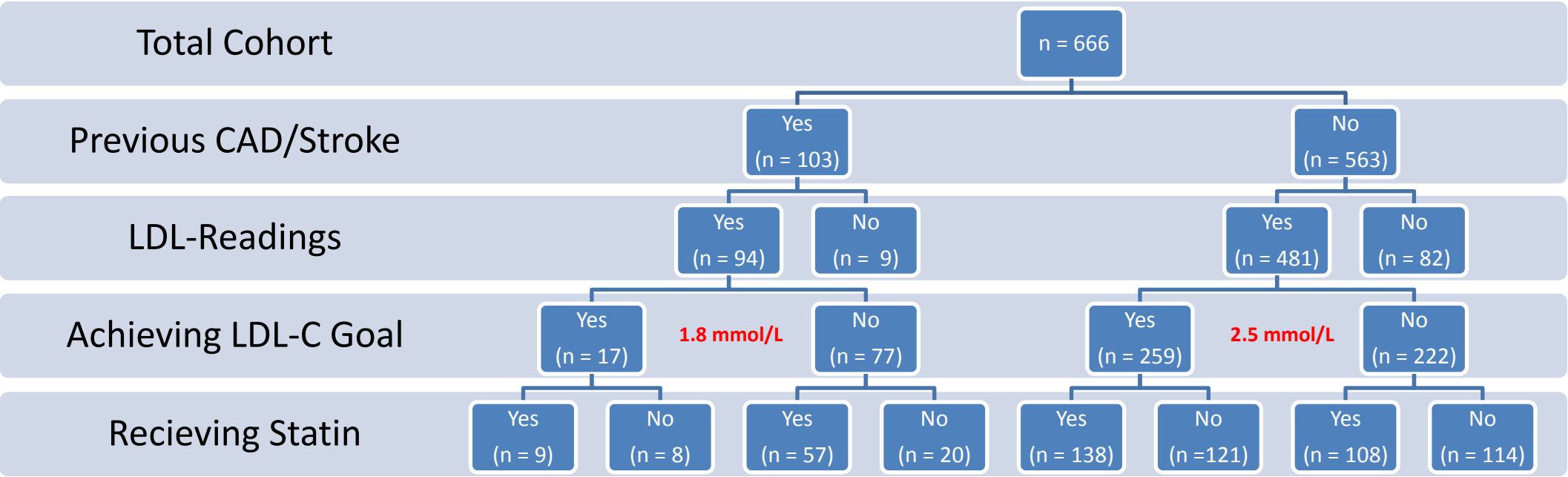


Figure 52 The use of lipid-lowering therapy in type 2 diabetic study population; CAD/Stroke LDL-C target (1.8mmol/L) (left), No CAD/Stroke LDL-C target (2.5mmol/L) (right)

Type 2 Diabetes Treatment Guidelines

<u>Treatment goal</u>	<u>SEMDSA (2009)</u>	<u>ADA (2008)</u>	<u>IDF (2005)</u>	<u>ESC/EASD (2007)</u>
Serum Glucose				
HbA _{1c} (%)	<7	<7	≤6.5	≤6.5
Blood Pressure				
Systolic (mmHg)	<130	<130	<130	<130
Diastolic (mmHg)	<80	<80	<80	<80
Systolic - Nephropathy patients (mmHg)	≤120	≤120	≤120	≤120
Diastolic - Nephropathy patients (mmHg)	≤70	≤70	≤70	≤70
Plasma Lipids				
Total Cholesterol (mmol/L)	<4.5	<4.5	<4.5	<4.5
LDL-Cholesterol (mmol/L)	<2.5	<2.6	<2.5	<2.5
LDL-Cholesterol - CAD/Stroke patients (mmol/L)	≤1.8	≤1.8	≤1.8	≤1.8
HDL-Cholesterol - Male patients (mmol/L)	>1.0	>1.0	>1.0	>1.0
HDL-Cholesterol - Female patients (mmol/L)	>1.2	>1.3	>1.2	>1.2
Triglyceride (mmol/L)	<1.7	<1.7	<1.5	<1.7

Table 10 Treatment goal summary for type 2 diabetics as set by different guidelines; Society for Endocrinology, Metabolism and Diabetes of South Africa (SEMDSA), American Diabetes Association (ADA), International Diabetes Federation (IDF) and European Society of Cardiology / European Association for the Study of Diabetes (ESC/EASD), CAD/Stroke - In patients with established vascular disease such as ischaemic heart disease, cerebrovascular disease or peripheral vascular disease, LDL-C target: ≤ 1.8 mmol/L

