

**The evaluation of low-density lipoprotein cholesterol
goals achieved in patients with established
cardiovascular disease and/or hyperlipidaemia
receiving lipid lowering therapy**

*The South African Not At Goal Study
(SA-NAG)*

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DECLARATION

I, Akash Ashley Ramjeeth declare that this dissertation is my own work. It is being submitted for the degree of Master of Science in Medicine in 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
_____ 2008.

Signature

DEDICATION

I dedicate this dissertation to God and my parents. I thank God for blessing me with the opportunity to study and to my parents for their constant support during my education.

PUBLICATIONS AND PRESENTATIONS

- Presentations:**
- (i) The University of the Witwatersrand Research day – August 2006 (Preliminary results).
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ABSTRACT

Background Cardiovascular disease (CVD) is the leading cause of morbidity and mortality worldwide. A major risk factor for CVD is hypercholesterolaemia. As a result the South African scientific community has updated its clinical guidelines for CVD management by adoption of the current European cardiovascular disease guidelines. The South African Not at Goal Study (SA-NAG) was a survey to determine the percentage of patients, on lipid-lowering therapy, who are not achieving guideline specified low density lipoprotein cholesterol (LDL-C) goals.

Design A cross-sectional study.

Methods In this study, dyslipidaemic and/or CVD patients on lipid lowering therapy for > 4 months were enrolled. Volunteers had their demographic data and previous medical history documented. Fasting lipid and blood glucose levels were measured in all subjects.

Results In total 1201 patients (age 58 ± 11.4 yrs) were recruited by physicians and general practitioners. Under the new guidelines, 41% of patients are defined as Low Risk (LR) and 59% of patients are High Risk (HR) for CVD. LDL-C target goals were not achieved in 63% of LR patients and 77% of HR patients (71% overall). LR and HR patients, who were not at their LDL-C goal, were on average 19% (0.7 mmol/L) and 31% (1.1 mmol/L) above their LDL-C target levels respectively.

Conclusions These results, in light of the new guidelines, suggest that a considerable percentage of patients will fall into the category of “not at goal” LDL-C. The adoption of the new guidelines will necessitate enhanced disease management to reduce the extent of hypercholesterolaemia and risk for CVD.

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List of Abbreviations and Acronyms

4S	– Scandinavian Simvastatin Survival Study
A to Z	– Aggrastat-to-Zocor Trial
ACE	– Angiotensin Converting Enzyme
ACS	– Acute Coronary Syndromes
AFCAPS/TexCAPS	– Air Force/Texas Coronary Atherosclerosis Prevention Study
AHA/NHLBI	– American Heart Association/National Heart, Lung, and Blood Institute
Apo	– Apolipoprotein
ARB	– Angiotensin Receptor Blocker
ASCOT-LLA	– Anglo-Scandinavian Cardiac Outcomes Trial—Lipid Lowering Arm
ASTEROID	– A Study to Evaluate the Effect of Rosuvastatin on Intravascular Ultrasound-Derived Coronary Atheroma Burden
BARC	– Bio Analytical Research Corporation
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
CM	– Cholesterol Monitor
CRF	– Case Report Form
CRP	– C-Reactive Protein
CVD	– Cardiovascular Disease
DBP	– Diastolic Blood Pressure
DETECT	– Diabetes Cardiovascular Risk-Evaluation: Targets and Essential Data for Commitment of Treatment
EUROASPIRE	– Survey of cardiovascular risk factors across Europe

ESC	– European Society of Cardiology
FBG	– Fasting Blood Glucose
FH	– Familial Hypercholesterolaemia
GOAL	– Global Opinion and Awareness of ChoLesterol
grp	– group
Hb_{A1c}	– Glycated Haemoglobin
HDL-C	– High Density Lipoprotein Cholesterol
HMG CoA	– HydroxyMethyl Glutaryl Coenzyme A
HPS	– Heart Protection Study
HR	– High Risk
HRT	– Hormone Replacement Therapy
IDEAL	– Incremental Decrease in End Points Through Aggressive Lipid Lowering study
IDL	– Intermediate Density Lipoprotein
INTERHEART	– Survey of cardiovascular risk factors across the world
L-CAT	– Lecithin Cholesterol Acyltransferase
L-TAP	– Lipid Treatment Assessment Project
LDL-C	– Low Density Lipoprotein Cholesterol
LIPID	– Long-Term Intervention with Pravastatin in Ischaemic Disease Study
LLDT	– Lipid Lowering Drug Therapy
LR	– Low Risk
mg/d	– milligram per day
MI	– Myocardial Infarction
MS	– Metabolic Syndrome
MSD	– Merck, Sharpe and Dohme
NAG	– Not At Goal
NCEP ATP	– National Cholesterol Education Program Adult Treatment Panel

NEPTUNE	– National Cholesterol Education Program (NCEP) Evaluation Project Utilising Novel E-Technology
OLYMPIC	– The contrOL of dYslipideMia in outPatlent clinics in GreeCe
PAI-1	– Plasminogen Activator Inhibitor - 1
PROSPER	– PROspective Study of Pravastatin in the Elderly at Risk
PROVE IT-TIMI 22	– Pravastatin or Atorvastatin Evaluation and Infection Therapy– Thrombolysis In Myocardial Infarction 22 Investigators
pt	– point
PVD	– Peripheral Venous Disease
REACT	– Reassessing European Attitudes about Cardiovascular Treatment
REVERSAL	– Reversal of Atherosclerosis with Aggressive Lipid Lowering
SA	– South Africa
SA-NAG	– South African Not At Goal Study
SANAS	– South African National Accreditation System
SBP	– Systolic Blood Pressure
SCORE	– Systematic Coronary Risk Evaluation
TC	– Total Cholesterol
TNT	– Treat to New Targets
tot	– total
UK	– United Kingdom
ULN	– Upper Level of Normal
USA	– United States of America
VLDL	– Very Low Density Lipoprotein
WOSCOPS	– West Of Scotland Coronary Prevention Study
yrs	– years

1. LITERATURE REVIEW

Cardiovascular diseases (CVD) are among the leading cause of morbidity and mortality throughout the world, affecting both developed and developing countries. In the next 15 years, it is expected that CVD will be the leading cause of death globally (Hansson, 2005). Atherosclerosis is the primary cause of most CVD. Coronary Heart Disease (CHD) (which results in myocardial infarction) and stroke are the result of atherosclerosis, and are the most prevalent of the CVD that result in death or disability. It is estimated that, annually, 20 million people survive heart attacks and strokes, with a further 12 million dying from these conditions (Puska, Mendis & Porter, 2003). In South Africa, it was estimated that in the year 2000, 17% of all deaths were due to CVD (Bradshaw, 2005).

CHD primarily affects South Africans of European descent and South Asian descent (people who originate from India, Sri Lanka, Bangladesh, Nepal, and Pakistan) (Yusuf, Reddy, Ôunpuu, et al., 2001). South Asians who reside in South Africa (SA), the United Kingdom (UK), Canada, Singapore and North America experience an estimated 1.5 to 4.0 fold higher rates of CVD than Asian Indians (Enas, Yusuf & Mehta, 1992). In SA, Indian populations have the highest rates of both CVD and diabetes (Bradshaw, Schneider, Norman, et al., 2006). The CHD rates among Black South Africans are comparatively lower than the other races, but the CVD that is present in this population is commonly manifested as stroke (Amira, Ntyintyane, Wilkinson, et al., 2006). The Coloured population ("a group of mixed race ancestry descending from the first South African nations, the Khoi and San people, as well as

European, African and Malaysian people”) in different regions of SA have comparable CVD rates to each of the other South African ethnic groups (Bradshaw, 2005; Steyn, Silwa, Hawken, et al., 2005). Available estimates on the rates of ischaemic heart disease and stroke in SA are shown in Table 1.1.

Table 1.1. Mortality rates per 100 000 population for ischaemic heart disease and stroke in South Africa, by population group and sex, 2000 (World Standard Population)

Race Group	Ischaemic Heart Disease		Stroke	
	MALE	FEMALE	MALE	FEMALE
African	85	66	145	160
White	323	187	72	84
Coloured	203	169	143	156
Indian	497	346	136	121
South Africa	169	102	125	124

(Source: Norman, Bradshaw, Schneider, et al., 2006)

It is possible to reduce more than half of the deaths or disability caused by CVD by simple, cost-effective national efforts and by individual actions to reduce the major disease risk factors such as high Blood Pressure (BP), high cholesterol, obesity and smoking (Kruger, Venter & Vorster, 2002). Atherosclerosis is a disease of modifiable risk factors and can be prevented and possibly reversed with optimal treatment (Nissen, Tuzcu, Schoenhagen, et al., 2004). Common “classical risk factors” include age, abnormal lipid levels, smoking, hypertension, diabetes, abdominal obesity, psychosocial factors, consumption of fruits, vegetables, and alcohol, and lack of regular physical activity (Yusuf, Hawken, Ôunpuu, et al., 2004). Among the most dominant of these risk factors is abnormal lipid levels, specifically Low-Density Lipoprotein Cholesterol (LDL-C), which plays an undisputed determinative role in the pathogenesis of atherosclerosis (Safeer & Ugalat, 2002). Interventions that target

dyslipidaemia therefore form the basis for strategies aimed at prevention and management of the disease.

Many guidelines have been released worldwide to govern the clinical assessment and management of dyslipidaemia by doctors and other medical professionals. Guidelines may differ from country to country, but all recognise LDL-C levels as the main target of intervention for CHD, stroke and related conditions. The assessment of a patient's global risk is another common feature of all guidelines. Optimally designed guidelines outline the best clinical strategies modeled on the most reliable evidenced-based medicine available at the time of publication (Ballantyne, Arroll & Sheperd, 2005).

South African medical professionals used (during the publication of this report: 2005-2007) a set of guidelines that were last updated in February 2000 (South African Medical Association and Lipid and Atherosclerosis Society of Southern Africa Working group, 2000). Since then, many major clinical end-point trials have been completed with major implications and information that was not previously available. European and American guidelines were subsequently published and updated based on the findings of these studies. Major evidence from the cholesterol-lowering trials has shown benefit for both patients with established CVD and at-risk patients without CVD, in reducing mortality from myocardial infarction and stroke (Raal, Schamroth, Klug, et al., 2004). Furthermore, the category for patients at highest risk has been broadened to include a new designation of patients processing the "CHD risk equivalent", defined as other clinical forms of atherosclerotic disease (peripheral

arterial disease, abdominal aortic aneurysm, and symptomatic carotid artery disease) diabetes, or multiple risk factors that confer a 10-year > 20% risk for CHD (National Cholesterol Education Program Adult Treatment Panel III guidelines [NCEP ATP III], 2001). Other important updates to guidelines are reduced LDL-C target levels in higher risk patients, and the acknowledgement of the metabolic syndrome as an even more threatening clustering of CVD risk factors (Raal et al., 2004).

The need for an update to the South African guidelines was of paramount importance so as to reduce the burden of CVD in SA (Raal et al., 2004). The South African Guidelines have recently been updated (June 2006), and the South African Scientific community has adopted the 2003 European guidelines in CVD prevention in clinical practice (Raal, Marais & Schamroth, 2006).

1.1. The South African guidelines: adoption of the European guidelines (European Society of Cardiology [ESC]) on cardiovascular disease prevention in clinical practice – Guide to lipid management.

The objective of the European guidelines is to advise caregivers on the best management options available to prevent the incidence of fatal or debilitating CVD events (De Backer, Ambrosioni, Borch-Johnson, et al., 2003). As a result of the numerous intervention trials, utilising several forms of therapy, which have been shown to prevent not only CHD but peripheral arterial disease and ischaemic stroke,

the current guidelines are aimed at prevention of all forms of CVD, not only Coronary Artery Disease (CAD).

The European guidelines are fittingly designed to target the modifiable risk factors associated with CVD. The guidelines support dyslipidaemia as a primary target of intervention. The focused management of this risk factor is fundamental to preventative strategies aimed at reducing CVD.

To estimate the risk of developing a fatal coronary event, the European guidelines utilise the Systematic Coronary Risk Evaluation (SCORE) multi-factorial risk model and charts, which were developed from data derived from European populations. The South African societies responsible for the update to guidelines, advise a deviation from the use of the SCORE model for risk assessment, as the data it is derived from is not applicable to the South African population, and rather recommend the use of the Framingham Risk model for risk assessment.

a) Plasma lipids and goals (acceptable guideline risk factor levels) (Table 1.2)

Patients are to be categorised according to the guidelines into either the (1.) High Risk (HR) or (2.) Low Risk (LR) categories:

1. High Risk patients – as stated below, are those with severe genetic lipid disorders or patients with a 10-year risk of developing a CVD event of $\geq 20\%$ (or if extrapolated to age 60 $\geq 20\%$).

2. Low Risk or asymptomatic patients – patients with no prior CVD history. Therapeutic decisions depend largely on the assessment of the 10-year risk for developing CVD.

Table 1.2. Guideline cholesterol goals for treatment [SA (ESC) guidelines 2006]

Risk Category	Goal of treatment	
	TC	LDL-C
Low Risk	< 5.0 mmol/L	< 3.0 mmol/L
High Risk	< 4.5 mmol/L	< 2.5 mmol/L

TC, total cholesterol; LDL-C, Low-density-lipoprotein-cholesterol.

High risk patients are specifically defined in the *adopted ESC guidelines* as:

1. Patients with established CHD, peripheral artery disease and cerebrovascular atherosclerotic disease.
2. Asymptomatic individuals who are at HR of developing atherosclerotic cardiovascular diseases because of:
 - a) multiple risk factors resulting in a 10 year risk of $\geq 20\%$ now (or if extrapolated to age 60) for developing a CVD event (*Framingham Risk Model adopted for SA guidelines*).
 - b) markedly raised levels of single risk factors: Total Cholesterol (TC) ≥ 8 mmol/l (320 mg/dL), LDL-C ≥ 6 mmol/l (240 mg/dL), and/or blood pressure $\geq 180/110$ mmHg.
 - c) diabetes type II and diabetes type I with microalbuminuria.
3. Close relatives of:

a) patients with early onset atherosclerotic CVD.

b) asymptomatic individuals at particularly higher risk.

4. Other individuals encountered in routine clinical practice.

For asymptomatic patients, with high multifactorial risk, with TC levels \approx 5mmol/L and LDL-C levels \approx 3 mmol/L, the guidelines advise that patients reduce their TC and LDL-C levels to $<$ 4.5 mmol/L and $<$ 2.5 mmol/L, respectively, with moderate doses of lipid-lowering drugs. These patients seem to reap additional benefit from the further lowering of goals. The guidelines do not declare the use of high dose statin therapy in patients with higher untreated lipid levels, but new evidence from trials published after the release of the European guidelines (2003), support even lower goals of therapy and high dose statin therapy (De Backer et al., 2003; Cannon, Braunwald, McCabe, et al., 2004; LaRosa, Grundy, Waters, et al., 2005; Nissen, Nicholls, Sipahi, et al., 2006).

b) Framingham risk assessment – Justification and validity

The application of risk scoring in the guidelines applies only to patients without established CHD, as the risk profiles of such individuals has great variation. Scoring allows a doctor to determine three things; (1) Classify the level of risk for that individual, (2) determine the intervention/s necessary to reduce that persons risk if they are sufficiently being threatened by CHD, and (3) motivation for patients to start and adhere to risk reduction therapies (Grundy, Pasternak, Greenland, et al., 1999).

The Framingham study is based in the town of Framingham, United States of America (USA). It was the first study of its kind to record cardiovascular risk factors in a population over an extensive period of more than 50 years with a sample size of more than 10 000 males and females (Wilson, D'Agostino, Levy, et al., 1998). These features of the study combined with validated clinical morbidity end-points, a detailed survey of standardised risk factor measurements and frequent re-examinations lead to the Framingham heart study becoming the most internationally recognised research in cardiovascular risk prediction (Hense, Schulte, Löwel, et al., 2003).

Using this data multivariate logistic regression equations were calculated to predict risk of a CHD event. Equations for risk prediction are regularly updated, taking into account the most current data collected from the study and the newest evidence from the fields of cardiovascular research. Using these equations, transformed into an easy to use chart a doctor is able to assess the absolute risk of developing a CHD event in patients without diabetes.

CVD is recognised as having a complex etiology and not merely being caused by a single risk factor. A combination of risk factors each with a unique contribution to the disease influences the development of CHD. With this in mind risk scoring is achieved by assigning a weighted score to each of the most influential risk factors for CHD and the summation of these scores for an individual allows for the prediction of the absolute risk of developing a CHD event over a given period of time (i.e. 10 or 20 yrs) (Knuiman & Vu, 1997).

Given that the Framingham sample was predominantly a suburban Caucasian population certain limitations were inevitable when estimating risk cross-culturally (Hense et al., 2003; Gordon & Kannel, 1982). Secular trends in clinical management also cannot be ignored as the population was surveyed in the 12 years between 1968 and 1975 onwards (Hense et al., 2003). Framingham does not consider several other risk factors for which a multitude of research has shown to play a role in the development in CVD. But the new guidelines do take into account some of the newer factors with the addition of diagnosis of the Metabolic syndrome.

Various studies have validated the Framingham risk function for risk prediction. In some countries in Southern Europe, with low CVD rates, the Framingham risk scoring charts demonstrated overestimation of CVD risk (Laurier, Chau, Cazelles, et al., 1994; Thomsen, Mcgee, Davidsen, et al., 2002; Menotti, Puddu & Lanti, 2000). In some populations who are at very high risk, for example the South Asian community, the framingham risk tables maybe inappropriate for use as risk in this population has been shown to be almost double that of high risk White communities (Grundy et al., 1999). Based on this evidence the use of risk prediction algorithms in populations outside from which they are derived is a controversial issue (Knuiman et al., 1997)

Risk calculation using scoring sheets is however superior to just merely targeting individual risk factors (Haq, Ramsay, Yeo, et al., 1999). South Africa does require the calibration of risk scoring, a practice that has been shown to be feasible in other populations (Laurier et al., 1994). Prospective research in cardiovascular risk factors in various South African populations is needed to accomplish this. The risk factor

profile, considering the economic and cultural status of South African patients will correct for possible inaccuracies from risk assessment with the current prediction scores. For the time being the reputation of the Framingham study and its impressive attributes provide the most credible avenue for risk stratification for patients without clinically manifest CHD into either the LR or HR categories (Lloyd-Jones, Wilson, Larson, et al., 2004). Also highlighted in the guidelines is that the training and experienced clinical judgement of doctors is the most essential component in exercising risk reduction strategies (Grundy et al., 1999)

c) Familial hypercholesterolaemia

Familial Hypercholesterolaemia (FH) is an autosomal, dominant condition characterised by elevated levels of LDL-C from birth. The excess LDL-C accumulates on the skin, tendons and in atheromas. It is a genetic disease that results from a mutation in the gene that encodes the LDL-receptor that normally removes LDL-C from the plasma. The disease may be expressed in the homozygous or heterozygous forms. In the homozygous form, the disease manifests as severely elevated cholesterol levels of between 17 to 26 mmol/L, while in the heterozygous form, 2-fold elevations of between 9 to 14 mmol/L are common. The prevalence of heterozygous FH is about 1 in 500, while the homozygous form is lower at about 1 in 1000 000, but in certain populations, for example the Afrikaner group in South Africa, the prevalence may be higher. Diagnosis of FH is identified by a demonstration of a decrease in LDL-receptor numbers, proof of mutation within the LDL-receptor gene or presence of clinical signs such as tendon xanthomas, xanthelasmas, autosomal dominant transmission and expression in childhood (Goldstein & Brown, 1989).

Patients with FH do not require risk assessment by virtue of elevated lipid levels and fall into the category of HR patients.

d) High-density lipoprotein cholesterol and triglycerides

Goals for High-Density Lipoprotein Cholesterol (HDL-C) and triglycerides are not specified in the guidelines, but fasting triglyceride levels of < 1.7 mmol/L (150 mg/dL), HDL-C levels of > 1 mmol/L (40 mg/dL) in males and > 1.2 mmol/L (46 mg/dL) in females, are considered optimal. The triglyceride and HDL-C levels should also guide choice of lipid-lowering drug therapy.

Currently, no long-term trial to evaluate outcomes based on rising HDL-C levels are available, but current evidence firmly established it as an independent risk factor for CHD (Sirtori & Fumagalli, 2006). The Effect Of Very High-Intensity Statin Therapy on Regression Of Coronary Atherosclerosis (ASTEROID) trial has further demonstrated substantial increases in HDL-C levels with intensive statin therapy (rosuvastatin), which correlate to a regression of the atherosclerotic plaque (Nissen et al., 2006). Based on the available evidence from clinical research and basic science, many await concrete evidence of CVD risk reduction promised by therapies that substantially increase HDL-C levels.

Triglycerides contribute to the risk of atherosclerotic disease although the relationship between triglycerides and atherosclerosis is not definitive. Large-scale meta-analysis has shown that the risk of CVD increases in patients with elevated triglyceride levels. This relationship is dependent on other risk factors and therefore triglycerides do not

appear to play a causative role in atherosclerosis (De Backer et al., 2003). However triglycerides are strongly related with HDL-C levels and diabetes.

e) *The Metabolic Syndrome*

The controversial Metabolic Syndrome (MS) consists of a combination of risk factors of metabolic origin that are common to both atherosclerotic CVD and diabetes (Grundy, Cleeman, Daniels, et al., 2005). Patients with the MS are thus considered at an elevated risk for both CVD and diabetes. The definition of the syndrome has varied considerably over the period since its identification but, the most commonly recognised risk factors are dyslipidaemia, hyperglycaemia, elevated BP and obesity/overweight. Patients presenting with the syndrome are also often in a prothrombotic and/or proinflammatory state (Grundy et al., 2005). Insulin resistance is also strongly related to the syndrome, as it is associated with the metabolic pathways of carbohydrates and lipids (Dandona, Aljada, Chaudhuri, et al., 2005). Insulin resistance and obesity, specifically upper body obesity (and visceral fat) are common characteristics of the MS. Ethnic and individual characteristics influence the occurrence of the metabolic risk factors present in obese and/or insulin resistant subjects. Insulin resistance influences the development of Type II diabetes through hyperglycaemia. Diabetes is also established as a strong determinant of atherosclerotic CVD. Certain patients experience the syndrome with moderate elevations in abdominal obesity and, of note, are those of South Asian descent, who suffer inherent insulin resistance (Grundy et al., 2005). These ethnic variations have been incorporated into the diagnostic criteria for the MS and are necessary for correct identification of individuals with MS (Alberti, Zimmet & Shaw, 2005).

The dyslipidaemia in the MS is characterised by low HDL-C levels, elevated serum triglyceride levels and apolipoprotein B (ApoB) and increased numbers/concentrations of small LDL particles (Grundy et al., 2005). All of these risk factors increase the risk of diabetes (by 5-fold) and CVD (by 3-fold) (Figure 1.1). Risk factors that have been associated with the syndrome but have not been integrated into the diagnosis criteria include elevated Plasminogen Activator Inhibitor-1 (PAI-1) concentrations and C-Reactive Protein (CRP) concentrations (Dandona et al., 2005). Measurement of these biomarkers may increase the predictive power of the syndrome for both diabetes and atherosclerotic CVD. Currently, there is a need to research the genetics, molecular biology and cellular signaling underlying the pathophysiology of the syndrome (Grundy et al., 2005).

The European guidelines support the identification of patients with MS and its treatment. The new SA guidelines use the newer definition proposed by the American Heart Association/National Heart Lung and Blood Institute (AHA/NHLBI) (2005) scientific statement for the diagnosis and management of the MS (Grundy et al., 2005). Any three of the criteria defined in Table 1.3 constitute diagnosis of the MS under the new South African Guidelines. For the South Africa population, waist circumference cut-offs need to be adjusted, using the specific South Asian cut-off points for Asians and European cut-off points for classifying the Black, Coloured and White populations (Alberti et al., 2005). Lifestyle change is an integral part of management of the MS, particularly efforts aimed at reduction in body weight and increasing physical activity. Reduction of other factors such as elevated BP,

dyslipidaemia and hyperglycaemia, may need additional drug treatment. Recent studies substantiate the reduction of the risk associated with treating patients with the MS with cholesterol-lowering therapies (Deedwania, Barter, Carmena, et al., 2006)

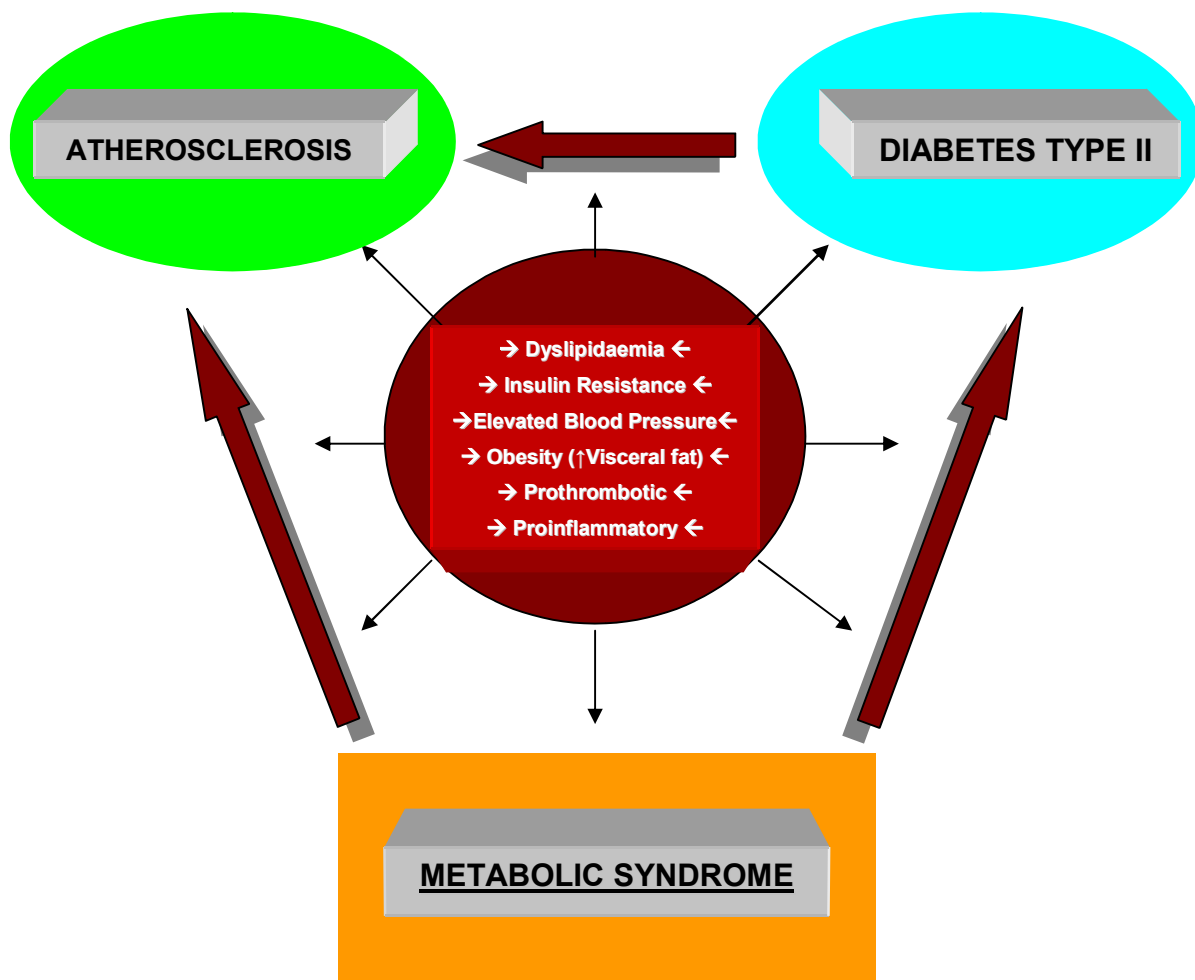


Figure 1.1. Diagrammatic representation of the factors influencing and influenced by the Metabolic Syndrome [arrows on central balloon shape of diagram illustrate that possibly all factors contained in the balloon affect all pathways to the MS, atherosclerosis and diabetes to different extents] (Grundy et al., 2005)

Table 1.3. Criteria for diagnosis of the Metabolic Syndrome

<i>Presence of 3 of the following criteria establish diagnosis for the Metabolic Syndrome</i>	<i>Cut-off values for each of the Metabolic syndrome criteria</i>
<i>Elevated waist circumference</i>	<ul style="list-style-type: none"> ▪ ≥ 94 cm for males and ≥ 80 cm for females – Black, Coloured and White patients ▪ ≥ 90 cm for males and ≥ 80 cm for females – Asian patients
<i>Raised triglycerides</i>	<ul style="list-style-type: none"> ▪ ≥ 1.7 mmol/L (150 mg/dL) ▪ or on triglyceride lowering medication
<i>Low HDL-C</i>	<ul style="list-style-type: none"> ▪ < 1.0 mmol/L (40 mg/dL) in males ▪ < 1.3 mmol/L (50 mg/dL) in females ▪ or on HDL-C raising medication
<i>High blood glucose</i>	<ul style="list-style-type: none"> ▪ ≥ 5.6 mmol/L (100mg/dL) ▪ or on medication for raised blood glucose
<i>High blood pressure</i>	<ul style="list-style-type: none"> ▪ systolic BP ≥ 130 mmHg ▪ or diastolic BP ≥ 85 mmHg ▪ or on anti-hypertensive medication

(Source: Grundy et al., 2005; Alberti et al., 2005) **HDL-C**, high-density lipoprotein cholesterol; **BP**, blood pressure.

1.2. Atherosclerosis: The rationale for LDL-C as the primary target for therapy

The pathogenesis of atherosclerosis is the result of a malfunction in the inflammatory system that regulates repair and defense mechanisms in response to injury (Ross, 1995). The response-to-injury hypothesis is one of the most substantiated theories of the disease based on the experimental evidence and clinical observations. The theory puts forth the proposal that under the influence of the various CVD risk factors, endothelial dysfunction occurs. This dysfunction leads to the inflammatory and fibro-proliferative responses that begin as a protective mechanism. The dysfunction occurs as a result of constant exposure of the endothelium to the risk factors, which results in elevated inflammatory responses leading to damage of the artery (Ross, 1995; 1999).

Atherosclerosis exhibits three defined progressive stages: the fatty streak, the intermediate lesion and the fibrous plaque. The order of disease progression is questionable and is an area of much debate because of the multi-factorial nature of the disease. The latter features of the atherosclerotic lesion cause disruption to the structure of the intima (inner layer of endothelium) (Stary, Chandler, Glagov, et al., 1994). These latter lesions protrude into the lumen of the affected artery, causing disruptions in blood flow to the heart, brain or periphery, and may result in an ischaemic episode that could possibly be fatal or debilitating (Ross, 1995).

a) *The fatty streak*

The fatty streak is thought to be the earliest type of lesion. The accumulation of atherogenic plasma-derived lipoproteins within the intima of the artery is a fundamental event in the initiation of lesions. This first stage of the disease is characterised by the accumulation of lipid-filled monocyte-derived-macrophages and T-lymphocytes at specific sites in the endothelium of the arteries (Ross, 1995). These foam cells fill multiple layers of the intima of the artery (Ross, 1995). The fatty streak is characterised by a yellow colour, as a result of the foam cells.

b) *The intermediate lesion*

Continued accumulation of foam cells is accompanied by migration of smooth muscle cells into the intima, and the formation of a connective tissue matrix consisting of collagen fibrils, elastic fibers and proteoglycans to form the intermediate lesion (Ross, 1995). The intermediate lesion is also characterised by extracellular pools of lipid droplets and particles on the smooth muscle cells of the intima.

c) *The fibrous plaque*

This advanced lesion comes about as a result of the prolonged presence of macrophages and T-cells that activate smooth muscle cells and growth of connective tissue that later leads to the formation of the fibrous plaque, which encloses a core region that is composed of foam cells and extracellular lipid droplets (Hansson, 2005). The fibrous plaque consists of fibrous connective tissue made up of smooth muscle cells enclosed in dense layers of connective tissue matrix, consisting of collagen, elastic fibers and other substances (Ross, 1995). At the shoulders of the fibrous

plaque, where atheroma growth occurs, there is a constant accumulation of macrophages, T-cells and mast cells. Instability of the fibrous plaque could result in thrombus formation and disruption of blood flow leading to clinical sequelae (Ross, 1995; 1997).

Atherosclerosis is a result of a number of risk factors (e.g. lipids, blood pressure, diet, exercise etc.) altering the homeostatic response of the artery walls. The disease is highly treatable and can be reversed by alteration of these risk factors. The best treatment strategies to prevent adverse CVD events have been shown through the modification of cholesterol levels and, specifically, reduction of LDL-C levels.

d) Lipids

Cholesterol and lipoproteins are lipids that are essential components of structural and metabolic mechanisms of all animal cells (Roper, 2004). Lipoproteins are synthesised in the liver and intestine (McGarry, 2002). Lipids are transported in the blood in lipoproteins. Lipoproteins are complexes of proteins and lipids that form distinct molecular aggregates (Schultz & Liebmann, 2002). Since cholesterol and triglycerides (triacylglycerols) are not water-soluble, they are incorporated into these hydrophilic macromolecular protein complexes for transportation in the plasma (Roper, 2004). There are 4 major classes of lipoproteins that are present in the human serum. These are the Very-Low-Density Lipoproteins (VLDL), Intermediate-Density Lipoproteins (IDL), LDL and the chylomicrons. The protein constituents of the lipoproteins are the apolipoproteins. Each class of lipoprotein contains either one or a

variety of the various apolipoproteins (Schultz & Liebmann, 2002). Certain cell surface receptors use apolipoproteins as recognition sites for receptor-mediated endocytosis (Schultz & Liebmann, 2002)

VLDL is synthesised in the liver. Fatty acids derived from triacylglycerols contained in VLDL particles are taken up by adipose tissue and other tissue (McGarry, 2002). In this process, IDL is formed. In the plasma, VLDL is broken down into smaller particles by the enzyme lipoprotein lipase, which is located on the vascular endothelium, reducing the proportion of triacylglycerols and therefore the size of the VLDL particle (Kwiterovich, 2000). Thereafter, the smaller VLDL particles take up cholesterol esters from HDL to form IDL. LDL particles are formed when the enzyme hepatic lipase, which is present on the liver plasma membrane, degrades triglycerides present in VLDL and IDL particles (Campbell, Smith & Peters, 2005). The LDL particles contain the highest proportion (60-70%) of total serum cholesterol (as esterified cholesterol) of all the lipoproteins (Campbell et al., 2005).

HDL particles are formed from a precursor-HDL molecule synthesised in the liver. These precursor molecules contain two forms of Apo A (Apo A-I and A-II) and Apo E. These precursor molecules also contain unesterified cholesterol and phosphatidylcholine (lecithin). The enzyme lecithin-cholesterol acyltransferase (L-CAT) transforms the precursor-HDL molecule into HDL (Campbell et al., 2005). The HDL particle serves to collect and excess cholesterol from the periphery to the liver where its will be incorporated into bile as bile salts or cholesterol, to be excreted (Glew, 2002).

LDL transports cholesterol to cells in the periphery. LDL is removed from the plasma by attaching to LDL-receptors on the surface membranes of tissues. This triggers an endocytotic process which internalises the LDL particle, and through a series of processes, cholesterol is released and utilised by the cell (Campbell et al., 2005). To counter this process, one of the functions of HDL is to remove excess cholesterol from the circulation and transport it back to the liver. High-density lipoprotein, in conjunction with LDL, could thus function to regulate cholesterol levels (Campbell et al., 2005).

Sources of cholesterol in the body are from absorption in the intestine from food and synthesis in the liver. Excess cholesterol can only be metabolised by conversion to bile acids (Campbell et al., 2005). Pharmacological and therapeutic strategies to reduce cholesterol are currently targeted at reducing cholesterol synthesis, decreasing absorption in the gut and sequestering bile acids to prevent its reabsorption. Extensive research has identified LDL as the main atherogenic lipoprotein and therefore guidelines uphold interventions that reduce LDL levels (NCEP ATP III guidelines, 2001).

1.3. Clinical trial evidence supporting LDL-C reduction with hydroxymethyl glutaryl coenzyme A (HMG-CoA) reductase inhibitors or statins for the primary and secondary prevention of coronary heart disease

Clinical trials currently form the basis of guideline formulation. The results further shape the ethical implications and considerations that need to be analysed before a trial can be carried out. The randomised, controlled trials influence the progress of drug research and development and various other treatment options (Isaacsohn, Black, Troendle, et al., 2002). Constant revision of guidelines has become periodic as more is learned, with frequent revolutionary results being made available. Over the last 2 decades, there have been many clinical trials published with many important implications for therapy.

The statin drug class is the most thoroughly, scientifically tested drug class available today. These drugs have been tested on diverse populations, with morbidity and mortality outcomes being the primary end-point. These drugs have demonstrated a superior effect in reduction of CVD in these various populations.

a) Secondary prevention trials (Table 1.4.)

Initially, the focus of many of the trials was on prevention of mortality in large populations of patients with established CVD (including sub-groups of patients with diabetes).

The Scandinavian Simvastatin Survival Study (4S) was the first trial to conclusively show a significant reduction in total mortality and, mortality and morbidity from CHD (Pedersen, Kjekshus, Berg, et al., 1994). This trial randomised patients, with what was considered at that time to be elevated cholesterol levels (5.5-8.0 mmol/L), to simvastatin or placebo over 5.4 yrs. Treatment with simvastatin decreased LDL-C levels by an average of 35%. This trial demonstrated a favourable long-term safety profile of administering simvastatin over a prolonged period. Furthermore, the trial also demonstrated benefit for female patients, the elderly (aged > 60 years), and patients with fatal and non-fatal cerebrovascular events. After the publication of the 4S report, the Cholesterol And Recurrent Events (CARE) trial and The Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) studies were also concluded (Sacks, Pfeffer, Moye, et al., 1996; Tonkin, Aylward, Colquhoun, et al., 1998). Both these trials, utilising pravastatin therapy in patients with established CHD, showed reduction in risk for CHD mortality in volunteers with a wide range of initial cholesterol levels (< 6.2 mmol/L in the CARE trial and 4.0 – 7.0 mmol/L in the LIPID trial). The LIPID trial also showed significant reduction in all cause and CVD mortality in its population.

These trials put the benefit of LDL-C lowering beyond doubt. Clinical practice was transformed and the statins emerged as the first-line therapy for the treatment of hypercholesterolaemia.

Table 1.4. Landmark statin outcome secondary prevention trials and trials in the elderly

Study Description	Design	Primary end-pt	Result	Conclusion
<p>4S Pedersen et al., 1994 Study to evaluate the effects of cholesterol-lowering with simvastatin on mortality and morbidity in patients with CHD.</p>	<p>-Simvastatin (titrated to) 10 ,20 or 40mg/d vs. placebo -Randomised, double-blind trial -Patients with CHD -4444 patients (aged 35-70 yrs) -5.4yrs follow-up (median)</p>	<p>-Total mortality</p>	<p>-With simvastatin: (significant) -30% ↓ in risk of the primary end-pt -More patients died in the placebo grp(12%) vs. simvastatin grp(8%) -42% ↓ in risk of coronary death -27% ↓ in risk of any coronary event -37% ↓ in risk of coronary death or non-fatal MI -35% ↓ in risk of all CVD events -simvastatin LDL-C ↓ 35%, triglycerides ↓ 10%, HDL-C ↑ 8%, tot cholesterol ↓ 28% in comparison to placebo</p>	<p>-Lipid-lowering reduces major coronary events in women, and improves survival in the elderly -Secondary prevention patients treated with simvastatin over 5 yrs have significant reductions in total mortality.</p>
<p>LIPID Tonkin et al., 1998 Study to determine the effect of cholesterol-lowering therapy by pravastatin on overall mortality or mortality from CHD alone.</p>	<p>-Pravastatin 40mg/d vs. placebo -Randomised, double-blind trial -Patients with CHD. -9014 patients (aged 31-75 yrs). -6.1 yrs follow-up.</p>	<p>-Fatal MI, sudden death, death in hospital after MI, death due to heart failure or another coronary cause</p>	<p>With pravastatin (significant): -24% ↓ in primary end-pt vs. placebo -LDL-C (median): initially 3.9 mmol/L, decreased by 25% more than the placebo group.</p>	<p>-Lowering cholesterol levels with pravastatin in patients with a broad range of initial cholesterol levels and a history of MI or unstable angina reduces risk of death from CHD. -Pravastatin reduces risk of all major CVD events.</p>
<p>PROSPER Shepherd et al., 2002 Study to establish the safety and efficacy of lipid-lowering in the elderly</p>	<p>-Pravastatin 40mg/d vs placebo -Randomised controlled trial -Primary and secondary prevention patients enrolled -5804 patients (aged 70-82 yrs) -3.2 yrs follow-up (mean)</p>	<p>-Coronary death, non-fatal MI, fatal or non-fatal stroke.</p>	<p>With pravastatin: (significant) -15% ↓ in the primary end-pt -24% ↓ in CHD mortality -LDL-C ↓ 34% vs. the placebo group</p>	<p>-Pravastatin administration to the elderly for a period of 4 yrs reduces the risk of CHD and, therefore, a similar treatment strategy utilised currently in middle-aged individuals are warranted in the elderly.</p>

pt, point; **CHD**, Coronary Heart Disease; **mg/d**, milligram per day; **yrs**, years; **grp**, group; **MI**, Myocardial Infarction; **CVD**, Cardiovascular Disease; **LDL-C**, Low-Density Lipoprotein Cholesterol; **HDL-C**, High-Density Lipoprotein Cholesterol; **tot**, total (For list of acronyms refer to text or Pp xvi).

b) Therapy in the elderly (Table 1.4.)

The effects of LDL-C level reduction on morbidity and mortality in elderly patients had not been adequately tested until the pravastatin in the elderly individuals at risk of vascular disease (PROSPER) trial (Shepherd, Blauw, Murphy, et al., 2002). Most of the larger trials enrolled middle aged populations, generally with an average age of about 60 years old. PROSPER randomised primary and secondary prevention patients in the 70-82 years age group to pravastatin or placebo. Significant reductions in LDL-C levels in the pravastatin group compared to placebo were also observed in this study. The trial showed a reduction in risk of CHD death and Myocardial Infarction (MI). The PROSPER trial however showed a concerning result in that the risk for cancers was 25% higher in the pravastatin group than in the placebo group. To put the finding into perspective, the authors undertook a meta-analysis of previous placebo-controlled studies with pravastatin lasting more than three years. In this meta-analysis, there was no overall increased risk of cancers. This result indicated that pravastatin should be used with caution in the elderly as this was the largest trial done in this age group, the results of which should be more closely evaluated.

The 4S trial also showed improvement in survival in patients aged > 60 years old (Pedersen et al., 1994). The Heart Protection Study (HPS) was another trial that enrolled a large proportion of elderly patients > 60 years of age, with no increase in side effects noted for the elderly patients enrolled. The conclusion of the PROSPER study taken with those from the 4S and HPS trials indicate that statin therapy could

be extended to older patients to reduce the risk of adverse coronary events (Pedersen et al., 1994; Shepherd et al., 2002; Collins, Armitage, Parish et al., 2002).

c) Primary prevention trials (Table 1.5.)

After exhibiting significant reductions in outcomes in the CHD populations, the research evolved to assess benefits of reducing cardiovascular outcomes in patients without established CHD but at risk for the disease. Again the results were statistically significant in the reduction of morbidity and mortality outcomes.

The West of Scotland Coronary Prevention Study (WOSCOPS) randomised male patients without a history of myocardial infarction to pravastatin or placebo over an average of 4.9 years, and there was a significant reduction in death from MI and cardiovascular events (Shepherd, Cobbe, Ford, et al., 1995). The Primary Prevention of Acute Coronary Events with Lovastatin in Men and Women with Average Cholesterol Levels (AFCAPS/TexCAPS) trial enrolled patients without a prior history of CHD (Downs, Clearfield, Weis, et al., 1998). This trial showed a reduction in the first coronary event in both males and females in patients with average TC and LDL-C levels. The Anglo-Scandinavian Cardiac Outcomes Trial – Lipid Lowering Arm (ASCOT-LLA) assessed the primary prevention of CHD in patients with hypertension and without dyslipidaemia, randomising a sub-group of patients treated with an anti-hypertensive agent to atorvastatin or placebo (Sever, Dahlof, Poulter, et al., 2003). The results of this trial indicated a significant reduction in fatal and non-fatal MI, coronary events, stroke and revascularisations. The ASCOT-LLA study was terminated prematurely as the effect of statin therapy was apparent early on. The trial

provided conclusive evidence of the benefits of treating patients at moderate risk with statin therapy (Sever et al., 2003).

Lowering of LDL-C levels was associated with a significant reduction in end-points for all of these primary prevention trials. These trials demonstrate that primary prevention of CHD with statins is beneficial in patients with a variety of cholesterol and risk factor levels. All of these trials exhibited a favourable safety profile for statins compared to placebo treatment. These trials also substantiate the assessment of global risk supported by guidelines to govern treatment options in patients both with and without established CHD or CVD.