Criteria For The Diagnosis Of Type 2 Diabetes Mellitus - SEMDSA

SEMDSA Guidelines for Diagnosis and Management of Type 2 Diabetes Mellitus for Primary Health Care - 2009	
<p>A.^a Symptoms of diabetes plus</p> <ul style="list-style-type: none"> Casual/random plasma glucose ≥ 11.1 mmol/l^b <p>Or</p> <ul style="list-style-type: none"> Fasting plasma glucose (FPG) ≥ 7.0 mmol/l^c <p>Or</p> <ul style="list-style-type: none"> 2-h plasma glucose (2PG) ≥ 11.1 mmol/l during OGTT^d 	
<p>^aThe classic symptoms of diabetes include polyuria, polydipsia and weight loss</p> <p>^bCasual is defined as any time of day without regard to time of last meal</p> <p>^cFasting is defined as no caloric intake for at least 8h</p> <p>^dThe test should be performed as described by the World Health Organisation using a glucose load containing the equivalent of 75-g anhydrous glucose dissolved in 250ml water over 5 minutes</p> <p>Note: In the absence of unequivocal hyperglycaemia accompanied by acute metabolic decompensation a confirmatory laboratory glucose test (a FPG, a casual PG or a 2hPG in a 75-g OGTT) must be done in all cases on another day. Different criteria are used to diagnose gestational diabetes in pregnant women.</p>	
<p>B. If asymptomatic</p> <p>The 75g OGTT is indicated in the following:</p> <ul style="list-style-type: none"> In the asymptomatic high-risk individuals If FPG is ≥ 5.6 - <7.0 mmol/l (in detection / screening programmes) if random plasma glucose ≥ 5.6 - <11.1[†] (on screening) 	
<p>[†] or do FPG.</p> <ul style="list-style-type: none"> - WHO 1998 / 2006 criteria should be used to diagnose diabetes, including the importance of not diagnosing diabetes on the basis of a single laboratory measurement in the absence of symptoms. - Diagnosis should be based on laboratory plasma glucose (preferred) or capillary plasma glucose. - Conversion factor: plasma glucose (mmol/l) = $0.102 + 1.066 \times$ capillary blood glucose. 	

Table 11 Criteria for the diagnosis of type 2 diabetes mellitus; Society for Endocrinology, Metabolism and Diabetes of South Africa (SEMDSA)

Criteria For The Diagnosis Of Type 2 Diabetes Mellitus - ADA

<p>ADA Standards of Medical Care in Diabetes - 2008</p> <p><i>Criteria for the diagnosis of diabetes</i></p> <p>1. FPG 126 mg/dl (7.0 mmol/l). Fasting is defined as no caloric intake for at least 8 h.*</p> <p>OR</p> <p>2. Symptoms of hyperglycemia and a casual plasma glucose 200 mg/dl (11.1 mmol/l). Casual is defined as any time of day without regard to time since last meal. The classic symptoms of hyperglycemia include polyuria, polydipsia, and unexplained weight loss.</p> <p>OR</p> <p>3. 2-h plasma glucose 200 mg/dl (11.1 mmol/l) during an OGTT. The test should be performed as described by the World Health Organization, using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water.*</p> <p>*In the absence of unequivocal hyperglycemia, these criteria should be confirmed by repeat testing on a different day.</p> <p><i>Criteria for testing for pre-diabetes and diabetes in asymptomatic adult individuals</i></p> <p>Testing should be considered in all adults who are overweight (BMI 25 kg/m²*) and have additional risk factors:</p> <ul style="list-style-type: none"> • physical inactivity • first-degree relative with diabetes • members of a high-risk ethnic population (e.g., African American, Latino, Native American, Asian American, and Pacific Islander) • women who delivered a baby weighing 9 lb or were diagnosed with GDM • hypertension (140/90 mmHg or on therapy for hypertension) • HDL cholesterol level 35 mg/dl (0.90 mmol/l) and/or a triglyceride level 250 mg/dl (2.82 mmol/l) • women with polycystic ovarian syndrome (PCOS) • IGT or IFG on previous testing • other clinical conditions associated with insulin resistance (e.g., severe obesity and acanthosis nigricans) • history of CVD <p>2. In the absence of the above criteria, testing for pre-diabetes and diabetes should begin at age 45 years</p> <p>3. If results are normal, testing should be repeated at least at 3-year intervals, with consideration of more frequent testing depending on initial results and risk status.</p> <p>*At-risk BMI may be lower in some ethnic groups.</p>
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Table 12 Criteria for the diagnosis of type 2 diabetes mellitus; American Diabetes Association (ADA)

Criteria For The Diagnosis Of Type 2 Diabetes Mellitus - IDF

International Diabetes Federation – Global Guideline For Type 2 Diabetes

Screening and diagnosis

Each health service should decide whether to have a programme to detect people with undiagnosed diabetes.