Table 1.5. Landmark outcome primary prevention statin trials

Study Description	Design	Primary end -pt	Result	Conclusion
<p>WOSCOPS Shepherd et al., 1995 Investigation into the influence of pravastatin on plasma lipids and clinical events in patients with moderate hypercholesterolaemia and no prior MI.</p>	<p>-Pravastatin 40mg/d vs. placebo -Randomised, double blind trial -6595 male patients (aged 45-64 yrs). -5 yrs follow-up</p>	<p>-The occurrence of non-fatal MI or death from CHD as a first event</p>	<p>With Pravastatin: (significant) -31% ↓ in the primary end-pt -28% ↓ in CHD mortality -32% ↓ in CVD mortality -22% ↓ in all cause mortality -Patients taking pravastatin had 26% lower cholesterol levels than the placebo group.</p>	<p>-In middle-aged patients with hypercholesterolaemia and no history of MI, pravastatin compared to placebo reduces the risk of fatal and non-fatal coronary events, and death from cardiovascular causes.</p>
<p>AFCAPS/TexCAPS Downs et al., 1998 Study of lipid-lowering in primary prevention patients with average cholesterol levels, to evaluate the incidence of first coronary event.</p>	<p>-Lovastatin 20-40mg/d vs. placebo -Randomised, double-blind trial -Primary prevention patients without clinically evident atherosclerotic CVD -6605 patients (aged 45-73 yrs). -5.2 yrs follow-up.</p>	<p>-First acute major coronary events (sudden cardiac death, fatal and non-fatal MI, and unstable angina)</p>	<p>With lovastatin: (significant) -37% ↓ in risk of the primary end-pt -40% ↓ in risk of fatal or non-fatal MI -32% ↓ in risk of unstable angina -33% ↓ in risk need for revascularisations -25% ↓ in risk both total cardiovascular and total coronary events -LDL-C ↓25%</p>	<p>-Relatively low risk primary prevention patients with average cholesterol levels obtain significant reductions in risk with lovastatin treatment.</p>
<p>ASCOTT-LLA Sever et al., 2003 Study into the effect of cholesterol-lowering in the primary prevention of coronary heart disease in hypertensives that are not deemed dyslipidaemic.</p>	<p>-Atorvastatin 10mg/d vs. placebo. -Primary prevention patients with hypertension and 3 other risk factors -Randomised, open-label trial -19342 patients (aged 40-79 yrs). -3.2 yrs (median) follow-up -Randomised to one of two anti-hypertensive regimens. -10305 patients was randomly assigned additional atorvastatin or placebo.</p>	<p>-Non-fatal MI and fatal CHD</p>	<p>With atorvastatin (significant) -36% ↓ in the primary end-pt -Fatal vs non-fatal stroke, total CVD events, and total coronary events were significantly reduced while taking atorvastatin vs placebo. -Atorvastatin ↓ tot cholesterol and LDL-C vs placebo. -LDL-C (mean): ↓ 3.4 mmol/L to 2.28 mmol/L in the atorvastatin grp.</p>	<p>-Atorvastatin treatment substantially reduces major cardiovascular events in hypertensive patients who are at moderate risk and are not conventionally deemed dyslipidaemic.</p>

For list of abbreviations and acronyms refer to Table 1.4., text or Pp xvi.

d) Diabetic sub-groups (Table 1.6.)

CVD is the leading cause of mortality among patients with diabetes type II (Farnier and Picard, 2001). People with diabetes are up to 4 times as likely to have CVD as compared to non-diabetic patients (Kannel and McGee, 1979; Lee, Cheung, Cape, et al., 2000). Diabetics without established CVD have a similar risk as non-diabetics with CVD (Haffner, Lehto, Rönnemaa, et al., 1998).

There is an association between Glycated Haemoglobin (Hb_{A1c}) and severity of a possible MI. Those diabetic patients who suffer fatal MI have a higher Hb_{A1c} than those patients with non-fatal MI (Stevens, Coleman, Adler, et al., 2004). Risk for MI also rises with elevated Hb_{A1c} . All of these factors have led to diabetes being recognised as a CVD risk equivalent. Management of diabetes has been revolutionised because of this, and the increasing use of cardio-protective agents has become a feature of management (Collins, Armitage, Parish, et al., 2003; Colhoun, Betteridge, Durrington, et al., 2004). Diabetes is particularly prevalent in patients of South Asian descent who seem to have a genetic predisposition to insulin resistance (Mather & Keen, 1985; McKeigue, Miller, & Marmot, 1989; Swerdlow, Laing, Dos Santos Silva, et al., 2004)

The benefit of lowering cholesterol levels with statin therapy in patients with diabetes has been confirmed by the analysis of three large scale trials, namely CARE (Goldberg, Margot, Sacks, et al., 1998), the HPS (Collins et al., 2002) and the Collaborative Atorvastatin Diabetes Study (CARDS) (Colhoun et al., 2004).

The CARE trial had a large cohort of diabetic patients that allowed for the assessment of lipid-lowering treatment in patients with CHD and diabetes with average cholesterol levels. In this trial statin treatment significantly reduced the incidence of coronary events in people with established CHD, diabetes and average cholesterol levels.

The HPS trial enrolled primary and secondary prevention patients with a sub-group of diabetic patients (diabetes type I and II). Patients were randomised to simvastatin treatment or placebo. HPS showed significant reductions in coronary events and total vascular events in both primary and secondary prevention diabetic patients. An important finding from the HPS trial was that patients on statin treatment had significant reductions in the rate of first major vascular events regardless of baseline LDL-C levels (either $>$ or $<$ 3.0 mmol/L). In the HPS trial, reduction of LDL-C levels from below 3.0 mmol/L to about 2.0 mmol/L reduced the risk of macrovascular disease by about 25%. HPS also demonstrated that simvastatin 40mg is safe and well tolerated in the diabetic population.

The CARDS trial enrolled primary prevention patients with diabetes type II, with average LDL-C levels. Patients were randomised to atorvastatin or placebo. This trial was also terminated prematurely as the objectives of the study were met while the study was in progress. Significant reductions in the risk for major CVD events, coronary events, revascularisations and stroke were demonstrated in the atorvastatin-treated group.

These three trials provide definitive proof that patients with diabetes gain considerable reductions in risk when on statin treatment. Treatment was shown to be safe and tolerable in the represented populations. These trials support statin therapy in all diabetic patients, in patients with or without CVD, and with a wide range of initial LDL-C levels, below or above 3.0 mmol/L.

In the Cholesterol Treatment Trialists Collaborators meta-analysis of randomised statin trials, a direct relationship between the reduction in LDL-C and 5-year incidence of major coronary events, coronary revascularisation, and stroke has been demonstrated (Baigent, Keech, Kearney, et al., 2005). This further substantiates the linear relationship between LDL-C reduction and risk reduction. The linear relationship between LDL-C and risk reduction is also supported by the intensive statin trials that show larger reductions in vascular disease risk with larger reductions in LDL-C levels (Baigent et al., 2005).

Table 1.6. Landmark outcome primary and secondary prevention statin trials with diabetic sub-groups

Study Description	Design	Primary end -pt	Result	Conclusion
<p>CARE Sacks et al., 1996 Investigation into the effects of lipid-lowering with pravastatin in diabetic patients with CHD and average cholesterol levels.</p>	<p>-Pravastatin 40mg/d vs. placebo -Patients with diabetes and CHD -4159 volunteers (aged 21-75 yrs) -5 yrs follow-up (median) -Diabetic subgroup of 586 patients</p>	<p>-Death from CAD: Fatal MI, either definite or probable; sudden death; death during a coronary intervention; and death from other coronary causes) or (unless during noncardiac surgery) nonfatal MI</p>	<p>With pravastatin: -LDL-C ↓ with pravastatin was similar in diabetic and non-diabetic grps. -Pravastatin ↓ absolute risk by 25% in diabetic grp and 23% in the non-diabetics. -Pravastatin ↓ relative risk of revascularisation procedures by 32%. -LDL-C ↓ 28%, triglycerides ↓ 14%, HDL-C ↑ 5%, tot cholesterol ↓ 20% in comparison to placebo</p>	<p>-Pravastatin reduces the risk of coronary events in diabetics and non-diabetic patients.</p>
<p>HEART PROTECTION Collins et al., 2003 Investigation of the effects on vascular morbidity and mortality with substantial lowering of cholesterol in patients with diabetes.</p>	<p>-Simvastatin 40mg/d vs. placebo -Patients with diabetes and coronary disease, occlusive disease of non-coronary arteries; or treated hypertension were enrolled. -20536 volunteers (aged 40-80yrs). -5 yrs follow-up. -Diabetic subgroup of 5963 patients.</p>	<p>-First major coronary event (non-fatal MI or coronary death) and first major vascular event (major coronary event, stroke or revascularisation)</p>	<p>With simvastatin: -↓ in first major coronary event of 27% among all patients -↓ of about a quarter in the first event rate of major coronary events, strokes and revascularisations among all patients -Among diabetic patients, there was a 20% ↓ in coronary mortality and a 37% ↓ in first non-fatal MI -33% ↓ for first major vascular event in diabetics without occlusive arterial disease or CHD and a 27% ↓ among diabetics with baseline LDL-C < 3.0mmol/L.</p>	<p>-Study provides direct evidence that cholesterol-lowering therapy is beneficial for diabetics with no prior elevated cholesterol or CHD. -Simvastatin reduced rate of major 1st vascular events by 25%. -Statin therapy is recommended for all diabetic patients at sufficiently high risk for major vascular events.</p>
<p>CARDS Colhoun et al., 2004 Investigation into the role of lipid-lowering in the primary prevention of CVD in patients with diabetes type 2.</p>	<p>-Atorvastatin 10mg/d or placebo -Primary prevention patients with diabetes and >1 other risk factor (eg. smoking). -Randomised, double-blind trial -2838 patients (aged 40-75 yrs). -3.9 yrs (median) follow-up</p>	<p>-Time to first occurrence of: acute coronary heart disease events, coronary revascularisation, or stroke.</p>	<p>With atorvastatin: -Reduction in the risk of all end-pts. -37% ↓ in the primary end-pt -LDL-C (mean): ↓ 3.04 mmol/L to 2.11 mmol/L in the atorvastatin grp. -Atorvastatin reduced the death rate by 27%</p>	<p>-Statin treatment (atorvastatin) in Type 2 diabetes patients with at least 1 additional risk factor, significantly reduces the risk of first CVD and stroke events, or adverse events, even in patients without high LDL-C levels.</p>

CAD, Coronary Artery Disease. For list of abbreviations and acronyms refer to Table 1.4., text or Pp xvi.

1.4. Intensive statin therapy: “Is lower better?”

After the initial trials, there were many questions that still needed to be answered. Most pertinent was the question of how to reduce the “residual risk” (remaining risk after risk is reduced by drug or lifestyle therapy) present in the affected populations. Given the benefits of reducing LDL-C levels, one avenue of research strongly supported was to lower cholesterol levels drastically, much lower than was possible with previous therapies. With the newer statins, rosuvastatin and atorvastatin, this was highly possible and subsequently led to intensive statin therapy trials. These trials, for the most part, compared intensive statin regimens (highest dose of most efficacious statins available - atorvastatin 80 mg, simvastatin 80 mg or rosuvastatin 40 mg) to moderate dose regimens (most common doses utilised).

In light of the landmark trials of the 1990’s and the irrefutable evidence of benefit from LDL-C lowering with statin therapy, there has, however, been no threshold LDL-C level established below which no further lowering would confer additional benefits. In light of the fact that a substantial proportion of patients are not achieving their LDL-C goal levels, it is predicted that even more patients will not meet the optional goal level of < 1.8 mmol/L (70 mg/dL), and that other therapeutic options for reducing LDL-C levels will be necessary (Pearson, Laurora, Chu, et al., 2000; Grundy, Cleeman, Merz, et al., 2004 [NCEP ATP III guidelines update]). A strategy to lower LDL-C levels aggressively with higher doses of statins compared to moderate doses (or

usual therapy) was suggested as an option (Schwartz, Olsson, Ezekowitz, et al., 2001; Athyros, Papageorgiou, Mercouris, et al., 2002).

The optimal lipid-lowering strategy and goal level is still controversial. This led to the question of “how low should we go?” in regard to reducing LDL-C. Given the roughly linear relationship established between percentage risk reduction and percentage LDL-C lowering, and the result of additional benefits gained by lowering LDL-C below goal levels in the HPS trial, further research into LDL-C lowering was warranted (Grundy et al., 2004). This led to many trialists embarking on studies to lower LDL-C levels below the current known threshold limits of benefit.

a) Trial evidence (Table 1.7.)

A wealth of trials has, in the last decade, established that a lower LDL-C level is better to reduce the risk of adverse CVD events even further. The consensus that has accrued on known trial evidence and in the intensive statin treatment trials is that reduction below 1.8 mmol/L (70 mg/dL) does confer a significant reduction in risk (Grundy et al., 2004). The NCEP ATP III guidelines update also supports the optional goal of < 1.8 mmol/L (70 mg/dL) in patients at very HR, i.e. patients with (i.) an acute coronary syndrome, (ii.) diabetics with established CAD, and (iii.) established CAD with multiple risk factors (Grundy et al., 2004).

Results from the intensive statin therapy trials demonstrate that high dose statin treatment seems to be more effective than moderate doses in reducing cardiovascular events (Cannon, Steinberg, Murphy, et al., 2006). In all of the

intensive statin therapy trials, the groups using the higher doses of statins achieved mean LDL-C levels well below both NCEP ATP III (2.59 mmol/L) and European guideline goal levels (2.5 mmol/L), with corresponding reductions in risk compared to comparator groups. Two trials, the Early Intensive vs a Delayed Conservative Simvastatin Strategy in Patients with Acute Coronary Syndromes Trial (A-to-Z) and High-dose atorvastatin vs usual-dose simvastatin for secondary prevention after myocardial infarction trial (IDEAL) (De Lemos, Blazing, Wiviott, et al., 2004; Pedersen, Faergeman, Kastelein, et al., 2005), have shown non-significant trends toward benefit in their pre-specified end-points with intensive statin therapy, while another two trials, the Intensive versus moderate lipid lowering with statins after acute coronary syndromes, Pravastatin or Atorvastatin Evaluation and Infection Therapy–Thrombolysis In Myocardial Infarction 22 (PROVE IT-TIMI 22) and Intensive lipid lowering with atorvastatin in patients with stable coronary disease trial (TNT), demonstrated a significant reduction in their primary end-points with intensive statin therapy (Cannon et al., 2004; LaRosa et al., 2005). In a meta-analysis of these four trials of intensive statin therapy, enrolling 27 548 patients with either acute coronary syndromes (PROVE IT TIMI-22 and A-to-Z) or stable coronary disease (TNT and IDEAL), it was found that intensive lipid-lowering therapy provides a significant benefit over standard-dose therapy for preventing predominantly non-fatal cardiovascular events (Cannon et al., 2006). Pooled analysis of these studies revealed that standard doses of statin therapy reduced LDL-C levels by 22% to 2.59 mmol/L (101 mg/dL) versus a 42% reduction by intensive statin therapy to 1.92 mmol/L (75 mg/dL). This is a difference of 25.7% between the two treatment strategies. The pooled analysis

demonstrated an overall significant reduction of coronary death or MI of 16%, in favour of intensive statin therapy.

These large trials have generated a massive amount of valid, quality clinical data. Patients with stable coronary disease and acute coronary syndromes can also benefit substantially from intensive statin therapy. Currently, the most potent statin available for reducing LDL-C levels, rosuvastatin, still awaits concrete long-term outcome trial data, but current evidence from the ASTEROID trial indicate that this statin has a integral part to play in reducing the risk of CVD (Nissen et al., 2006).

Table 1.7. Intensive statin therapy outcome trials.

Trial	Design	Primary end-pt	Result	Conclusion
<p>PROVE-IT TIMI22 Cannon et al., 2004 Study to evaluate intensive statin therapy vs. moderate statin therapy on outcomes in patients with ACS</p>	<p>-Atorvastatin 80mg/d vs. pravastatin 40mg/d. -Hospitalised for ACS within the preceding 10 days. -Double-blind-double-dummy trial -4162 patients (aged >18yrs). -24 months (mean) follow-up.</p>	<p>-Composite of death for any cause, MI, unstable angina requiring hospitalisation, revascularisation and stroke.</p>	<p>-16 % reduction in the hazard ratio in favour of atorvastatin. -LDL-C (median) ↓ to 1.6 mmol/L atorvastatin grp and 2.46mmol/L pravastatin grp.</p>	<p>-ACS patients benefit from early, continued LDL-C lowering with intensive statin therapy vs. standard therapy. -Lowering LDL-C substantially below current target levels provides additional benefit to patients with ACS.</p>
<p>Phase Z of A-to-Z De Lemos et al., 2004 Evaluation of benefit of early intensive statin strategy vs. a delayed conservative approach in ACS patients</p>	<p>-Simvastatin 40mg/d [month1] followed by simvastatin 80mg/d vs. placebo [month4] followed by simvastatin 20mg/d. -Patients with ACS enrolled within five days of symptom onset. -Randomised, double-blind trial -4497 patients (aged >70 yrs). -721 days (median) follow-up.</p>	<p>-CVD death, non-fatal MI, readmission for ACS and stroke.</p>	<p>-Risk reduction of 11% in the primary end-pt in favour of the early intensive statin treated grp. LDL-C (median): early intensive - simvastatin 40 month 1 = 1.76mmol/L simvastatin 80 month 8 = 1.63 mmol/L vs. late conservative placebo month 1 = 3.16 mmol/L simvastatin 20 month 8 = 1.99mmol.L.</p>	<p>-Did not reach pre-specified end-pt. -Early initiation of an aggressive simvastatin regimen resulted in a favourable trend towards ↓ in major vascular events.</p>
<p>TNT LaRosa et al., 2005 Study to evaluate if lowering LDL-C to <1.8 mmol/L with intensive statin therapy is associated with better outcomes than moderate therapy to LDL-C <2.6 mmol/L</p>	<p>-80mg/d vs. 10 mg/d atorvastatin. -Patients with established CHD -Randomised, double-blind trial -10 001 patients (aged 35 -75 yrs). -4.9 yrs (median) follow-up.</p>	<p>-Occurrence of a first major CVD event, defined as death from CHD, non-fatal, non-procedure-related MI, resuscitation after cardiac arrest, or fatal or non-fatal stroke</p>	<p>-22% relative risk reduction in primary end-pt -LDL-C (mean): ↓ to 2.0 mmol/L atorvastatin 80mg grp and 2.6 mmol/L atorvastatin 10mg grp. -No difference between the two treatment groups in overall mortality. -Persistent elevations in liver aminotransferase level- 0.2% in atorvastatin 10 mg/d vs 1.2% in atorvastatin 80 mg/d</p>	<p>-80 mg/d atorvastatin in patients with stable CHD provides significant clinical benefit beyond that afforded by treatment with 10 mg/d atorvastatin.</p>
<p>IDEAL Pedersen et al., 2005 Evaluation of the benefit of highest dose atorvastatin 80mg vs. moderate dose simvastatin 20mg</p>	<p>-Atorvastatin 80mg/d vs. simvastatin 20mg/d. -Patients with established CHD enrolled. -Randomised, double blinded trial -8888 patients (aged <80 yrs). -4.8 yrs (median) follow-up.</p>	<p>-Coronary death, non-fatal MI, cardiac arrest with resuscitation.</p>	<p>-Relative risk reduction of 11% in the primary end-pt in favour of atorvastatin treatment. -LDL-C (mean): ↓ to 2.09 mmol/L in the atorvastatin grp and 2.69 mmol/L in the simvastatin grp.</p>	<p>-Patients with previous MI, intensive LDL-lowering did not result in a significant reduction in the primary end-pt.</p>

ACS, Acute Coronary Syndrome. For list of abbreviations and acronyms refer to Table 1.4., text or Pp xvi.

b) Imaging studies

The intensive statin therapy trials have shown an effect on the progression and regression of atherosclerosis. Strong evidence from the Effect of Intensive Compared With Moderate Lipid-Lowering Therapy on Progression of Coronary Atherosclerosis: trial (REVERSAL) and ASTEROID trials show a halting of atherosclerotic progression and in some cases, regression of the disease (Nissen et al., 2004; Nissen et al., 2006). In the REVERSAL trial, comparing atorvastatin 80 mg/d versus pravastatin 40 mg/d, there was a significantly lower progression rate in the atorvastatin-treated group. The atorvastatin-treated patients achieved a mean LDL-C level of 2.1 mmol/L (79 mg/dL) (48% reduction from baseline) versus the 2.9 mmol/L (110mg/dL) (28% reduction from baseline) achieved in the pravastatin-treated group. Patients on the atorvastatin regimen had a regression in atheroma volume of 0.4% in comparison to a mean progression of 2.7% in the pravastatin-treated patients. The ASTERIOD trial recruited patients with established CHD to receive intensive statin therapy with rosuvastatin 40 mg/d. In the ASTEROID trial, LDL-C levels were reduced from a mean baseline level of 3.4 mmol/L (130 mg/dL) to 1.6 mmol/L (60.8 mg/dL), a mean decrease of 53.2%. HDL-C levels increased from a baseline level of 1.1 mmol/L (43.1 mg/dL) to 1.3 mmol/L (49 mg/dL), a 14.7% increase. The mean change in atheroma volume was -0.98%, indicating regression. What these studies demonstrate is that the coronary atherosclerosis disease process, once considered to be irreversible, can be stopped or possibly reversed with intensive "lipid-modulating strategies" (Nissen et al., 2004).

c) Safety and tolerability of high dose statin therapy

The side effect profile of the statins has been well characterised. The most common side effects of the statins are myopathy, rhabdomyolysis, and elevated liver enzyme levels. Patients in the landmark clinical trials, utilising the standard doses of statins, had favourable adverse event profiles (Baigent et al., 2005). The 4 major intensive statin therapy trials provide ample data to scrutinise with regards to the safety and tolerability of utilising higher doses of statins.

In recent landmark trials of high-dose statin therapy, atorvastatin 80 mg/d (until the release of rosuvastatin) was the most common dose utilised for comparison to either placebo or moderate doses. Other statins used in major trials included simvastatin 80 mg and rosuvastatin 40mg (De Lemos et al., 2004; Nissen et al., 2006). Safety of high-dose atorvastatin in these trials has demonstrated rare cases of serious adverse events and most adverse events being reversible with appropriate dose reductions. In an analysis by Newman, Tsai, Szarek, et al. (2006) comparing trials with atorvastatin 80 mg versus atorvastatin 10 mg or placebo, with a pooled analysis of 49 trials that included 14 236 patients (between 1992 and 2004), the overall adverse event profiles were found to be similar between all three groups (atorvastatin 80 mg, 10 mg and placebo). Gastrointestinal system adverse effects were the most common across the treatment groups. Myalgia and creatine kinase elevations of >10 Upper Level of Normal (ULN) were similar in the atorvastatin groups, with no cases of rhabdomyolysis in this analysis. Furthermore, in the analysis by Newman et al. (2006) there was no direct relation shown between the dose of atorvastatin and of muscle-related adverse events. Another meta-analysis by Hulten, Jackson, Douglas, et al. (2006) of trials comparing intensive statin therapy for patients with acute

coronary syndromes, with analysis of 13 randomised trials and a pooled sample size of 17 963 patients (between 1974 and 2006), showed that high-dose statin therapy exhibited a similar tolerability between control groups and intensive treatment groups. In this analysis, there were only 3 cases (0.02%) of rhabdomyolysis in the 17 963 patients (all in the intensive simvastatin arms of treatment).

Simvastatin at 80 mg may produce more adverse effects. In the A-to-Z trial, a dose of simvastatin 80 mg was utilised in one of the arms of the study and resulted in a higher than normal rate of myopathy (De Lemos et al., 2004). A point of concern from the results of the A-to-Z trial is that the 80 mg/d dose of simvastatin may border on the limits of toxicity (Nissen et al., 2004). Patient differences in drug pharmacokinetics could influence certain patients to be more vulnerable to the side effects of statin therapy (De Lemos et al., 2004; Nissen et al., 2004; Newman et al., 2006). Statins, on the whole, however, have exhibited a remarkable safety profile (Law and Rudnicka, 2006). A recent review too highlighted the safety of statin therapy (Armitage, 2007).

d) Are very low LDL-C levels dangerous?

The aim of high-dose statin therapy is to reduce LDL-C levels below goal to determine the optimum LDL-C level to achieve CVD risk reduction. Does high dose statin therapy and the subsequent lowering of LDL-C lead to an increase in adverse events? A sub-study by Wiviott, Cannon, Morrow, et al. (2005) of the PROVE IT-TIMI 22 trial, the issue of the safety of very low levels of LDL-C was addressed. In this analysis, there was no relationship established between low levels of LDL-C and development of muscle-related and liver-related side effects. At 4 months, those

patients who had LDL-C levels of > 2.59 mmol/L (100 mg/dL) had similar adverse event profiles compared to those who achieved substantially lower LDL-C levels. A relationship between adverse safety events (e.g. myopathy or liver enzyme elevations etc.) and achieved LDL-C levels was not evident from this analysis.

The extremely low cholesterol levels in these trials of between 1.3 - 1.8 mmol/L (50 – 70 mg/dL) do not cause any increase in adverse effects of any type. These levels of LDL-C, in the range of 1.3 –1.9 mmol/L (50 – 75 mg/dL), are seen in certain hunter-gather populations (Pygmy, San, Inuit and Hazda) around the world (O’Keefe, Cordain, Harris, et al., 2004). In these populations, those individuals who still follow their indigenous lifestyles show no evidence of atherosclerosis and thus these levels could be physiologically normal and the levels we currently consider to be normal should possibly require re-evaluation (O’Keefe et al., 2004).

e) Take home points of intensive statin therapy

Benefit from intensive statin therapy is possible, and is a viable therapeutic option for those patients who are at very HR for coronary events and/or have high LDL-C levels.

What we know about intensive statin therapy -

1. More patients attain goal LDL-C levels with high dose therapy.
2. Substantial reductions in risk for CVD events are possible, with intensive statin therapy.
3. Statins even at high doses (e.g. atorvastatin 80 mg or rosuvastatin 40mg) is well tolerated.
4. Very low LDL-C levels do not increase mortality and morbidity rates or increase adverse events.
5. High dose statin therapy reinforces the linear relationship between LDL-C levels and CHD risk.
6. It is possible to reverse the atherosclerosis disease process, and not just halt progression.
7. Patients with the Metabolic Syndrome and patients who are at risk for a stroke derive additional benefits from high-dose statin therapy.
8. Currently, no trial has established an LDL-C level beyond which no further reduction in risk is afforded (Barter and Rye, 2006).

The intensive statin trials indicate a change in lipid management. The dilemma remains in finding the balance between reducing LDL-C levels, cost and reduction of adverse effects in order to maximise benefits from LDL-C lowering.

1.5. Combination therapy

Statin therapy has become integral in lipid management but many patients are still not achieving goal while under statin therapy (Pearson et al., 2000; Ruiz, Ibáñez, Pérez-Jiménez, et al., 2004; Diamantopoulos, Athyros, Yfanti, et al., 2005; Assmann, Benecke, Neiss, et al., 2006; Kristiansson, Björholt, Siewert-Delle, et al., 2007). Certain guidelines support very low LDL-C levels for patients at very HR (Grundy et al., 2004; Williams, Poulter, Brown, et al., 2004). These lower targets will be challenging to achieve with current statin mono-therapies available. If statin treatment is initiated and a patient fails to achieve goal LDL-C levels, subsequent increases or doubling of the statin dose results in only minimal further decreases in LDL-C (approximately 6-8 % LDL-C on each dose doubling) (Jones, Kafonek & Laurora, 1998; Davidson, Palmisano, Wilson, et al., 2003). Even at the highest statin doses, some patients do not achieve goal LDL-C levels (Pearson, Denke, McBride, et al., 2005).

Combination therapy to achieve goal LDL-C levels has emerged as a management alternative. The use of combination therapy allows the dosage of two or more drugs to be reduced while minimising their respective adverse effects, and increasing the desired effect of each drug. The use of combination therapy has already demonstrated promising results in randomised clinical trials (Blankenhorn, Nessim, Johnson, et al., 1987; Brown, Albers, Fisher, et al., 1990; Kane, Malloy, Ports, et al., 1990; Brown, Zhao, Chait, et al., 2001).

a) Ezetimibe

Ezetimibe is a selective cholesterol transport inhibitor that exerts its effects in the intestine by inhibiting absorption of dietary and biliary cholesterol while permitting the absorption of fat-soluble vitamins (Stone, 2002). Ezetimibe as monotherapy causes moderate effects on a patient's lipid profile (Balbisi, 2006). Ezetimibe when used in combination with a statin, causes a dual inhibition of LDL-C synthesis and LDL-C absorption from the gastrointestinal system thus reducing plasma LDL-C levels.

The addition of ezetimibe to ongoing statin therapy, on average, causes a further 25-30% decrease in LDL-C levels. Substantial proportions of patients also achieve their goal LDL-C levels with the combination therapy of ezetimibe and a statin (Ballantyne, Hourii, Notarbartolo, et al., 2003; Ballantyne, Blazing, King, et al., 2004; Pearson et al., 2005; Simons & Symons, 2007; McKenney, Jones, Bays, et al., 2007).

The combination of ezetimibe and a statin have exhibited high safety and favourable adverse effect profiles without any significant drug interactions (Stone, 2002; Ballantyne et al., 2003; Pearson et al., 2005; Mikhailidis, Wierzbicki, Daskalopoulou, et al., 2005; Simons & Symons, 2007; McKenney et al., 2007). Furthermore, the side-effect profile is better compared to other previously used agents in combination with a statin, namely niacin and fibrates (Pearson, Denke, McBride, et al., 2006). Ezetimibe, in combination with all marketed brands of statin, have been tested and shown to be safe and efficacious (Davidson, McGarry, Bettis, et al., 2002; Gagne, Bays, Weiss, et al., 2002; Ballantyne et al., 2003 & 2004). Presently, what is needed is long-term safety and outcome data to establish ezetimibe as an evidence-based therapeutic option and currently trials to establish these are underway (Mikhailidis et al., 2005).

b) Niacin

Niacin is an optional drug that can be used in combination with a statin. The unfavourable adverse effect profile of this class of drugs limits its use. Niacin increases blood sugar and uric acid levels, and can cause abnormal liver function (Stone, 2002). Currently, in the drug delivery pipeline, is a compound that could be used in combination with niacin to reduce its side effects, making it a more tolerable option for lipid management. Niacin provides substantial increases in HDL-C levels when used alone or in combination with a statin. The usage of a statin-niacin combination could intensify LDL-C lowering to get patients to guideline goal levels, while increasing HDL-C levels, which could contribute to reducing the residual risk of CHD.

c) Fibrates

Fibrates used in combination with statins is more widely utilised for the reduction of LDL-C levels. Fibrates were commonly administered to patients with elevated triglyceride and/or decreased HDL-C levels (Balbisi, 2006). Again, the use of this combination results in myositis and rhabdomyolysis in susceptible patients. The fibrates complement the LDL-C lowering effects of the statins. The fibrates also produce substantially greater reductions in triglyceride levels. This combination has important implications for patients with complex dyslipidaemias (Corsini, Bellosta & Davidson, 2005).

1.6. Difficulty in achieving guideline recommended goals

Currently there seems to be a worldwide phenomenon of patients not achieving guideline-specified treatment targets (Erhardt, 2005).

a) Gap between guidelines and clinical practice

a.i) Lipid Treatment Assessment Project (L-TAP)

The multi-center L-TAP study investigated the extent to which LDL-C goals were being reached according to the NCEP ATP II treatment guidelines in the USA (Pearson et al., 2000). The study enrolled 4888 volunteers to receive lipid-lowering therapy, of which 4137 (85%) volunteers received drug therapy, while 751 (15%) volunteers received non-drug therapy. Only 68% of LR patients (n=1143, <2 risk factors, no CHD), 37% of HR patients (n=2285, > 2 risk factors, no CHD), and 18% of patients with CHD (n=1460) receiving lipid-lowering therapy achieved NCEP ATP II specified LDL-C target levels (Pearson et al., 2000). Overall, 38% of patients achieved goal LDL-C. Drug therapy was more successful in the treatment of patients and achieving goal levels in all risk groups when compared to non-drug treatment. From the available data, it is apparent that a significant gap exists between NCEP guidelines and clinical practice (Pearson et al., 2000). It is evident from this study that the enforcement of the guidelines needs to be monitored closely in order to reach treatment goals.

a.ii) National Cholesterol Education Program Evaluation Project Utilising Novel E-Technology (NEPTUNE II)

In a more recent study conducted in the USA, the NEPTUNE II survey, goal achievement was shown to be superior (under the newer NCEP ATP III guidelines) in

comparison to the L-TAP study, with 67% of patients achieving goal levels (Davidson, Maki, Pearson, et al., 2005). Patients at highest risk for CVD were still the least likely to achieve goal LDL-C levels. Patients taking statin therapy were the most likely to achieve goal LDL-C. A total of 10% of the patients were taking combination therapy. More patients with CHD achieved goal LDL-C goals compared to those with diabetes, CHD risk equivalents, non-CHD clinical atherosclerosis and a 10-year risk of CHD events of >20%. These patients were a new addition to the NCEP ATP III guidelines, and the NEPTUNE II survey showed that there is a significant treatment shortfall in these categories. The increase in treatment success among patients in the NEPTUNE II study compared to other surveys was probably because of the awareness created by prior surveys, and the availability of more efficacious statins and the use of higher doses (Davidson et al., 2005). In recent surveys, it has been shown that there has been a decrease in total cholesterol and LDL-C levels in the USA population, which has also been attributed to the increase in the use of lipid-lowering drugs (Carroll, Lacher, Sorlie, et al., 2005). Although there was an improvement in goal achievement between the two surveys, there is still a gap in guideline implementation that will necessitate improved CVD management.

a.iii) Diabetes Cardiovascular Risk-Evaluation: Targets and Essential Data for Commitment of Treatment (DETECT)

In a larger survey, the DETECT study in Germany, recruited 55 518 unselected consecutive patients, and the point prevalence of treated and untreated dyslipidaemia was assessed (Böhler, Scharnagel, Freisinger, et al., 2007). Of these patients, 6815 patients between the ages of 20-79 years old were additionally analysed by means of an extensive laboratory program focusing on cardiovascular risk assessment for a

period of 12 months. In total, 4086 of the 6815 patients were deemed dyslipidaemic, with only 1170 (27%) of these patients receiving lipid-lowering medication. Only 41% of patients receiving lipid-lowering drugs and 11% of patients treated without lipid-lowering drugs achieved NCEP specified LDL-C goal levels. In this study, those patients at lowest risk were the most likely to achieve goal (13.2 %), while those at moderate to HR were less likely to achieve goal (8.6 and 11.7%, respectively).

This study further showed that 45.6% of the patients enrolled were not diagnosed by their doctor as being dyslipidaemic according NCEP ATP III guidelines. Twenty one percent of patients were diagnosed as dyslipidaemic, but did not receive lipid-lowering medication, while 13.2% of patients were recognised and treated for dyslipidaemia but did not achieve their guideline-recommended goals. As expected, the most commonly used lipid-lowering medication was the statins. Combination therapy for lipid-lowering was infrequently used, with 6.5% and 0.5% of patients taking combinations of 2 or 3 drugs, respectively. Key findings of this study were that (a) diagnosis of dyslipidaemia is low, with only 50% of patients with dyslipidaemia being diagnosed and (b) treatment and goal achievement rates were low. These results show both an under-recognition and an under-treatment of patients with dyslipidaemia (Böhler et al., 2007). There is thus a need for improved treatment and diagnosis of dyslipidaemia among patients at risk for CVD (Böhler et al., 2007).

Current statistics show that many dyslipidaemic patients are not even diagnosed with dyslipidaemia. Of those patients that are diagnosed, only a few receive treatment for this condition (Ford, Mokdad, Giles, et al., 2003; Böhler et al., 2007). There are numerous surveys showing that LDL-C goals are not being met in clinical practice (in

addition to those discussed above) (Ruiz et al., 2004; Diamantopoulos et al., 2005; Assmann et al., 2006; Kristiansson et al., 2007) (Table 1.8). As a result many patients are suffering preventable morbidity and premature mortality because of this treatment deficit (Erhardt, Pearson, Bruckert, et al., 2004).

Table 1.8. Surveys of population cholesterol levels

<i>Clinical Trial</i>	<i>Inclusion criteria</i>	<i>Guidelines</i>	<i>Results</i>
<p>- Wood, De Backer, Graham, et al., 1997 (EUROASPIRE I) - 4863 medical records reviewed</p> <p>- 9 European countries: Czech Republic, Finland, France, Germany, Hungary, Italy, The Netherlands, Slovenia, Spain</p>	<p>- Consecutive patients were identified retrospectively with CHD - Data collection was based on a review of medical records at least 6 months after hospital admission</p>	<p>European 1994</p>	<p>- 44% of patients overall had TC levels of ≥ 5.5 mmol/L</p> <p>- 13% of patients overall had TC levels of ≥ 6.5 mmol/L</p>
<p>- Steyn, Fourie, & Shepherd, 1998 (Cholesterol Monitor) - 12 842 patients enrolled</p> <p>- Country: South Africa</p>	<p>- Consecutive patients (convenience sample), study to evaluate the frequency of cholesterol testing and level at which there is active therapeutic intervention.</p>	<p>South African Heart foundation Action Limits 1988</p>	<p>- 72% of patients overall had TC levels of ≥ 5.5 mmol/L</p> <p>- 25% of patients overall had TC levels of >6.5 mmol/L - 76% of CHD patients had TC levels of ≥ 5.0 mmol/L</p>
<p>- Pearson et al., 2000 (L-TAP) - 4888 patients enrolled</p> <p>- Country: USA</p>	<p>- Patients being treated with the same dietary therapy and/or LLDT for at least 3 months were eligible for inclusion.</p>	<p>National Cholesterol Education Program (NCEP): Adult Treatment Panel (ATP) II</p>	<p>- 62% of patients overall failed to achieve LDL-C treatment goal</p> <p>- 32% low-risk, - 63% high-risk, and - 82% of CHD patients failed to achieve goal</p>
<p>- De Backer, Ambrosio, Amouyel, et al., 2001. (EUROASPIRE II) - 8181 medical records reviewed</p> <p>- 15 European countries: Belgium, Czech Republic, Finland, France, Germany, Greece, Hungary, Ireland, Italy, the Netherlands, Poland, Slovenia, Sweden, Spain and the UK</p>	<p>- As EUROASPIRE I above</p>	<p>European 1998</p>	<p>- 58% of patients overall had TC levels of ≥ 5 mmol/L</p> <p>- 50% of patients on LLDT had TC levels of ≥ 5 mmol/L</p>
<p>- Davidson et al., 2005 (NEPTUNEII) - 4885 patients enrolled</p> <p>- Country: USA</p>	<p>- As L-TAP above.</p>	<p>NCEP: ATP III</p>	<p>- 33% of patients overall did not achieved LDL-C treatment goal</p> <p>- 11% with 0 or 1 risk factor, - 24% with >2 risk factors or CHD and - 43%, with CHD risk equivalents did not achieve goal</p>
<p>- Diamantopoulos et al., 2005 (OLYMPIC) - 2211 patients enrolled</p> <p>- Country: Greece</p>	<p>- Patients with dyslipidaemia who had been receiving hypolipidaemic diet and/or LLDT for at least 3 months were included. Patients were followed up for another 3-month period.</p>	<p>NCEP: ATP III</p>	<p>- 74% of patients overall and 70% of those receiving LLDT did not achieve LDL-C treatment goal</p> <p>- low risk 33%, - medium risk 71%, and - high risk 80% did not achieve treatment goal</p>
<p>- Böhler et al., 2007 (DETECT) - 7519 (of 55 518) patients chosen for extensive, standardised laboratory program</p> <p>- Country: Germany</p>	<p>- Unselected consecutive patients</p>	<p>NCEP: ATP III</p>	<p>- 89% of all dyslipidaemic patients and 59% of the patients on LLDT did not achieve their LDL-C treatment goal</p>
<p>- Kristiansson et al., 2007 - 683 patients enrolled</p> <p>- Country: Sweden</p>	<p>- Eligible study participants recruited were consecutive patients on statin treatment for more than 6 weeks</p>	<p>Swedish (Similar to European 1998)</p>	<p>- 40% of patients overall did not achieve treatment goal</p>

CHD, Coronary Heart Disease; TC, Total Cholesterol; LLDT, Lipid-Lowering Drug Therapy.

b) Reasons for the shortfall of guideline implementation

Implementation of guidelines can be categorised into 3 primary levels of organisation: system or governmental, doctor or caregiver, and patient level. Deficits at each of these levels could lead to the inefficient implementation of guidelines.

b.i) Governmental level

A poor government health strategy to aid prevention of CVD and implementation of guidelines is a major reason cited for the treatment gap (Graham, Stewart & Hertog, 2006). The formulation and publication of guidelines are not adequate to drive clinical practice (De Backer et al., 2001). The first step to guideline implementation, after formulation, is education. Once both doctor and patient are aware of the burden of CVD and the benefits of following guidelines, the treatment gap will surely decrease.

In every country it should be imperative that guidelines are regularly available and publicised frequently in the scientific community and that goals and benefits should be translated into a form that is easily understood by the general population. Regular workshops and updates are also important to drive implementation of the guidelines. These messages should be motivating and attention-grabbing enough to provoke action (Erhardt et al., 2004).

b.ii) Doctor level

At the doctor level, many may believe they are knowledgeable about the details of guidelines, but in reality, very few know the exact recommendations (Erhardt et al., 2004). It has also been shown that the majority of doctors do not titrate doses of lipid-lowering drugs and fewer still utilise combination therapies to get patients to the guideline-recommended cholesterol goals (Wood et al., 1997; De Backer et al.,

2001). Doctors may not change to more efficacious drugs when the present drugs are not achieving goal (Banegas, Vegazo, Serrano, et al., 2006). Another area of concern is that many doctors do not use risk charts to assess a patient's risk for CHD, thereby underestimating many asymptomatic patients' susceptibility for CHD events, and consequently under-treating these patients (Hobbs & Erhardt, 2002; Graham et al., 2006).

There may also be too many guidelines available with many not being appropriate to the setting of the doctors, and therefore none may be used. Many doctors are exposed to multiple guidelines over the period of their training and some may not have the motivation to change to newer guidelines. In some countries, there is no requirement for continued medical education. This further reduces the need to adhere to the most current guidelines available (Erhardt et al., 2004). Clinical inertia ("failure to act even though the problem is recognised") may also lead to doctors not treating dyslipidaemia effectively (Banegas et al., 2006). Some doctors site the complexity of guidelines as another explanation for low adherence (Erhardt et al., 2004; Graham et al., 2006). Cost issues and time constraints are also major factors influencing the doctors' ability to adhere to guidelines (Graham et al., 2006). Another possible reason for the treatment gap is that doctors often overestimate the general awareness patients have of the risk factors and goals of treatment for CVD (Erhardt, 2005).

In a survey measuring patient awareness of CVD, the Global Opinion and Awareness of ChoLesterol (GOAL) study, a substantial proportion of patients (> 40%) were not aware of the prevalence of CHD and/or the link between cholesterol and CHD, while

in the Reassessing European Attitudes about Cardiovascular Treatment (REACT) survey, doctors estimated that 92% of patients knew of the cholesterol-CHD link (Erhardt, 2005). Doctors may also overestimate their own treatment success in achieving recommendations for their patients (Hobbs & Erhardt, 2002; Banegas et al., 2006). In another study of guideline adherence in female patients, it was shown that very few doctors actually had a system in place to follow patient's adherence to prescription regimens (26% of primary care doctors, 11% of obstetricians/gynaecologists and 28% of cardiologists had a practical system) (Mosca, Linfante, Benjamin, et al., 2005). Only a few caregivers had a means to measure the rate of patients who successfully implemented the advice given or complied with drug therapy. This implies that many doctors do not have an objective means of measuring whether their patients are adherent or not. This could be a problem in assessing if a patient requires additional management (in regard to compliance issues).

b.iii) Patient level

The barriers that prevent patients from realising the benefits of guideline recommendations are just as numerous and complex as those hindering doctors. As soon as a patient is identified as being at increased risk for CVD, he or she needs to be informed of the threat to their well-being, and the need for therapy as it has been demonstrated that patients' awareness to the risk factors of CVD is low (Erhardt, 2005). In the REACT study, it was shown that even in patients with established disease, promoting awareness is extremely difficult (Hobbs and Erhardt, 2002). Furthermore, many patients that are dyslipidaemic have not even been identified and others that are aware that they are dyslipidaemic might not be able to acquire

treatment because of limited access to healthcare (Ford et al., 2003; Böhler et al., 2007).

The life-long utilisation of drug therapy is difficult to enforce on a patient, especially an asymptomatic patient who does not believe that they are ill and may not notice any direct benefit from therapy (Erhardt et al., 2004). One of the primary problems is that of patient compliance to lifestyle changes and drug therapy (Erhardt et al., 2004; Graham et al., 2006). Other patients may not find the motivation to change lifestyle behaviours because they are so set in their own way of life. It might be extremely difficult for certain patients to change because of cultural, psychological and economic factors (Erhardt et al., 2004). Costs of treatment are another barrier to effective implementation of guidelines.

Any chronic disease management requires intimate knowledge of disease history or epidemiology. In South Africa we are at an advantage in that being a developing nation, we can learn from the developed countries (who have previously experienced high CVD rates) the best-proven strategies to minimise the impact that CVD has on the country. Worldwide, many clinical trials and epidemiological studies have been completed that provide a wealth of information to efficiently manage CVD.

In South Africa, population statistics for CVD are sparse, and often only reflect estimations based on supporting data. Not much is known of the extent to which guidelines are followed and LDL-C target levels are achieved in clinical practice. From current information, it is apparent that even in developed countries where CVD is the primary cause of morbidity and mortality, and in settings where more resources

are available for disease management than in SA, a significant disparity exists between guideline recommendations and clinical practice (Pearson et al., 2000). An evaluation of current utilisation of guidelines and the extent to which patients are achieving LDL-C goals on current lipid-lowering therapy, is necessary to reduce the disease burden in South Africa.

1.7. Study objectives

In order to evaluate the gap between guidelines and clinical practice, the objectives of this research were to:

- Determine the percentage of patients with established CVD and/or hyperlipidaemia on lipid-lowering therapy who are not at target LDL-C goal.
- Determine the percentage reduction in LDL-C levels required to achieve goal in patients not meeting guideline-recommended target levels.
- Evaluation of secondary CVD risk factors.

2. METHODS AND MATERIALS

2.1. Study design

The South African-Not At Goal (SA-NAG) survey was a cross-sectional, multi-centre study. This study was designed by both the sponsors of the study (Merck, Sharpe and Dohme [MSD] and Schering Plough), the Pharmacy and Pharmacology Department, and the Department of Medicine, University of the Witwatersrand (refer to the acknowledgements section for further information). This study design was based on the Lipid Treatment Assessment Project survey conducted in the USA (Pearson et al., 2000). The L-TAP study was chosen as it is an internationally recognised survey of lipid guidelines and satisfied the objectives of the current research. Certain deviations were made from the L-TAP survey for feasibility of the research in South Africa and to possibly improve the quality of the data obtained (discussed below and in the limitations section).

A sample size of 1400 patients was calculated according to the prevalence of achieving goal in the L-TAP study. Assuming the prevalence's of reaching target LDL-C levels in the L-TAP project, samples of 323 low risk patients, 359 high risk patients and 227 CHD patients were required to estimate to an accuracy of 5% the expected prevalences for attaining target LDL-C of 68%, 37% and 18%. However, in L-TAP the three patient groups were not evenly distributed (23.4% ; 46.7% ; 29.9%) and to simplify sampling a random sample of 1400 patients, were enrolled for the study to ensure the required sample sizes were met or exceeded (i.e. 327 ; 654 ; 419). The high risk and CHD samples are considerably bigger but have the added

advantage of a diabetic sub-group analysis in the expected 238 diabetics (21% of high risk and 24% of CHD patients were expected to be diabetic).