- This decision should be based on the prevalence of undiagnosed diabetes and on the resources available to conduct the detection programme and treat those who are detected.
- Universal screening for undiagnosed diabetes is not recommended.
- Detection programmes should target high-risk people identified by assessment of risk factors.

Detection programmes should use measurement of plasma glucose, preferably fasting.

For diagnosis, an oral glucose tolerance test (OGTT) should be performed in people with a fasting plasma glucose ≥ 5.6 mmol/l (≥ 100 mg/dl) and < 7.0 mmol/l (< 126 mg/dl).

Where a random plasma glucose level ≥ 5.6 mmol/l (≥ 100 mg/dl) and < 11.1 mmol/l (< 200 mg/dl) is detected on opportunistic screening, it should be repeated fasting, or an OGTT performed.

The WHO 1999 criteria (1) should be used to diagnose diabetes; these include the importance of not diagnosing diabetes on the basis of a single laboratory measurement in the absence of symptoms.

People with screen-detected diabetes should be offered treatment and care. This guideline does not deal with lesser degrees of hyperglycaemia detected on screening.

This guideline does not deal with lesser degrees of hyperglycaemia detected on screening.

World Health Organization. Definition, Diagnosis and Classification of Diabetes Mellitus and its Complications. Report of a WHO Consultation. Part 1: Diagnosis and Classification of Diabetes Mellitus. Geneva: WHO Department of Non-communicable Disease Surveillance. 1999: 1-59. <http://www.who.int>

Table 13 Criteria for the diagnosis of type 2 diabetes mellitus; International Diabetes Federation (IDF)

Criteria For The Diagnosis Of Type 2 Diabetes Mellitus – ESC/EASD

European Society of Cardiology / European Association for the Study of Diabetes (ESC/EASD)

Impaired glucose tolerance (IGT) can be recognized by the results of OGTT only: 2-h post-load plasma glucose (2hPG) 7.8 and 11.1 mmol/L (140 and 200 mg/dL).

A standardized OGTT test performed in the morning, after an overnight fast (8–14 h); one blood sample should be taken before and one 120 min after intake of 75 g glucose dissolved in 250–300mL water in a course of 5 min (note: timing of the test is from the beginning of the drink).

The currently valid clinical classification criteria have been issued by WHO and ADA. These are currently under review by WHO and updated criteria will be introduced soon. The WHO recommendations for glucometabolic classification are based on measuring both fasting and 2-hPG concentrations and recommend that a standardized 75 g OGTT should be performed in the absence of overt hyperglycaemia.

Table 1 Criteria used for glucometabolic classification according to the WHO (1999), ADA (1997) and (2003)

Glucometabolic category	Source	Classification criteria mmol/L (mg/dL)
Normal glucose regulation (NGR)	WHO	FPG < 6.1 (110) + 2-h PG < 7.8 (140)
	ADA (1997)	FPG < 6.1 (110)
	ADA (2003)	FPG < 5.6 (100)
Impaired fasting glucose	WHO	FPG ≥ 6.1 (110) and < 7.0 (126) + 2-h PG < 7.8 (140)
	ADA (1997)	FPG ≥ 6.1 (110) and < 7.0 (126)
	ADA (2003)	FPG ≥ 5.6 (100) and < 7.0 (126)
Impaired glucose tolerance (IGT)	WHO	FPG < 7.0 (126) + 2-h PG ≥ 7.8 and < 11.1 (200)
Impaired glucose homeostasis (IGH)	WHO	IFG or IGT
Diabetes mellitus (DM)	WHO	FPG ≥ 7.0 (126) or 2-h PG ≥ 11.1 (200)
	ADA (1997)	FPG ≥ 7.0 (126)
	ADA (2003)	FPG ≥ 7.0 (126)

Values are expressed as venous plasma glucose.

FPG = fasting plasma glucose; 2-h PG = two-hour post-load plasma glucose (1 mmol/L = 18 mg/dL).

WHO Consultation. Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus. Geneva: World Health Organisation; 1999. Report no. 99.2.

Table 14 Criteria for the diagnosis of type 2 diabetes mellitus; European Society of Cardiology / European Association for the Study of Diabetes (ESC/EASD)