The survey was carried out at general practices in the private sector across South Africa. Patients between the ages of 18 to 85 years old and satisfying the inclusion and exclusion criteria were recruited into the study. The study was designed as a single visit of the participant to their investigator. At this visit, a sample of blood was drawn and sent to the laboratory for the determination of fasting lipid and blood glucose levels. The results from this visit formed the basis of the intended research. Patient demographic data and the patient's past medical history were analysed in conjunction with study data to develop relevant conclusions about goal achievement.

2.2. Ethics and protocol approval

The study protocol, patient information sheet (Appendix A) and patient consent form (Appendix B) were submitted to the Human Research Ethics Committee, and the Postgraduate Committee of the University of the Witwatersrand. Approval for the study was obtained from both regulatory committees (Protocol approval, Appendix C; Ethics approval, Appendix D).

The patient information sheets and consent forms were designed using a template extracted from – “Guide to Clinical Trials (Spilker, 1996)”, and adapted for the present study.

a) Confidentiality

Patient confidentiality was maintained by means of code systems that were prearranged between the sponsor, the investigator, and the laboratory. One of the codes (CRF code) was a simple 4-digit number that was printed on the top right-hand corner of a patient's Case Report Form (CRF) (Appendix E). The patients' identity was further masked during laboratory investigations as the laboratory arranged for coded numerical stickers to identify a patient's laboratory results. The investigators were instructed to attach this coded sticker to both the laboratory kits sent to the central laboratory and to each patient's CRF. Data capture of the patients' laboratory results were further masked as a patient's data could only be matched to a specific set of laboratory results by means of this coded, numerical laboratory sticker and the CRF code. The investigator was the only person that could match a code to a specific patient's identity if deemed necessary.

2.3. Investigator recruitment and training

a) Investigator recruitment

In consideration of the large sample size required for the study, investigator recruitment had to be approached in a highly co-ordinated manner. It had to be taken into account that regular blood sampling and couriering to the central laboratory would have to be feasible from all participating sites. It was also necessary for sites to be throughout the country in populations affected by the disease. A group of

established hospitals that are located throughout the country, with multiple doctors per site and a large patient pool, was highly practical in achieving the objectives of feasibility and co-ordination for the study.

The Medicross group of private hospitals, located across South Africa, were approached to participate in this study, as it fitted the criteria for the study. The Medicross group made all their sites aware of the study via their head office and informed sites about the nature and magnitude of the study through a summarised study protocol. The directors of the hospitals that were interested in participating in the study indicated their willingness to participate. Those sites participating (Appendix F) specified how many doctors from their site would be willing to participate and the sample size of 1400 patients were divided between sites accordingly.

During the study, it became apparent that certain sites were not capable of recruiting their allocated number of patients. It therefore became necessary to both reallocate patient numbers to sites that were more successful at patient recruitment, and to recruit more investigators. Sites that completed recruitment of their allocated patient numbers were contacted about recruiting additional patients and those sites in agreement indicated how many more patients they were willing to recruit. During the study, two additional Medicross sites and four private practices (not Medicross affiliated), in areas of high disease prevalence, were recruited into the study. Patients were recruited from both general practitioners and specialist cardiologists.

b) Investigator training

In order to inform investigators of study procedures, they were given appropriate instructions on how to conduct patient recruitment, preparation of blood samples for the laboratory and patient data documentation (summary contained in Table 2.1). The sponsors of the study trained fieldworkers to educate investigators in study procedures. All fieldworkers were sales representatives, medical advisors and clinical researchers employed by the sponsors. The exact qualifications of each of the fieldworkers was not recorded but we assume that the fieldworkers have extensive knowledge of the CVD field as the sponsors market a variety of CVD drugs. The field workers were taught about the various study procedures (i.e. the study protocol, filling out patient CRF and patient informed consent forms, administering patient information sheets and preparation of blood samples). Besides training the investigators, the fieldworkers primarily collected CRF forms and monitored the study. Only patient's who read, understood and signed the informed consent, and met the inclusion criteria (Table 2.2), were allowed to participate in the study. Investigators were remunerated at a standard consultation fee for each patient enrolled into the study. Once suitable patients were enrolled into the study, information about their medical history was documented and relevant laboratory tests were carried out.

Table 2.1. Summary of study procedures to be conducted by investigator

<u>Study protocol</u>
➤ One copy given to each investigator participating in the study.
<u>Case report forms (Appendix E)</u>
➤ Printed on pads of 20, containing three carbonised duplicates of each patient number (one was returned to study sponsor and two were stored on site in patient's file)
<u>Patient informed consent (Appendix B)</u>
➤ Patients were informed about the nature of the study (risks and benefits) and asked to complete the informed consent form with the aid of the investigator. Form was stored in patient's file.
<u>Patient information sheets (Appendix A)</u>
➤ One copy was given to patients to take home, while they were informed about the nature of the study (risks and benefits)
<u>Preparation of blood samples for laboratory procedures</u>
➤ Refer to section on <u>Blood Sampling and Biochemistry</u>

All information was recorded onto the CRF for each patient. Patient CRFs contained demographic information regarding age, gender, race, waist circumference, height and weight. Body Mass Index (BMI) was calculated as: $\text{mass(Kg)}/[\text{height(m)}]^2$. Obesity was defined as a BMI of $\geq 30 \text{ kg/m}^2$, while overweight was defined as a BMI of >25 but $<29 \text{ kg/m}^2$. Other information recorded on the CRF were the patients risk factors: CVD history (defined by clinical diagnosis by investigator of angina, stroke, MI or peripheral vascular disease [PVD]), family history of CVD (FH and/or family history of CAD before 55 years of age in male first-degree relatives, or before 65 years of age in female first-degree relatives), patients BP on the day of the investigation (average of two BP readings) and if patient had a history of hypertension (investigator diagnosed or on an anti-hypertensive medication), smoking, exercise or diet therapies, diabetes (investigator diagnosed or on an anti-diabetic medication), if the patient was female, the result of a urine pregnancy test; and the results of blood

analysis (TC, LDL-C, triglycerides, HDL-C, blood glucose and, Hb_{A1c} percentage if the patient was diabetic). All medications and doses utilised were recorded on the CRF.

2.4. Patient enrolment

This was a convenience sample of patients attending general practitioners and cardiologists. Patients with established CVD and/or hyperlipidaemia on lipid-lowering therapy were enrolled into the study. Patients were given a patient information sheet to read through, and the risks and benefits of the study were discussed with the patients before they signed the informed consent form. The period considered sufficient for total efficacy of the lipid-lowering therapy to be exhibited on lipid levels (with allowance for dose titration) was four months. Patients enrolled in the study would therefore have to have been on the same lipid-lowering therapy for four months or more in order to make valid conclusions about goal attainment and drug therapies. As stated earlier this study was based upon the L-TAP conducted in the USA, and that study used three months as an inclusion criteria for patients to be on lipid lowering therapy. This is the only deviation between the inclusion criteria between L-TAP and this study, as this deviation was thought to be an improvement for the reasons stated above.

Among the exclusion criteria selected for the study were conditions that would likely affect lipid measures (Table 2.2.). Patients who were type I diabetics were excluded from the study, as well as patients with type II diabetes with an Hb_{A1c} of > 10%. Other exclusion criteria used for selecting the patient population were patients who had a change in their diet in the last month before enrolment, pregnant patients or patients who were breast feeding or 6 months or less post-partum, patients with any recent

trauma or surgery that required anesthesia or who had suffered a myocardial infarction within the 3 months prior to study enrolment, or patients who were on antibiotic therapy (Pearson et al., 2000).

Table 2.2. Inclusion and exclusion criteria

<u>INCLUSION CRITERIA</u>
<ul style="list-style-type: none"> ➤ Patient that has been treated with lipid-lowering therapy for at least four months ➤ Patient willing to sign informed consent ➤ Age 18–80 years ➤ If patient has type II diabetes, only patients with Hb_{A1c} < 10% were enrolled
<u>EXCLUSION CRITERIA</u>
<ul style="list-style-type: none"> ➤ Patients with type I diabetes mellitus ➤ Patients who had trauma or recent surgery that required anesthesia within the 12 weeks before enrollment ➤ Patients who had myocardial infarction within the 12 weeks before enrollment ➤ Patients who have an acute infection that requires current antibiotic therapy ➤ Patients who had a change in their diet within the preceding month ➤ Women who were pregnant, breast feeding or 6 months or less post-partum

2.5. Laboratory procedures

All Laboratory determinations were compiled at a central laboratory (Bio Analytical Research Corporation S.A. Pty Ltd [BARC], a division of Lancet Laboratories, Clinical Trials Laboratory, Richmond, Johannesburg). This laboratory is a South African National Accreditation System (SANAS) accredited laboratory and complies with ISO/IEC 17025 interpreted for medical laboratories.

a) Blood sampling and biochemistry

Blood was drawn from patients using the vacuum blood sampling technique. Doctors were provided with laboratory kits containing test tubes, cotton wool, vacutainer needles, webcol swabs and a requisition form. Two laboratory kits were available for diabetic and non-diabetic patients, with the only difference between the two being an extra test tube for Hb_{A1c} measurement for a diabetic patient. Fasting blood samples were taken from volunteers while seated or lying down. Female patients had a urine pregnancy test carried out on site. Patients with triglyceride levels of > 10.34 mmol/L (915 mg/dL) were not included in the statistical analysis because excessive elevations in triglycerides affect Friedewald equation LDL-C measurements.

All lipid (except LDL-C) and blood glucose measurements were carried out using an Abbot Laboratories Aeroset[®] c8000 System. LDL-C was determined indirectly using the Friedewald equation (Friedewald, Levy & Fredrickson, 1972). Haemoglobin A_{1c} measurements were made using a Bio-Rad VARIANT[™] II Hemoglobin testing system. All assays and reagents were standardised according to the manufacture's recommendations.

Doctors were instructed to see patients in the morning so that blood specimens were taken fasting to ensure timely pick-up by the courier. Blood samples were couriered to the central laboratory within 24 hours of collection. Blood biochemistry analysis was available after 24 hours, with the final results available after 48 hours. A hard copy of the results was sent to sites after completion of all tests.

2.6. Data capture, cleaning and query resolution

Once the CRF forms were completed, the field workers would collect these forms continuously and return them to the data capturer to be entered into a database. Once the database was complete, missing fields and fields that were biologically improbable or in conflict with the entry criteria were queried. Queries were resolved at individual sites with data verification forms. If a field was questionable, the data verification form, with the patients' initials, CRF number, the specific description of the query and an area to fill in the correct information regarding the query, was faxed to the respective sites. Those queries that were resolved by the specific site were faxed back to the data capturer for correction or to be filled in. Certain sites did not send through all CRFs and these sites were contacted telephonically and by fax to retrieve all outstanding forms.

Certain laboratory results were inconsistent with the information contained in the CRFs and were queried with the laboratory. Once those queries were resolved, both the SA-NAG database and the laboratory's result database were corrected/updated and checked for consistency.

2.7. Statistical analysis

Patients were classified into two groups based on the new South African lipid guidelines, namely high and low risk, and LDL-C goals were determined according to those defined for each risk category. Patients' 10 year risk estimation for major coronary events was calculated using the Framingham risk scoring system (Appendix G). A patients' risk score extrapolated to age 60 years was done by subtracting the age points for a 60 year old from the age points of a specific individual (aged < 60 years and not in the HR group) and adding that to the total

points score of that individual patient. Patients with established CHD, peripheral artery disease, cerebrovascular atherosclerotic disease, diabetes, patients with markedly raised levels of a single risk factor, or a 10 risk of a CHD event $\geq 20\%$ (or extrapolated to age 60 $\geq 20\%$), were classified as HR. Markedly raised levels of a single risk factor were defined as TC of ≥ 7.5 mmol/L (290 mg/dL), LDL-C of ≥ 6 mmol/L (240 mg/dL) or BP of $\geq 180/110$ mmHg. The LDL-C target level in the HR group was considered to be < 2.5 mmol/L (100 mg/dL) and TC target < 4.5 mmol/L (180 mg/dL). Asymptomatic patients and patients with a 10-year risk of a CHD event of $< 20\%$ were classified as LR. The target levels for the LR patient was a LDL-C of < 3.0 mmol/L (116 mg/dL) and TC of < 5.0 mmol/L (194 mg/dL).

There were 26 patients older than 85 years of age included in analysis. Of these patients, 15 had established CVD and/or diabetes. A risk score was calculated in the remaining 11 patients without established CVD or diabetes by using the highest age category on the Framingham risk charts. The criteria used for diagnosis of the MS were those set forth by the AHA/NHLBI scientific statement published in 2005 (Grundy et al., 2005).

The primary study end-point was rate of failure, which is the percentage of patients who did not achieve SA guideline (ESC) specified LDL-C target levels. Data was analysed using databases, frequency distributions and descriptive statistics between all risk factors and therapies. Statistical analyses were carried out using Graphpad InStat™, V2.05 (ANOVA & T-Tests) and Stata Ver 8.0 (two-sample test of proportion). Data are presented as means (\pm standard deviation) and percentages. The Turkey-Kramer multiple comparisons test was used for comparing differences

between groups and a probability level of < 0.05 was considered significant. The Turkey-Kramer test was utilised because it was the most appropriate for multiple comparisons between paired comparisons, given the sample size, and the data followed a Gaussian distribution. The two sample test of proportion was used to compare differences between the proportions of patients in different groups and again a probability level of < 0.05 was considered significant.

3. RESULTS

The survey was conducted from November 2005 to November 2006. There were 29 sites that recruited patients in the SA-NAG study. In total, 1345 volunteers were screened of which 144 did not meet the inclusion criteria. The most common reason for exclusion was an elevated Hb_{A1c} of > 10%. The data for 1201 evaluable patients (44% female) were statistically analysed in this report. The mean age of patients was 58 (\pm 11.4) years old.

3.1. Patient demographics

Patients were categorised into their risk groups according to the system set forth in the SA (ESC) guidelines. As described, patients without established CVD or diabetes were classified by means of the Framingham risk scoring system. Risk group as well as gender classifications are shown in Table 3.1. In total there were 489 patients classified as LR and 712 patients classified as HR. After grouping the patients it was found that there was a significantly higher proportion of female patients in the LR group while there were more males in the HR group ($p < 0.05$). Data was analysed by separating the patients achieving goal LDL-C from those not at goal levels and it was found that similar proportions of male and female patients in the either the LR and HR groups were not achieving goal levels (no statistically significant differences between males and females not achieving goal LDL-C).

Table 3.1. Proportions of patients by gender and risk group enrolled into study

	Low Risk	High Risk	Total NAG	Total
Female n.	329 (62%)	204 (38%)		533
Male n.	160 (24%)	508 (76%)		668
Female NAG n. (%)	213 (65%)	157 (77%)	370 (70%)	
Male NAG n. (%)	93 (58%)	391 (77%)	484 (73%)	
Total NAG n. (%)			854 (71%)	
TOTAL n.				1201

NAG, Not At Goal

The race demographics of patients enrolled into the survey are shown in Table 3.2. There were 994 (82%) White patients, 126 (10.5%) Indian patients, 73 (6.1%) Coloured patients and 8 (0.7%) Black patients included in the analysis. The most noticeable feature when patients are separated by race and risk group is the proportion of Indian patients that fall into the HR category (109 [86.5%]) compared to the other races (significantly higher proportion of Indian patients in HR group [$p < 0.001$]). There is also a low recruitment of black patients which could reflect the low utilisation of lipid lowering medications as result of the current lower incidence of CHD in this population, as this study enrolled patients who were on lipid lowering therapy for at least 4 months.

Table 3.2. Proportions of patients by race group and risk category

Race	Low Risk	High Risk	Total
	n. (%)	n. (%)	n. (%)
Indian	17 (13.5%)	109 (86.5%)	126 (11%)
Black	3 (37.5%)	5 (62.5%)	8 (0.7%)
Coloured	31 (42.5%)	42 (57.5)	73 (6%)
White	438 (44%)	556 (56%)	994 (82%)
TOTAL	489 (41%)	712 (59%)	1201

In total, 283 (26%) patients had established CVD which automatically classified them as HR patients. The most common form of CVD reported was some type of angina with 149 (12.4%) patients reported, followed by MI with 125 (10.4%) patients reported (Table 3.3). A family history of CHD, of either premature CHD or FH was present in 492 (41%) patients.

Table 3.3. Proportion of patients classified by type of CVD

	n. (%)	Age
Stroke	46 (3.8%)	62.8 (±10.8)
MI	125 (10.4%)	61.4 (±11.2)
PVD	23 (1.9%)	66.7 (±11.7)
Angina	149 (12.4%)	62.4 (±11.0)
Established CVD	283 (23.6%)	62.3 (±11.1)
Family History	492 (41.0%)	--

MI, Myocardial Infarction; PVD, Periferal Vascular Disease; CVD, Cardiovascular Disease.

Seventeen percent of the SA-NAG population were smokers, with 75 (14%) female and 128 (19%) male patients (Table 3.4.). There was a high prevalence of hypertension in the study group, of which 729 (60.7%) patients were diagnosed as being hypertensive (Table 3.4.). Of the patients enrolled, 854 patients (71.2%) were classified as being overweight or obese (Table 3.4.). No formal standardised assessment of diet or exercise was evaluated in this study but investigators did report if patients were adhering to any type of diet or exercise therapy. In total 37.6% (452) of patients indicated they were engaging in exercise therapy (70% [313] not at goal LDL-C) and 55.6% (668) of patients were adhering to some sort of diet therapy (69% [460] not at goal LDL-C) (Table 3.4.).

Table 3.4. CVD risk factors present in SA-NAG population classified by risk group

Risk Factor	Low risk n. (%)	High risk n. (%)	Total n. (%)
Hypertension	247 (50.5%)	482 (67.7%)	729 (60.7%)
Smokers	50 (10.2%)	153 (21.5%)	203 (16.9%)
Exercise therapy	182 (37.2%)	270 (37.9%)	452 (37.6%)
Diet therapy	269 (55.0%)	399 (56.0%)	668 (55.6%)
Obese [BMI ≥30 kg/m²]	150 (30.7%)	302 (42.4%)	451 (37.6%)
Overweight [BMI 26-29 kg/m²]	165 (45%)	201 (55%)	366 (30.5%)
Metabolic Syndrome	180 (36.8%)	460 (64.6%)	640 (53.3%)

BMI, Body Mass Index.

There were significantly more *obese* and *overweight* male patients in the HR category as compared to the LR category ($p < 0.001$). In the female population there were significantly more *obese* patients in the HR group as compared to the LR group ($p < 0.001$).

There were 244 (20.3%) diabetic patients enrolled in the study (Table 3.5), and were also automatically classified as HR patients according to the new lipid guidelines. The most defining feature of the groups when divided by race was that 70% (87 patients) of the Indian patients recruited were diabetics (significantly higher proportion than other comparable races [$p < 0.001$]).

Table 3.5. Diabetic (high risk) patients classified by race

Race	n. (% of race group)
Indian	87 (70%)
Black	4 (50%)
Coloured	24 (32.9%)
White	128 (13%)

3.2. Guideline recommended lipid goals

The 1201 patients included in analysis were categorised into the HR and LR categories of the new SA guidelines, as described earlier. In total, 489 (40.7%) patients were classified as LR and 712 (59.3%) patients were classified as HR.

When the results were analysed 63% of LR patients and 77% of HR patients did not achieve their guideline-specified LDL-C levels (Figure 3.1) (significantly more patients in the HR group were not at goal LDL-C [$p < 0.001$]). Overall, 71% of patients did not achieve LDL-C goal (Figure 3.2).

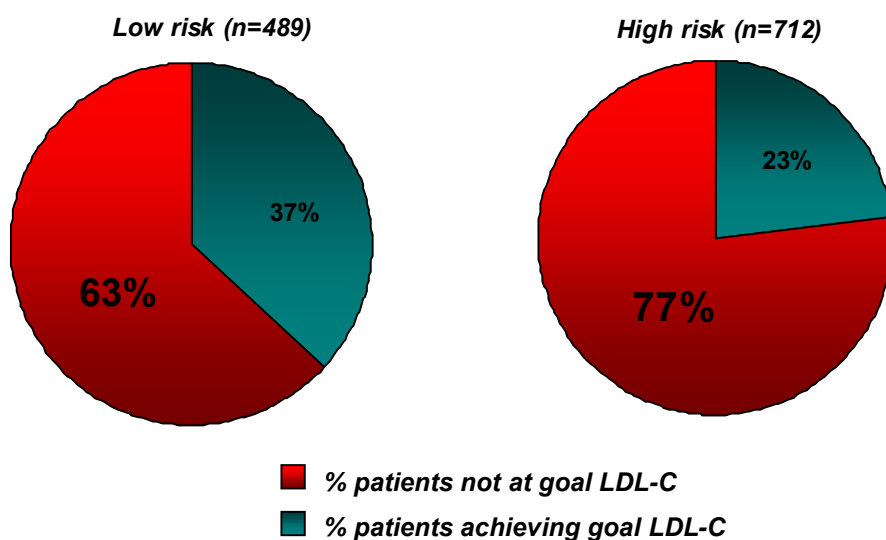


Figure 3.1. Graph representing proportions of patients in the low and high risk categories that are successful or failing to achieve guideline-specified LDL-C goals

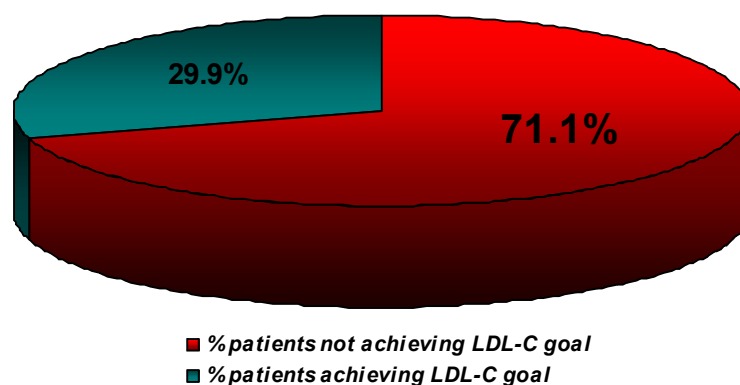


Figure 3.2. Pie-chart representing proportion of total patients achieving and not achieving guideline-specified LDL-C goals [n=1201]

The mean LDL-C levels of those patients who did not achieve LDL-C goal was 3.7 mmol/L and 3.6 mmol/L (143 and 139 mg/dL) in the LR and HR groups, respectively (Table 3.6.). The mean LDL-C levels for those LR and HR patients

achieving target level was 2.5 and 2.1 mmol/L (81 and 100 mg/dL), respectively (Table 3.6.). Thus the LDL-C levels of both groups were similar.

Table 3.6. LDL-C levels for SA-NAG population

	Low risk	High risk
	mean \pm SD (mmol/L) [n (%)]	Mean \pm SD (mmol/L) [n (%)]
<u>LDL-C levels</u>		
LDL-C of patients <u>achieving goal levels</u>	2.5 \pm 0.4 [183 (37%)]	2.1 \pm 0.3 [164 (23%)]
LDL-C of patients <u>not-achieving goal levels</u>	3.7 \pm 0.5 [306 (63%)]	3.6 \pm 1.1 [548 (77%)]

LDL-C, Low-density lipoprotein cholesterol.

The patients not attaining goal were, on average, 0.7 mmol/L (19%) and 1.1 mmol/L (31%) above target level in the LR and HR groups, respectively (Figure 3.3).

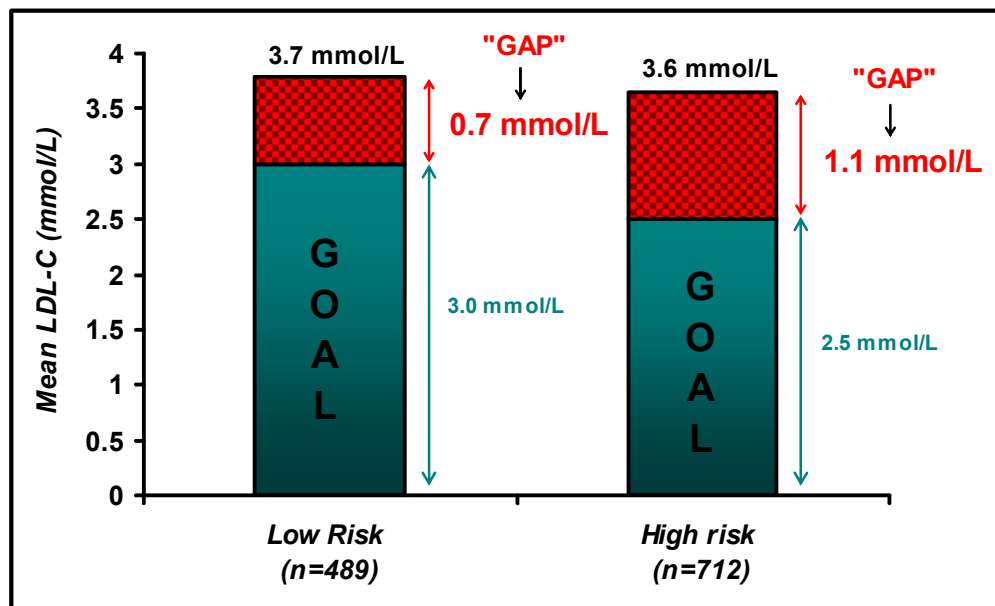


Figure 3.3. Graph representing low risk and high risk patients' mean "gap" away from goal LDL-C levels (numbers in red font are the mean difference between achieved LDL-C and goal levels for patients who did not achieve target LDL-C levels)

In all age groups, mean LDL-C of patients not achieving goal was significantly greater than the guideline specified goal LDL-C levels across the LR and HR categories ($p < 0.05$). In the LR group there were no significant differences established between any

of the groups analysed for the difference between recommended goal and actual attained LDL-C levels (Figure 3.4. & Table 3.7.). High risk female patients in the ≤ 49 year old age group had the largest difference between recommended goal and actual attained LDL-C levels compared to other males and females across all age groups ($p < 0.05$) (Figure 3.5. & Table 3.7.).

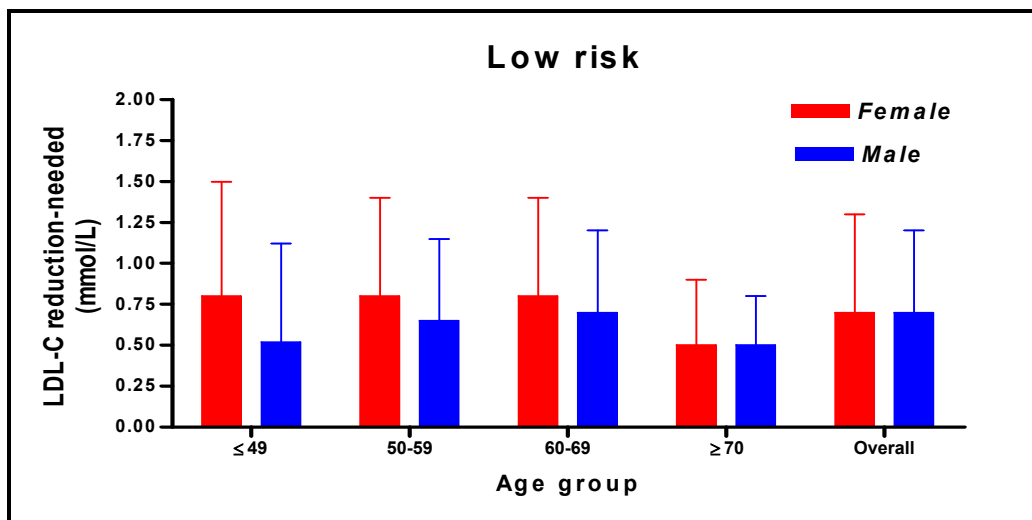


Figure 3.4. Graph of the difference between recommended goal and actual attained LDL-C levels for low risk patients

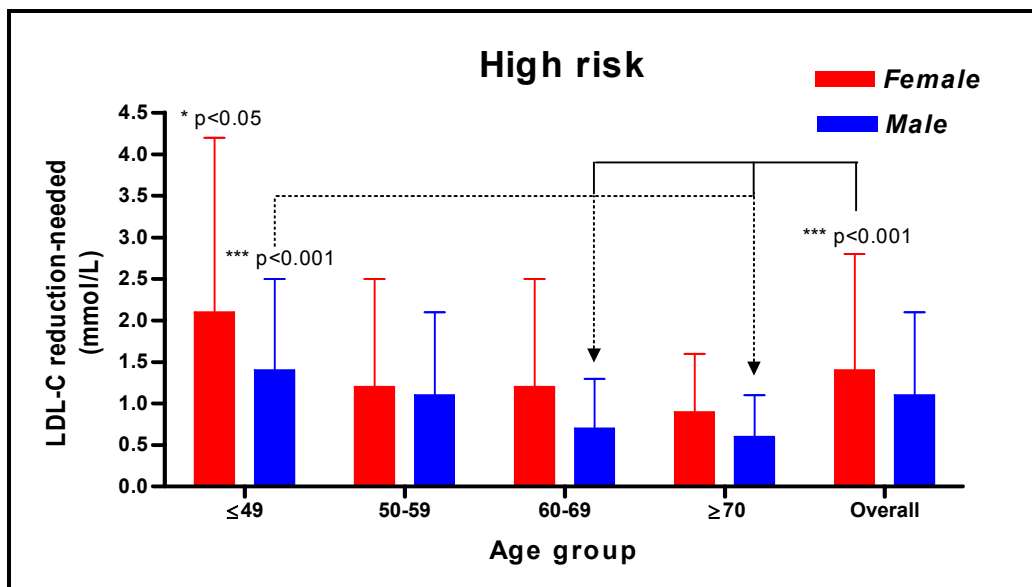


Figure 3.5. Graph of the difference between recommended goal and actual attained LDL-C levels for high risk patients (female patients ≤ 49 years old significantly different from all other categories, male patients ≤ 49 years old significantly different than males in age groups 60-69 and ≥ 70 years old, and female patients overall are significantly different from males in age groups 60-69 and ≥ 70 years old)

Table 3.7. Lipid risk factor mean and frequency table for female and male patients

LDL-C, Low Density Lipoprotein Cholesterol; HDL-C, High Density Lipoprotein Cholesterol; NAG, Not At Goal;

Risk Group	LOW RISK					HIGH RISK				
Age Group	≤ 49	50-59	60-69	≥ 70	overall	≤ 49	50-59	60-69	≥ 70	overall
Gender	Female (n=329)					Female (n=204)				
	n=41	n=115	n=113	n=61	n=329	n=46	n=49	n=63	n=46	n=204
Total Cholesterol, Mean (±SD)	5.7 (0.8)	5.6 (0.9)	5.6 (0.8)	5.4 (0.7)	5.6 (0.8)	6.3 (2.3)	5.6 (1.6)	5.7 (1.3)	5.4 (1.0)	5.7 (1.6)
LDL-C, Mean (±SD)	3.5 (0.9)	3.3 (0.8)	3.4 (0.8)	3.1 (0.6)	3.3 (0.8)	4.1 (2.2)	3.3 (1.3)	3.4 (1.1)	3.1 (0.8)	3.5 (1.5)
HDL-C, Mean (±SD)	1.5 (0.4)	1.6 (0.5)	1.6 (0.3)	1.6 (0.4)	1.6 (0.4)	1.4 (0.4)	1.5 (0.4)	1.5 (0.4)	1.5 (0.4)	1.5 (0.4)
Triglycerides, Mean (±SD)	1.5 (0.8)	1.5 (0.9)	1.6 (0.9)	1.5 (0.7)	1.5 (0.8)	1.7 (1.1)	2.0 (1.3)	1.7 (0.8)	1.7 (1.2)	1.8 (1.1)
LDL-C NAG, no. (%)	32 (78%)	72 (63%)	72 (64%)	37 (61%)	213 (65%)	36 (78%)	37 (76%)	50 (79%)	34 (74%)	157 (77%)
LDL NAG (mmol/L), Mean (±SD)	3.8 (0.7)	3.8 (0.6)	3.8 (0.6)	3.5 (0.4)	3.7 (0.6)	4.6 (2.1)	3.7 (1.3)	3.7 (1)	3.4 (0.7)	3.9 (1.4)
mmol/L away from goal (±SD)	0.8 (0.7)	0.8 (0.6)	0.8 (0.6)	0.5 (0.4)	0.7 (0.6)	2.1 (2.1)	1.2 (1.3)	1.2 (1.0)	0.9 (0.7)	1.4 (1.4)
% away from goal	21%	21%	21%	14%	19%	46%	32%	32%	27%	36%
Gender	Male (n=160)					Male (n=508)				
	n=5*	n=49	n=83	n=23	n=160	n=178	n=134	n=116	n=80	n=508
Total Cholesterol, Mean (±SD)	4.9 (0.5)	5.3 (0.8)	5.3 (0.9)	5.2 (0.6)	5.3 (0.8)	5.9 (1.2)	5.5 (1.2)	4.9 (0.9)	4.6 (0.9)	5.3 (1.2)
LDL-C, Mean (±SD)	2.9 (0.7)	3.1 (0.8)	3.2 (0.8)	3.1 (0.6)	3.2 (0.7)	3.6 (1.2)	3.3 (1.5)	2.9 (0.7)	2.7 (0.7)	3.2 (1.0)
HDL-C, Mean (±SD)	1.1 (0.1)	1.5 (0.3)	1.4 (0.3)	1.5 (0.2)	1.4 (0.3)	1.2 (0.2)	1.2 (0.3)	1.2 (0.3)	1.3 (0.4)	1.2 (0.3)
Triglycerides, Mean (±SD)	1.8 (1.1)	1.64 (1)	1.6 (1.1)	1.3 (0.5)	1.6 (1.0)	2.3 (1.5)	2.2 (1.4)	1.7 (0.9)	1.6 (0.8)	2.0 (1.3)
LDL-C NAG, no. (%)	2 (40%)	28 (57%)	50 (60%)	13 (57%)	93 (58%)	154 (87%)	105 (78%)	85 (73%)	47 (59%)	391 (77%)
LDL NAG (mmol/L), Mean (±SD)	3.5 (0.6)	3.7 (0.5)	3.7 (0.5)	3.5 (0.3)	3.7 (0.5)	3.9 (1.1)	3.6 (0.9)	3.2 (0.6)	3.1 (0.5)	3.6 (0.9)
mmol/L away from goal (±SD)	0.5 (0.6)	0.7 (0.5)	0.7 (0.5)	0.5 (0.3)	0.7 (0.5)	1.4 (1.1)	1.1 (0.9)	0.7 (0.6)	0.6 (0.5)	1.1 (0.9)
% away from goal	14%	19%	19%	14%	19%	36%	31%	22%	19%	31%

There were 667 (78%) patients that were > 10 % away from their respective risk group goal levels. Figure 3.6. represents the proportion of patients in each of the risk groups who did not achieve goal and how far away from goal patients are.

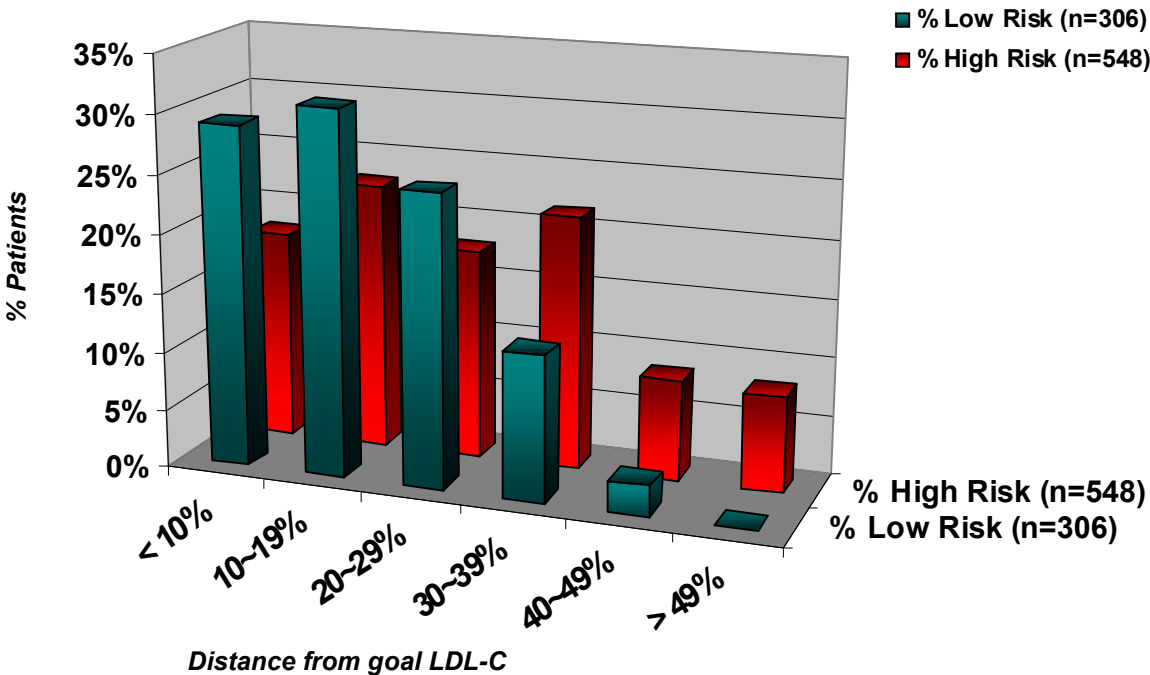


Figure 3.6. Representation of percentage of male and female patients that are not achieving goal LDL-C levels versus %LDL-C reductions required to achieve goal levels

Total cholesterol levels were also elevated in a high proportion of both LR and HR patients. In total, 881 (73%) of both LR and HR patients were not at TC goal levels. The mean TC levels for both the LR and HR patients not-achieving-goal, was 5.9 mmol/L (228 mg/dL) (Table 3.8.).

The optimal levels for triglycerides, namely 1.7 mmol/L, were achieved in only a third of the LR population, and in about half the HR population (Table 3.8.). In contrast the majority of both LR and HR patients attained HDL-C levels that are considered favourable according to SA guidelines (Table 3.8.). In both male and female groups, approximately 80 – 90 % of patients achieved favourable HDL-C levels.

Table 3.8. Lipid levels for SA-NAG population

	Low risk mean \pm SD (mmol/L) [n (%)]	High risk mean \pm SD (mmol/L) [n (%)]
<u>TC levels</u>		
TC of patients <u>achieving</u> goal levels	4.5 \pm 0.4 [152 (31%)]	4.0 \pm 0.4 [168 (24%)]
TC of patients <u>not achieving</u> goal levels	5.9 \pm 0.6 [337 (69%)]	5.9 \pm 1.2 [544 (76%)]
<u>Triglyceride levels</u>		
Triglyceride \geq 1.7mmol/L	2.6 \pm 1.0 [143 (29%)]	2.9 \pm 1.3 [323 (45%)]
Triglyceride < 1.7mmol/L	1.1 \pm 0.3 [346 (71%)]	1.2 \pm 0.3 [389 (55%)]
<u>HDL-C levels</u>		
<u>Men</u>		
HDL-C < 1.0	0.9 \pm 0.1 [9 (6%)]	0.9 \pm 0.1 [93 (18%)]
HDL-C \geq 1.0	1.4 \pm 0.3 [151 (94%)]	1.3 \pm 0.3 [415 (82%)]
<u>Women</u>		
HDL-C < 1.2	1.1 \pm 0.1 [37 (11%)]	1.0 \pm 0.1 [45 (22%)]
HDL-C \geq 1.2	1.7 \pm 0.4 [292 (89%)]	1.6 \pm 0.3 [159 (78%)]

TC, Total Cholesterol; HDL-C, High-Density Lipoprotein Cholesterol.

3.3. Lipid lowering drug therapies

The primary lipid-lowering drug therapies utilised by the patients were the HMG-CoA reductase inhibitors (statins). The other drugs used were the fibrates (1.3% - 16/1201 patients), while one patient used cholestyramine and one other patient used niacin. Predominantly, simvastatin (50.3%) and atorvastatin (41.6%) were the lipid lowering drug therapies of choice (Figures 3.7. & 3.8.). A minority of patients used fluvastatin (4.1%), pravastatin (2.4%) and lovastatin (0.25%). The most common doses of statin used were simvastatin 10, 20 or 40 mg, atorvastatin 10, 20 and 40 mg, and fluvastatin 80 mg. Only 7 patients used atorvastatin 80mg and 9 patients used combination lipid lowering drug therapy of a statin and a fibrate. In general, few patients were prescribed the highest dose of statins available.

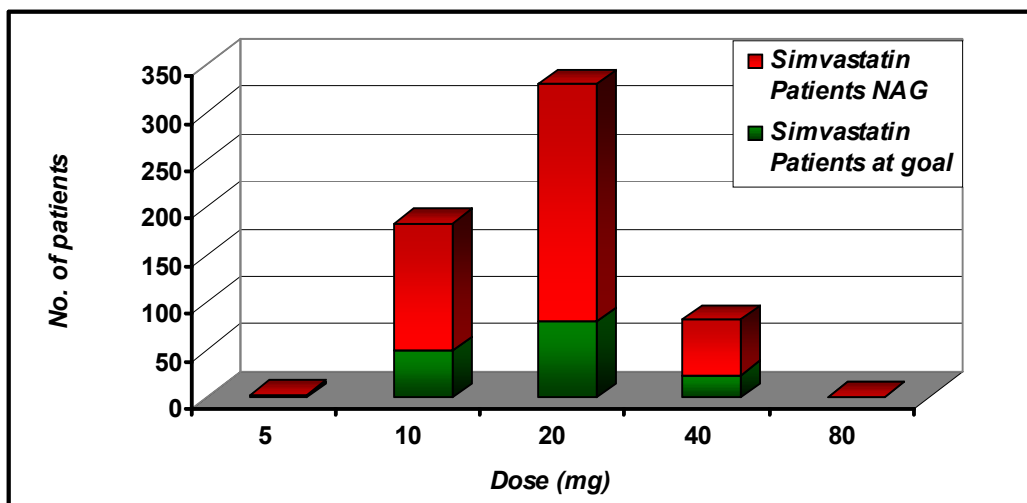


Figure 3.7. Bar-graph of the proportion of patients, classified by dose, achieving goal LDL-C utilising Simvastatin

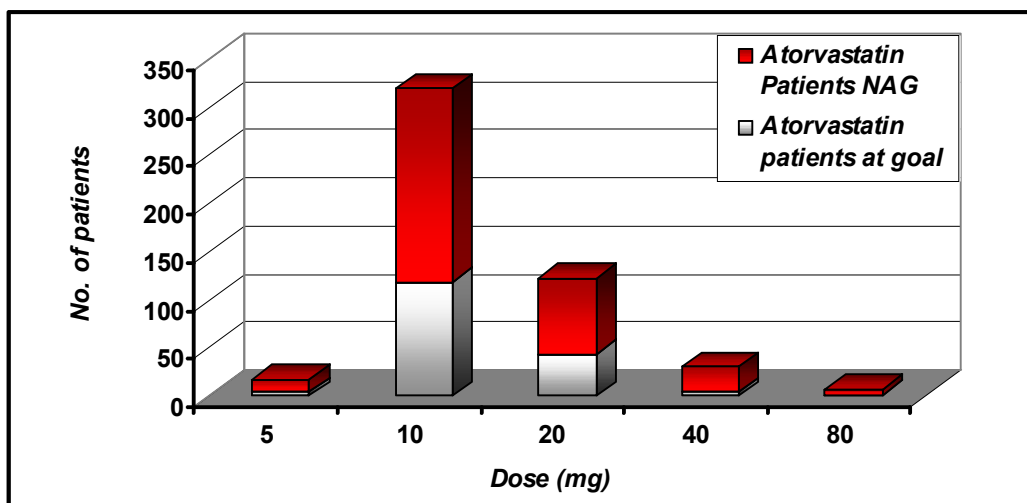


Figure 3.8. Bar-graph of the proportion of patients, classified by dose, achieving goal LDL-C utilising Atorvastatin

3.4. Secondary goals of treatment

A large proportion of the population have the MS, under the AHA/NHLBI (2005) definition (Grundy et al., 2005). In total, 640 (53.3%) patients were diagnosed with MS. The most common combination of risk factors for the MS was the presence of elevated BP, elevated blood glucose levels and an elevated waist circumference. Analysis demonstrated that 42% of MS patients had this combination of risk factors. For the MS patients with any combination of risk factors, 378 (59%) patients had 3 risk factors, 211 (33%) patients had 4 risk factors and 51 (8%) patients had 5 risk factors. There was a significantly higher proportion of HR males or females presenting with the MS than the LR group ($p < 0.001$).

The rates of obese and overweight patients among the study population were 37.6% and 33.6%, respectively. The mean waist circumference of the population was 97.7 (± 14.1) cm (Table 3.9.). The mean waist circumferences of both the male and

female patients are higher than the cut-offs specified for the metabolic syndrome. In the total population 427 (80%) female and 515 (77%) male patients had elevated waist circumference (≥ 80 cm for females, ≥ 94 cm for White, Black and Coloured males and ≥ 90 cm for Asian males). There was significantly higher waist circumferences and BMI's in the HR groups compared to the LR groups for both the male and female patients ($p < 0.001$).

Table 3.9. Risk factors for CVD classified by risk group

	<i>Low Risk</i>	<i>High Risk</i>	<i>Total population,</i>
	<i>Mean (\pmSD)</i>	<i>Mean (\pmSD)</i>	<i>Mean (\pmSD)</i>
Waist (cm)	93.8 (\pm 13.8)	100 (\pm 14.0)	97.7 (\pm 14.1)
Mass (kg)	77.7 (\pm 16.2)	86.5 (\pm 18.7)	82.9 (\pm 18.3)
Height (cm)	166.6 (\pm 11.7)	171.6 (\pm 11.4)	169.6 (\pm 11.8)
BMI (kg/m²)	27.7 (\pm 4.7)	29.1 (\pm 5.2)	28.5 (\pm 5.1)

BMI, Body Mass Index.

There were 60 (6.3%) non-diabetic patients and 124 (50%) diabetic patients who had a fasting blood glucose levels > 6 mmol/l (Table 3.10.). In the non- diabetic group male patients had significantly higher blood glucose levels than female patients ($p < 0.001$). Note that this was a single measurement of fasting blood glucose with no Hb_{A1c} value measured for non-diabetic patients. A substantial number of diabetic and non-diabetic patients were also not at their BP goals of $<130/80$ and $<140/90$ mmHg, respectively. In total 77% (189) of diabetic patients were not achieving goal BP levels and 32% (303) of non-diabetics were not at BP goal (Table 3.10.).

Table 3.10. Table of risk factors for CVD classified by risk group, gender and age group

FBG, Fasting Blood Glucose; BP, Blood Pressure; HbA_{1c}, Glycated Haemoglobin.

Risk Group	LOW RISK					HIGH RISK				
	Age Group	≤ 49	50-59	60-69	≥ 70	overall	≤ 49	50-59	60-69	≥ 70
Gender	Female (n=329)					Female (n=204)				
	n=41	n=115	n=113	n=61	n=329	n=46	n=49	n=63	n=46	n=204
<i>FBG non-diabetics, Mean (±SD)</i>	5.2 (1)	5.3 (1)	5.3 (0.8)	5.4 (1.5)	5.3 (1.1)	7.2 (2.5)	5.4 (0.7)	5.6 (1.7)	5.3 (0.9)	5.4 (1.2)
<i>FBG > 6 mmol/l no. (%) [All patients]</i>	5 (12%)	13 (11%)	14 (12%)	8 (13%)	40 (12%)	17 (37%)	10 (20%)	21 (33%)	13 (28%)	61 (30%)
<i>FBG diabetics, Mean (±SD)</i>	xx	xx	xx	xx	xx	7.0 (2.4)	6.2 (2.0)	6.8 (2.2)	7.1 (2.2)	6.7 (2.1)
<i>HbA_{1c} > 6.1% diabetics, no. (%)</i>	xx	xx	xx	xx	xx	16 (76%)	15 (65%)	19 (83%)	9 (75%)	59 (69%)
<i>BP diabetics ≥130/80 mmHg, no. (%)</i>	xx	xx	xx	xx	xx	16 (76%)	12 (52%)	23 (85%)	12 (92%)	63 (73%)
<i>Hypertensives, no. (%)</i>	12 (29%)	55 (48%)	65 (58%)	38 (62%)	170 (52%)	16 (35%)	36 (74%)	56 (89%)	43 (94%)	151 (74%)
<i>BP non-diabetics ≥ 140/90 mmHg, no. (%)</i>	7 (17%)	29 (25%)	38 (34%)	23 (38%)	97 (30%)	3 (12%)	10 (39%)	21(58%)	22 (71%)	56 (48%)
Gender	Male (n=160)					Male (n=508)				
	n=5*	n=49	n=83	n=23	n=160	n=178	n=134	n=116	n=80	n=508
<i>FBG non-diabetics, Mean (±SD)</i>	xx	5.5 (0.7)	5.7 (1.2)	5.3 (0.5)	5.6 (1.0)	5.6 (1)	5.9 (1.2)	6.0 (1.7)	5.7 (1.5)	5.8 (1.3)
<i>FBG > 6 mmol/L no.% [All patients]</i>	xx	4 (8%)	17 (21%)	2 (9%)	24 (15%)	52 (29%)	65 (49%)	60 (52%)	27 (34%)	204 (40%)
<i>FBG diabetics, Mean (±SD)</i>	xx	xx	xx	xx	xx	7.2 (2.1)	8.1 (2.1)	7.5 (1.8)	7.7 (2.3)	7.6 (2.0)
<i>HbA_{1c} > 6.1% diabetics, no. (%)</i>	xx	xx	xx	xx	xx	30 (71%)	36 (80%)	37 (74%)	13 (65%)	116 (74%)
<i>BP diabetics ≥ 130/80 mmHg, no. (%)</i>	xx	xx	xx	xx	xx	35 (83%)	33 (73%)	39 (78%)	19 (95%)	126 (80%)
<i>Hypertensives, no. (%)</i>	xx	18 (37%)	41 (49%)	17 (74%)	77 (48%)	80 (45%)	93 (69%)	88 (76%)	70 (88%)	331 (65%)
<i>BP non-diabetics ≥ 140/90 mmHg, no. (%)</i>	xx	6 (12%)	30 (36%)	12 (52%)	49 (31%)	41 (30%)	28 (32%)	25 (38%)	27 (45%)	101 (28%)

3.5. Adjunctive therapies

The most common drugs utilised besides lipid lowering drug therapy were blood pressure lowering medications (Appendix H). Aspirin was the most commonly prescribed drug. Angiotensin Converting Enzyme (ACE) inhibitors, Angiotensin Receptor Blockers (ARB), Ca²⁺ channel blockers, beta blockers and diuretics were the foremost prescribed CVS drugs. There were 387 patients utilising combination drug therapy to treat hypertensive conditions (Figure 3.9.). The anti-diabetic drugs were the second most utilised with insulin, metformin and the sulfonylureas being the predominantly prescribed diabetic medications (Appendix I). In total 99 (8%) patients was utilising thyroxine. Of the female patients 126 (24%) patients were utilising Hormone Replacement Therapies (HRT).

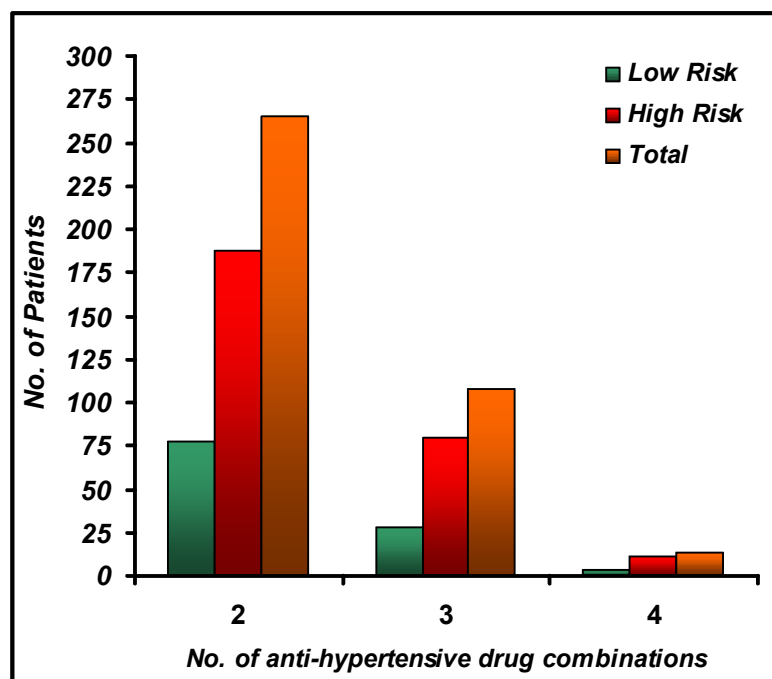


Figure 3.9. Bar-graph of proportion of patients utilising combinations of anti-hypertensive drugs, classified by risk group and no. of medications

3.6 Drug therapy options to get patients to goal LDL-C levels

In light of the evidence that every doubling of the statin dose causes a further 6 % reduction in LDL-C, we can determine theoretically how many patients can achieve goal LDL-C levels in each group. Patients might require their dose to be doubled once, twice or thrice depending on their current statin dosage. The add-on of ezetimibe with a statin has shown further decreases in LDL-C of about 20-25% on average on any dose of a statin, therefore we can also determine how many patients might theoretically require just an add-on of ezetimibe to get to goal. Certain patients will not achieve goal on drug mono- or combination – lipid lowering drug therapy and will be required to find other adjunctive therapies to achieve target LDL-C levels.

Table 3.11. shows the percentage of patients who qualify for change in current therapy to get to goal LDL-C levels. If the statin dosage is doubled once (1X), this would mean that a patient requires $\leq 6\%$ drop in LDL-C levels to achieve target goal, and further doubling the dose would therefore lower LDL-C in multiples of 6. For example if a patient were on atorvastatin 10 mg and required 6% reduction in the LDL-C level to achieve target goal, then doubling that patients atorvastatin dose to 20 mg would theoretically be sufficient. If a patient is on the maximum dose of a statin then he/she will not be able to increase the dose and will therefore have to add-on another drug (combination therapy). Patients with excessive elevations in LDL-C might need both an add-on drug and an increase in statin dose.

Table 3.11. Therapeutic drug options to get patients to goal LDL-C

<u>Drug Therapy option</u>	<u>HIGH RISK</u>	<u>LOW RISK</u>	<u>TOTAL</u>
	<u>[n=712]</u> No. (%)	<u>[n=489]</u> No. (%)	<u>[n=1201]</u> No. (%)
[‡] <i>Statin doubling 1X</i>	49 (7%)	47 (47%)	96 (8%)
[†] <i>Statin doubling 2X</i>	65 (9%)	50 (10%)	115 (10%)
[‡] <i>Statin doubling 3X</i>	36 (5%)	28 (6%)	64 (5%)
[§] <i>Combination Therapy</i>	92 (13%)	60 (12%)	152 (13%)
[¶] <i>Combination therapy + statin doubling</i>	264 (37%)	87 (18%)	351 (30%)
<i>Change current (non-statin) lipid-lowering drug</i>	14 (2%)	5 (1%)	19 (2%)
<i>At goal with current therapy</i>	192 (27%)	212 (43%)	404 (34%)

[‡]**Statin doubling 1X** – patient on statin dose of either 10, 20 or 40mg - ≤ 6.4% LDL-C reduction required to attain goal.

[†]**Statin doubling 2X** – patient on statin dose of either 10 or 20mg - > 6.4 & ≤ 12.4% LDL-C reduction required to attain goal.

[‡]**Statin doubling 3X** – patient on statin dose 10mg - >12.4 & ≤ 18.4% LDL-C reduction required to attain goal.

[§]**Combination therapy** – > 18.4 & < 25 % LDL-C reduction required to attain goal and dose doubling alone will not be sufficient to achieve goal LDL-C.

[¶]**Combination therapy + statin doubling** - >25% LDL-C reduction required to attain goal.

4. DISCUSSION

The SA-NAG survey is the first in South Africa to measure the treatment gap between lipid guidelines and actual goal achievement in dyslipidaemic patients with and without established CVD. It is no surprise that a large disparity exists between practice and recommended goal levels. The results of this survey indicate that a majority of patients are not achieving newly defined guideline specified goal levels. In total 71% of patients were not at goal LDL-C target levels. High risk patients were less likely to be at goal levels with 77% of patients not attaining goal and 63% of LR patients not attaining goal levels. Those patients who were not at goal were also far from their respective targets, as HR patients were on average 1.1 mmol/L (31%) away from goal, and LR patients were 0.7 mmol/L (19%) away. It is evident from the results of this survey that South Africa's adoption of the European guidelines for lipid management will place a majority of patients in the category of not at goal LDL-C.

When the data is analysed according to the previous South African guidelines, 58% (851) of patients are not at goal LDL-C level of < 3.0 mmol/L, and 63 % (758) patients were not at TC goal of < 5.0 mmol/L. Currently the new goals of therapy are lower than the previously recommended levels. A previous survey in SA, the Cholesterol Monitor (CM) which was carried out in South Africa during 1993-1994, demonstrated that overall 72% of all patients treated by private practice and 76% of those with established CHD had total cholesterol levels > 5.0 mmol/L (Steyn et al., 1998). This study clearly shows under both new and old guidelines, that high proportions of patients in South African private practice have had unfavourably high

lipid levels for an extensive period of time and thus the situation is not improving.

The situation in South African practice will inevitably become worse as newer guidelines are expected to have even lower goals of therapy as new evidence suggests that cholesterol levels lower than current recommendations confer additional benefits (Erhardt et al., 2004).

This study has also identified certain age groups of female patients who require larger reductions in LDL-C than male patients to achieve goal levels. Under treatment and under recognition of CVD in female patients has been a problem for many years (Steyn et al., 1998; Pearson et al., 2000; Diamantopoulos et al., 2005). This could possibly be due to CVD manifesting 10-20 years later in females patients compared to male patients (Zagrosek, 2006). In this study a substantial number of female patients have not been treated to goal, and furthermore those that are not attaining goal require higher reductions in LDL-C to achieve optimal goal levels. In the USA, more female patients suffer from CVD than male patients (Mosca et al., 2005). South Africa does not currently have accurate cause of death and disease incidence statistics but under estimation of the incidence of CVD in female patients will lead to increased disease burden in the country (Bradshaw, 2005).

4.1. Recommendations to increase guideline implementation

a) Guideline formulation

Guidelines need to be formulated for the settings for which they are intended. The guidelines need to be formulated with the input of local stakeholders (nurses, specialists, general practitioners, pharmacists, dieticians etc.). This will also increase awareness of guidelines and give caregivers a sense of ownership (Erhardt et al., 2004). South Africa has different regions and populations that are experiencing various stages of epidemiological transition; therefore guidelines should be designed to take into account various risk factors, economic factors, ethnic differences and genetic variation of various communities (Yusuf et al., 2004). The strategies that have proven to be successful in developed countries should also be benchmarks from which developing countries should incorporate into their guidelines (Yusuf et al., 2001).

Those who are responsible for formulating guidelines should design them in such a way that they are easy to follow and practical to implement. In this light it may be necessary to sacrifice some scientific evidence in an attempt to increase utilisation of guidelines (Erhardt et al., 2004). Guidelines should be designed to maximise all available resources to minimise cost to the healthcare system. Possible reasons for the shortfall in lipid goal attainment could be that the therapies available are not sufficiently efficacious to achieve goal levels, non-compliance, tolerability of drugs, inadequate titration of doses, cost issues and failure to utilise combinations of lipid-lowering therapies to achieve goal levels (Pearson et al., 2000).

Population based interventions to reduce risk factors in society have proved the most fruitful and cost effective. Examples of population-based strategies are seen in many developed and developing countries. Successful strategies include various efforts to modify the nutrient intake of the population by government promoted programs to reduce salt intake in manufactured foods over several years, changing the types of oils used for cooking, promoting traditional diets, decreases in saturated fat intake and introduction of labelling logos for healthier foods (Puska et al., 2003). A good example of a population-based strategy that has been successful in SA is the reduction in tobacco use due to the banning and restriction of public smoking.

Research into the guidelines gap is imperative. Important issues of research are; the problems facing doctors in guideline implementation and problems that patients experience in following advice. In certain countries in the US and Europe societies have been formed to monitor the standards of health-care and make necessary changes where there is a shortfall. These types of bodies are essential to realise the needs of health care to reduce the morbidity and mortality from epidemics.

b) Role of the Caregiver

More doctors need to be aware of patients' adherence to therapy in order to advise them on strategies to improve compliance. In the present age of technology, doctors and pharmacists can communicate through various electronic media and can synchronise this type of communication by the click of a mouse. Educating patients in the risks and benefits of recommended treatments could be another fruitful avenue in addressing the issue of non-compliance (Tarn, Heritage, Paterniti, et al., 2006). Newer technologies could provide printouts of drug dosing frequency and reasons why the drug has been administered to increase awareness among patients (O'Connor, 2006). Other promising studies indicate that the appointment of a "transition coach" (to assure correct medication administration after discharge) and reminder systems (active telephone outreach to patients) improves patient compliance to therapy (Feldstein, Smith, Perrin, et al., 2006). Medication non-adherence increases according to the number of medications used (Grant, O'Leary, Weilburg, et al., 2004; O'Connor, 2006). Many patients practicing polypharmacy benefit from the use of combination tablets and research into the polypill (combining several generic medications into one pill), could both be avenues to increase compliance. In the future newer more creative approaches to improve patient compliance are directed at doctors, policy makers and insurance products (O'Connor, 2006). Time issues can be solved by increasing the number of available medical staff trained in treatment and prevention (Graham et al., 2006). This will reduce the burden placed upon the doctors at each consultation. Costs could be decreased by more individualised approach to management.

c) Drug therapy options

Doctors need to titrate doses more frequently to get patients to goal. Doctors rarely titrate doses once treatment has been initiated (Assmann et al., 2006). Doctors may also not know what options are available to get patients who are already on lipid lowering drug treatment, to goal levels (Assmann et al., 2006). Titration is one option that has exhibited therapeutic success for getting patients to goal and has also been shown to be cost-effective (Barter & O'Brien, 2000; Jönsson, 2001; Durrington, 2002). Many recent trials have demonstrated favourable safety profiles with higher dose statin therapy. But for the majority of patients titration alone will not be sufficient to get patients to goal and in these cases other adjunctive therapies will be required. It has also been demonstrated that achieving reductions in LDL-C of > 50% is challenging (De Backer et al., 2001).

In this survey a small number of patients were utilising high dose statin therapy and even fewer patients were on any combination drug therapies. It is evident from the results of this and similar surveys that larger LDL-C reductions than are possible with currently utilised lipid-lowering drug therapies are required to get patients to goal (Diamantopoulos et al., 2005). Guidelines recognise the need for drug therapy in the majority of patients to achieve target lipid levels. Patients who are currently on statin therapy who achieve guideline goal levels have better outcomes than patients who are on statins and do not attain goal levels (Baessler, Fischer, Hengstenberg, et al., 2002). Recent trials have clearly demonstrated that more patients achieve guideline recommended goals with both intensive statin therapy and combination drug therapy, and these trials further reiterate the benefits of lowering cholesterol (Cannon et al., 2004; LaRosa et al., 2005; Pearson et al., 2005; Ballantyne, Bertolami, Garcia, et al., 2006). In view of these trials the most logical course for caregivers is to employ a

potent statin at the appropriate dose in combination with another lipid-lowering drug, like ezetimibe, to maximise the LDL-C lowering and thereby getting more patients to goal (Diamantopoulos et al., 2005; Ballantyne et al., 2006).

d) Assessment of risk

Doctors need to make use of risk charts to accurately assess patients risk to tailor therapy. The use of subjective means to assess risk has been shown to underestimate patients' risk for CHD. Guidelines do encourage the use of individual clinical experience in conjunction with recommendations in implementation of guidelines but the use of risk charts should be made compulsory. Unfortunately at this time South Africa does not have the resources available to formulate its own risk assessment charts. Currently in use is the Framingham risk scoring system developed in the USA. Once more South African data is available it is envisioned that a risk scoring system for CVD will be produced to accurately assess risk (Raal et al., 2006). The Framingham risk assessment charts have been adopted in many countries and have incorporated the most significant risk factors for CHD in its compilation and therefore in the interim will suffice as a reliable means to assess 10-year CHD risk. The future of risk scoring however is predicted to incorporate the "traditional risk factors" for CVD (plus those of the metabolic syndrome), imaging techniques and the various biomarkers (e.g. C-Reactive Protein [CRP]) that are currently being investigated.

e) Cost implications

Lipid-lowering therapies are expensive. Getting patients to goal will have considerable cost implications. Patients that are presently on lipid-lowering drug

therapy will require add on therapies, change of drug or higher doses of present therapy. This will require doctor consultations, laboratory investigations and prescribing costs. These increased costs will also contribute to patients failing to achieve goal (Balbisi, 2006). Furthermore many trials demonstrate that the benefits of LDL-C lowering accrue over many years of treatment with a lag phase before treatment benefit of 6 months to 2 years and the full benefits being exhibited after 4 to 5 years of treatment (Van Hout & Simoons, 2001). There are many studies that demonstrate that statins are highly cost effective for reducing risk for CVD and getting patients to goal, in both secondary and primary prevention patients, over these extensive periods (Van Hout & Simoons, 2001; Mihaylova, Briggs, Armitage, et al., 2006; Kohli, Attard, Lam, et al., 2006). This reduction in risk translates into decreased mortality and morbidity, and cost savings from reduced hospitalisations and rehabilitation from CVD.

4.2. Treatable risk factors

The INTERHEART study has shown that five risk factors (smoking, lipids, hypertension, diabetes and obesity) account for about 80% of the population-attributable risk for acute myocardial infarction worldwide (Yusuf et al., 2004). The INTERHEART study has also substantiated the finding that risk factors are additive. In addition to the lipid goals of treatment there is a high frequency of other modifiable CVD risk factors such as elevated blood glucose levels, smoking, elevated blood pressure and obesity in the SA-NAG population. Specifically blood pressure, blood glucose levels and elevated waist circumference contribute strongly to the metabolic syndrome, which increases the risk for CVD and diabetes substantially. Additionally,

recent evidence has shown that patients with the metabolic syndrome derived significant benefit from intensive LDL-C lowering with high dose statin therapy (Deedwania et al., 2006).

a) Blood Pressure

Blood pressure lowering with antihypertensive therapies in clinical trials has demonstrated a significant effect in the reduction of morbidity and mortality from cardiovascular diseases. It is estimated worldwide that approximately 1 billion people have hypertension (Chobanian, Bakris, Black, et al., 2003). Patients who control blood pressure within normal limits substantially reduce their risk for CVD, renal complications and cerebrovascular events (Israili, Hernández & Valasco, 2007). In this study 30% of non-diabetic patients failed to meet the blood pressure goal of 140/90 mmHg and 76% of diabetic patients failed to meet BP goals of 130/80 mmHg. Furthermore, research into the impact of blood pressure on the progression of coronary atherosclerosis in CHD patients has indicated that even lower goals for blood pressure might be beneficial to reduce coronary disease (Sipahi, Tuzcu, Schoenhagen, et al., 2006). Blood pressure, similarly to LDL-C, has also has no threshold value below which there is no further decrease in risk established (Lewington, Clarke, Qizilbash, et al., 2002).

b) Obesity and overweight

Higher levels of BMI ($> 25 \text{ kg/m}^2$) have been shown to increase overall mortality (Matsuzawa, Funahashi, Kihara, et al., 2004; Adams, Schatzkin, Harris, et al., 2006). Adverse conditions associated with increased adiposity are hypertension, type II diabetes mellitus, cardiovascular disease and cancer (Villareal, Apovian, Kushner, et

al., 2005). Adipose tissue is being commonly recognised as an endocrine organ as it secretes hormones and other substances that lead to insulin resistance, lipid abnormalities, hormonal alterations, and chronic inflammation (Balkwill & Mantovani, 2001; Calle & Kaaks 2004). The global epidemic of obesity is rife and is clearly highly prevalent in this study group (37.6% obese and 33.6% overweight) and South Africa as a whole (Alberts, Urdal, Steyn, et al., 2005; Haslam, Sattar & Lean, 2006). Furthermore a significantly higher proportion of HR males and females were shown to be obese and overweight and this further substantiates the negative effects coupled to these conditions.

Particularly prone to the adverse metabolic effects of obesity are patients of South Asian descent (primarily South African Indians), who show a genetic predisposition to insulin resistance (Yoon, Lee, Kim, et al., 2006). People of Asian descent as a whole develop insulin resistance and diabetes at lower thresholds of obesity and at younger ages than other races (Yoon et al., 2006). The levels of obesity are increasing in South Africa because of increasing urbanisation and the effects of obesity are likely to impact on public health and medical costs. The World Health Organisation has also emphasised obesity and prevention of diabetes type II as a high priority (Yoon et al., 2006).

c) Smoking

Smoking has a substantial effect on the risk of cardiovascular diseases and in particular coronary disease. It has been described as one of the most avoidable CVD risk factors (Jatoi, Jerrard-Dunne, Feely, et al., 2007). The rates of smoking have declined substantially in South Africa due to national legislation and intensive

implementation of smoking laws (Saloojee, 2006). This study in comparison to the CM survey demonstrates a decrease in the proportion of patients who smoke (Steyn et al., 1998). In the CM survey 72% of patients were smokers compared to the 17% of smokers in the SA-NAG survey (55% difference). This is a very promising statistic as research indicates that in MI patients the risk for reinfarction, sudden cardiac death, and total mortality decreases by as much as 50% after smoking cessation (Critchley & Capewell, 2003).

d) Lifestyle therapy

Lifestyle changes are the first line of therapy to modify risk factors. Because of increasing urbanisation, industrialisation, economic development and food market globalisation more and more people are adopting westernised lifestyles (Puska et al., 2003). People tend to consume more energy dense, nutrient poor diets rich in saturated fats, salt and refined carbohydrates, and there is also low consumption of fresh fruit and vegetables (Puska et al., 2003). In this study although diet and exercise therapy were not formally assessed only 62% of patients were practicing these lifestyle therapies. Ideally 100% of patients should be receiving professional advice for maintaining a healthy balanced diet, and engaging in daily physical activity.

4.3. Study limitations

This study unfortunately had a low recruitment of Black patients. The sites chosen for the study were primarily in private sector and the majority of Black patients are treated in government hospitals. The low recruitment rate could also reflect a low awareness of CVD in Black patients. It has also been observed that black patients

are reluctant to donate blood in these types of surveys because of the negative stigma associated with HIV/AIDS epidemic and secrecy regarding HIV status is common (Alberts et al., 2005). The incidence of CVD in Black South Africans is on the increase and surveys to quantify the prevalence of disease are necessary in all ethnic groups (Amira et al., 2006).

This is a biased metropolitan sample of patients exclusively from the private sector. The number of patients who are on medical aid is also a factor that could influence the treatment and results obtained. We can assume that the majority of patients in this study have medical insurance because it was in the private sector. These results also tell us about the low numbers of Black patients that have medical insurance in South Africa. Those with medical aid would ultimately have better access to medical care. The unfortunate reality is that these patients possibly have better treatment and a higher rate of success for achieving guideline recommendations. Inferences of this data to the public sector would be inappropriate. But what can be said is that the situation is likely to be worse in the public sector as South Africa has a poor recent record of dealing with public healthcare, and this been highlighted extensively at international conferences and in the international media. Statins are however frequently accessible even in the public sector as it has been approved to be on the national Essential Drug List (Maritz, 2006). Taking all of this into account the treatment and achievement of guideline targets should be met both in the public and private sectors.

A questionnaire to assess the doctors knowledge of guidelines would of improved the quality of the present study. A questionnaire on the adherence to and awareness of

the guidelines should be addressed in a separate study. As mentioned earlier, the guidelines changed during the study and this also influences practice. Knowledge of the exact guidelines in use by the majority of doctors would aid in our understanding of guideline adherence in conjunction with this study. Taking into account the reality that the guidelines changed during the course of the study, another major limitation of the study in that sufficient time for guidelines to be utilised by all the doctors who participated was not allowed for. Even though this is so, when analysed under the old South African guidelines the majority of patients were failing to achieve goal.

The exact number of investigators was not recorded with the number of patients recruited by each. This would have an impact on the treatment, as a specialist cardiologist would have a better knowledge of the treatment options in their own field. This would also influence the subsequent results obtained. For the time being this is the data we have and the results should be more relevant for General practitioners as they recruited the majority of patients. Another bias that could of influenced the results of the study is the drug formulary of the Medicross groups of hospitals and their influence over prescriptions. The relationship of the sites used for the study would also be influenced by the relationships between MSD and the doctors as MSD recruited the sites.

This survey did not assess the number of patients in clinical practice who are dyslipidaemic but are undiagnosed. This is also an area of concern as it has been observed that a large percentage of patients who are dyslipidaemic are undiagnosed are not treated (Böhler et al., 2007; Ford et al., 2003). The HDL-C levels of the population were higher than expected but all results were analysed at an accredited

central laboratory. One of the strengths of the study is that patients were recruited over 1 year in practices throughout South Africa therefore the lipid levels are highly reflective of this population. Standardised assessment of diet and exercise therapies will also improve further studies of this type.

For the time being this type of data is not available in the public sector because of a lack of resources therefore although the data presented in this study has limitations, for the moment it is the best available to answer the research question.

4.4. Conclusions

Guidelines are published to present the most effective targets for intervention and the best treatments available to reduce the risk of CVD. Goal levels of 2.5 and 3.0 mmol/L, for HR and LR patients respectively, have been established as the practical attainable levels that will minimise the risk of adverse CVD events. Available resource is not being maximised to reduce the prevalence of CVD. Patients are not receiving the comprehensive benefits possible from the therapies that are available. Cardiovascular diseases accounted for an estimated R 4-5 billion in cost to SA in 1991 (Pestana, Steyn, Leiman, et al., 1996). Given the immense costs being incurred by the HIV/AIDS epidemic and other infectious disease in SA, the rise in CVD, as predicted by epidemiologic transitions of developing nations, will place significant strain on the South African medical expenditure. It is imperative that adequate treatment and education to minimise the burden CVD has on the nation be set in place.

A substantial proportion of patients that are utilising the most efficacious drug therapies available for lipid management are not achieving goal LDL-cholesterol levels. In this survey 71% of patients are not achieving guideline specified goal levels. In addition there are also a high proportion of other secondary risk factors that are not optimally treated. The time is now to act on these treatment shortfalls before they are too overwhelming to control. The publication of the new guidelines, combined with the results of this survey necessitates enhanced disease management to reduce the burden of CVD in SA.

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6. APPENDICES



Appendix A

Patient Information Sheet

NAG STUDY WITWATERSRAND UNIVERSITY 2005

Patient Information Sheet

The evaluation of patients receiving lipid lowering therapy and achieving low-density lipoprotein cholesterol goal

1 Purpose of this study

This study will benefit patients (like you) that are being treated with cholesterol-lowering therapy. A high blood cholesterol level is a major cause of heart disease. Patients that receive cholesterol-lowering treatment need to reach certain targets to reduce the risk of heart disease. This study will look at cholesterol levels by drawing blood from patients and performing lab tests to check the various cholesterol levels within the blood. These lab tests are done to check how many patients are not achieving the required blood cholesterol levels.

This study has been approved by the Human Ethics Committee of the University of the Witwatersrand to ensure that human rights are protected. This study is under the direction of Prof D. Raal and Dr N. Butkow.

2 Procedures to be followed

If you agree to take part in this study your blood will be drawn to test cholesterol levels.

As part of the study patients will make one clinical visit to their doctor to draw blood for lab testing.

3 Risks

Blood sampling will be done once. The procedure of taking blood may cause pain at the point of blood collection, bruising or swelling.

4 Benefits

As a volunteer in this study your lab tests will be done free of charge to assess blood cholesterol levels and blood glucose levels.

5 Confidentiality of Records

Your medical records that are related to this study, and past patient history used, will be maintained in confidentiality with a coding system.

6 Obtaining Additional Information

You are encouraged to ask any additional questions that occur to you at this time or to ask any questions at any time during your participation in this study. You will be given a copy of this agreement for your own information. If you desire more information at a later date you may call Akash Ramjeeth at 082 296 3248 or Dr Neif Butkow at 011 717-2371 (during daytime hours).

Appendix B

Patient Consent Form



Volunteer Consent Form

The evaluation of patients receiving lipid lowering therapy and achieving low-density lipoprotein cholesterol goal

Name of Patient Date 20

Date of Birth Age Sex

Address

Telephone (H) Cell

E-mail

1

Purpose of this study

This study will benefit patients (like you) that are being treated with cholesterol-lowering therapy. A high blood cholesterol level is a major cause of heart disease. Patients that receive cholesterol-lowering treatment need to reach certain targets to reduce the risk of heart disease. This study will look at cholesterol levels by drawing blood from patients and performing lab tests to check the various cholesterol levels within the blood. These lab tests are done to check how many patients are not achieving the required blood cholesterol levels.

This study has been approved by the Human Ethics Committee of the University of the Witwatersrand to ensure that human rights are protected. This study is under the direction of Prof D. Ruel and Dr N. Butkow.

2

Procedures to be followed

If you agree to take part in this study your blood will be drawn to test cholesterol levels. As part of the study patients will make one clinical visit to their doctor to draw blood for lab testing.

3

Risks

Blood sampling will be done once. The procedure of taking blood may cause pain at the point of blood collection, bruising or swelling.

4

Benefits

As a volunteer in this study your lab tests will be done free of charge to assess blood cholesterol levels and blood glucose levels.

5

Confidentiality of Records

Your medical records that are related to this study, and your past patient history used, will be maintained in confidentiality with a coding system.

6

Obtaining Additional Information

You are encouraged to ask any additional questions that occur to you at this time or to ask any questions at any time during your participation in this study. You will be given a copy of this agreement for your own information. If you desire more information at a later date you may call Akash Ramjath at 082 288 3248 or Dr Neil Butkow at 011 717-2371 (during daytime hours).

7

Basis of your Participation

You are free to withdraw your consent to participate in this study at any time. If you choose to do so, your rights to present future medical care by Dr _____ or at hospital will not be affected.

8

Signature

I have read the above information and have had an opportunity to ask any questions and all of my questions have been answered. I consent to my blood being tested for the purposes of this study. I have been given a copy of this consent form.

Signature (Patient)

Date 20

I, the undersigned, have fully explained the relevant details of this study to the patient named above. I am qualified to perform this role.

Signature (Investigator)

Print name

Date 20

Signature (Witness)


Print name

Date 20

Address of Witness

Appendix C

Protocol Approval

 UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG
FACULTY OF HEALTH SCIENCES

University of the Witwatersrand **ASSESSORS MEETING**

Date of Assessor Group Meeting: 4/5/05 Assessor Group: Group 1.

Is the research question clearly identified and described?
 Yes No

Comments:

Is the design of the study and methods the methods used appropriate for the research question being asked? ..
 Yes No Not entirely

Comments and suggestions:

* Change recruitment of patients only if they have been on treatment with lipid lowering treatment for at least 4 months.

* If on preliminary assessment only patients recruited on simvastatin then this to be reviewed by supervisor and changed.

Ethics approved. No. MO 50322.

Candidate: AA RAMJEETH Student Number: 0107526R

Is the study feasible within:

- i. the applicant's resources? Yes No
- ii. the departments resources? Yes No
- iii. the time frame? Yes No

Do you recommend:

- i. shortening / lengthening of the protocol? Please specify and explain.

- ii. the appointment of a co-supervisor? Yes No

Nominee/s : _____

Overall recommendation regarding the protocol :

- i. revision of the protocol to the Supervisor / Head of Department: Yes No
- ii. revision of the protocol to the satisfaction of the Assessor Group: Yes No
- iii. revision of the protocol and resubmission of the revised protocol to the next Assessor Group Meeting: Yes No
- iv. candidate goes ahead: Yes No

Assessor Names and Signatures :

A.T.O. ABSOOL-CARRIM

M.R. ESSOP

J KOTZEN

G.J. OETTLER

A.T.O. ABSOOL-CARRIM

M.R. ESSOP

J KOTZEN

G.J. OETTLER

4 MAY 2005

Date

Appendix D

Ethics Clearance Certificate

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

Division of the Deputy Registrar (Research)

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

R14/49 Ramjeeth

CLEARANCE CERTIFICATE

PROTOCOL NUMBER M050322

PROJECT

The Evaluation of Patients Receiving
Lipid Lowering Therapy and Achieving
Low-Density Lipoprotein Cholesterol Goal

INVESTIGATORS

Mr AA Ramjeeth

DEPARTMENT

Pharmacy Pharmacology

DATE CONSIDERED

05.04.01

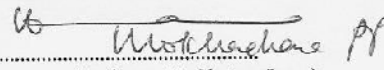
DECISION OF THE COMMITTEE*

Approved unconditionally

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

DATE 05.04.18

CHAIRPERSON


(Professor PE Cleaton-Jones)

*Guidelines for written 'informed consent' attached where applicable

cc: Supervisor : Dr N Burkow

DECLARATION OF INVESTIGATOR(S)

To be completed in duplicate and **ONE COPY** returned to the Secretary at Room 10005, 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

Appendix E

Case Report Form

NAG STUDY WITWATERSRAND UNIVERSITY · 2 · 0 · 0 · 5 ·

Case Report

Patient Number

Date 20

Patient Demographics		Waist circumference <input type="text"/> <input type="text"/> <input type="text"/> cm
Initials <input type="text"/> <input type="text"/> <input type="text"/>		Weight <input type="text"/> <input type="text"/> <input type="text"/> kg
Date of Birth <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> 19 <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>		Height <input type="text"/> <input type="text"/> <input type="text"/> cm
Gender: Male <input type="checkbox"/> Female <input type="checkbox"/>		BMI <input type="text"/> <input type="text"/>
Race: White <input type="checkbox"/> Black <input type="checkbox"/> Asian <input type="checkbox"/> Coloured <input type="checkbox"/>		Body Mass Index (BMI) = Mass(kg) ÷ [height(m)] ²
Pre-existing Cardiovascular Disease <i>(please tick appropriate box)</i>		
Stroke <input type="checkbox"/>	MI <input type="checkbox"/>	PVD <input type="checkbox"/> Angina <input type="checkbox"/>
Family History <i>(please tick appropriate box)</i>		
Familial Hypercholesterolemia <input type="checkbox"/>		Premature CHD (<55_ / <65_) <input type="checkbox"/>
Risk Factors for Coronary Heart Disease <i>(please tick appropriate box)</i>		
Hypertension <input type="checkbox"/>	Hyperlipidaemia <input type="checkbox"/>	Smoking <input type="checkbox"/> Diabetes <input type="checkbox"/>

Vital Signs
Blood Pressure <input type="text"/> <input type="text"/> <input type="text"/> / <input type="text"/> <input type="text"/> <input type="text"/> mmHg
Pregnancy Test Negative <input type="checkbox"/> Positive <input type="checkbox"/>

Investigations	<input type="text"/> Laboratory Barcode
Fasting Lipogram and Blood Glucose done <input type="checkbox"/> Y <input type="checkbox"/> N	
HbA _{1c} <input type="text"/>	High Density Lipoprotein (HDL-C) <input type="text"/>
Triglycerides <input type="text"/>	Total Cholesterol <input type="text"/>
Low Density Lipoprotein (LDL-C) <input type="text"/>	Blood Glucose <input type="text"/>

Current Lipid Lowering Treatment		
Tradename	Dose (mg)	Duration
e.g. Zocor	20 mg daily	2 years

Other concomitant medication		
Tradename	Dose (mg)	Duration
e.g. Paracet	10 mg daily	5 years

Exercise therapy Diet therapy

Doctor's Signature

Date 20

APPENDIX F

List of sites that participated in the survey

	Region	Primary Investigator	Clinic Name	Type of Practice	Street Address
1	KZN	Louis Minders	BLUFF	Medicross Hospital	54 Lighthouse Rd, Bluff Durban
2	PE	Carolien	CAPE ROAD	Medicross Hospital	171 Cape Rd, Millpark, Port Elizabeth
3	PTA	Handri Els	CONSTANTIA PARK	Medicross Hospital	Cnr Chopin & Duvernoy Street, Garsfontein
4	EL	John Filmer	EAST LONDON	Medicross Hospital	Cnr Peace & Lukin Road, Baysville East London
5	PTA	Hugo Swanepoel	GEZINA	Medicross Hospital	Michael Brink Street, Gezina
6	CT	N Wellington	KENILWORTH	Medicross Hospital	67 Rosemead Ave, Kenilworth
7	CT	JB Bekker	LANGEBERG	Medicross Hospital	Cnr Brighton & Kipling Street, Cape Town
8	Bloem	Koos van der Merwe	NOORDSTAD (Bloem)	Medicross Hospital	Eeufees Ave, Noorstad Bloemfontein
9	CT	Pieter De Bruin	NORTHPINE	Medicross Hospital	Northpine Drive, Northpine, Cape Town
10	CT	C Bester	PAROW	Medicross Hospital	Cnr McIntyre & Voortrekker Rd, Parow
11	KZN	J Drew	PINETOWN	Medicross Hospital	Cnr Old Main & Mellor Rds, Pinetown
12	WR	Vorster	POTCHEFSTROOM	Medicross Hospital	Cnr Lombard & van Riebeeck Streets, Potchefstroom
13	PTA	Dirk Brink	PRETORIA NORTH	Medicross Hospital	291 Burger Street, Pretoria North
14	PTA	D de Jongh	PRETORIA WEST	Medicross Hospital	Church Street, Pretoria West
15	KZN	Wil Watson	RICHARDS BAY	Medicross Hospital	3 Lira Link, Richards Bay
16	WR	Louis Kruger	ROODEPOORT	Medicross Hospital	Princess Crossing, Ontdekkers Rd, Roodepoort
17	PTA	J Kotze	SAXBY	Medicross Hospital	Cnr Saxby & Frederich Streets, Eldoraigne, Centurion
18	PTA	D de Jongh	SILVERTON	Medicross Hospital	310 Pretoria Street, Silverton, Pretoria
19	ER	Johan Coetzee	SPRINGS	Medicross Hospital	1 Nigel Rd, Selection Park, Springs
20	CT	J van de Merwe	STELKOR	Medicross Hospital	
21	CT	Roussow	TABLE VIEW	Medicross Hospital	95 Blaauwberg Rd, Tableview Cape Town
22	CT	Pete Vincent	TOKAI	Medicross Hospital	Cnr Tokia Rd & Keyser Rivier Drive, Tokai
23	JHB	J Du Plesis	MELDENE DOCTORS	Medicross Hospital	27A Third Ave, Melville
24	PE	Neil Venter	WALMER	Medicross Hospital	Cnr Buffelsfontein & 17th Ave, Port Elizabeth
25	JHB	Dr J Joubert	NELMED	Medicross Hospital	
26	JHB	Dr K O'Hare	VEREENIGING	Medicross Hospital	Cnr Nile Drive & The Square, Three Rivers
27	JHB	Dr Ashraf Karolia	MAYFAIR	Remedium Medical Centre	110 Sixth Avenue, Mayfair
28	JHB	Dr Hemant Makan	LENASIA	Private Practice	80 Gemsbok Avenue, Lenasia
29	KZN	Dr A Ahmod	CHATSWORTH	Chatsmed Medical Centre	Suite 215, 80 Woodhurst Drive
30	KZN	Dr AS Ramdass	CHATSWORTH	Chatsmed Medical Centre	Suite 117, 80 Woodhurst Drive

APPENDIX G

Framingham Risk Scoring Chart

Framingham 10-year Risk Assessment Chart

Estimate of 10-year risk for **MEN**: (Framingham point scores)

Age (yr)		Points	
20-34		-9	
35-39		-4	
40-44		0	
45-49		3	
50-54		6	
55-59		8	
60-64		10	
65-69		11	
70-74		12	
75-79		13	

Total Cholesterol (mmol/l)	Points					
	Age:	20-39	40-49	50-59	60-69	70-79
<4		0	0	0	0	0
4.10 - 5.00		4	3	2	1	0
5.10 - 6.20		7	5	3	1	0
6.21 - 7.20		9	6	4	2	1
≥7.2		11	8	5	3	1

	Points					
	Age:	20-39	40-49	50-59	60-69	70-79
Nonsmoker		0	0	0	0	0
Smoker		8	5	3	1	1

HDL (mmol/l)		Points	
≥1.6		-1	
1.30 - 1.59		0	
1.00 - 1.29		1	
<1		2	

Systolic BP (mmHg)	Points	
	If untreated	If treated
<120	0	0
120-129	0	1
130-139	1	2
140-159	1	2
≥160	2	3

Point total	10-year risk %
<0	<1
0	1
1	1
2	1
3	1
4	1
5	2
6	2
7	3
8	4
9	5
10	6
11	8
12	10
13	12
14	16
15	20
16	25
≥17	≥30

Estimate of 10-year risk for **WOMEN**: (Framingham point scores)

Age (yr)		Points	
20-34		-7	
35-39		-3	
40-44		0	
45-49		3	
50-54		6	
55-59		8	
60-64		10	
65-69		12	
70-74		14	
75-79		16	

Total Cholesterol (mmol/l)	Points					
	Age:	20-39	40-49	50-59	60-69	70-79
<4		0	0	0	0	0
4.10 - 5.00		4	3	2	1	1
5.10 - 6.20		8	6	4	2	1
6.21 - 7.20		11	8	5	3	2
≥7.2		13	10	7	4	2

	Points					
	Age:	20-39	40-49	50-59	60-69	70-79
Nonsmoker		0	0	0	0	0
Smoker		9	7	4	2	1

HDL (mmol/l)		Points	
≥1.6		-1	
1.30 - 1.59		0	
1.00 - 1.29		1	
<1		2	

Systolic BP (mmHg)	Points	
	If untreated	If treated
<120	0	0
120-129	1	3
130-139	2	4
140-159	3	5
≥160	4	6

Point total	10-year risk %
<9	<1
9	1
10	1
11	1
12	1
13	2
14	2
15	3
16	4
17	5
18	6
19	8
20	11
21	14
22	17
23	22
24	27
≥25	≥30

Framingham scoring system for calculating the 10-year risk of major coronary events in adults without diabetes.

HDL denotes high-density lipoprotein cholesterol & BP blood pressure. All age denotes are given in years.

Reprinted from National Institutes of Health, National Heart, Lung & Blood Institute. Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation and Treatment of High blood Cholesterol in Adults (Adult Treatment Panel III). Executive Summary. NIH Publication No. 01-3670; May 2001.

APPENDIX H

Table of concomitant cardiovascular medication

	Low Risk (n=489) no. (%)	High Risk (n=712) no. (%)	Total (n=1201) no. (%)
Acarbose	0	1	1
Aldosterone Antagonist	1	11 (2%)	12 (1%)
Allopurinol	21 (4%)	37 (5%)	58 (5%)
Alpha & Beta Blocker	5 (1%)	21 (3%)	26 (2%)
Alpha Blocker	1	12 (2%)	13 (1%)
Angiotensin Converting Enzyme Inhibitor	99 (20%)	239 (34%)	338 (28%)
Angiotensin II Receptor Blocker	48 (10%)	89 (13%)	137 (11%)
Anti-arrhythmic	1	10 (1%)	11 (1%)
Anti-coagulant agent	4 (1%)	24 (3%)	28 (2%)
Anti-platelet agent	1	16 (2%)	17 (1%)
Aspirin	86 (18%)	270 (38%)	356 (30%)
Benzbromarone	1	2	3
Beta-Blockers	81 (17%)	158 (22%)	239 (20%)
Bisphosphonates	14 (3%)	7 (1%)	21 (2%)
Ca²⁺ Channel Blockers	33 (7%)	116 (16%)	149 (12%)
Centrally Acting Anti-adrenergic agents	3 (1%)	4 (1%)	7 (1%)
Colchicine	0	2	2
Digitalis Glycosides	2	8 (1%)	10 (1%)
Hormone Replacement Therapy (HRT)	77 (16%)	38 (5%)	115 (10%)
HRT-progesterone	6 (1%)	5 (1%)	11 (1%)
Hydrazinophthaline derivative	0	1	1
Insulin	13 (3%)	44 (6%)	57 (5%)
K⁺	4 (1%)	16 (2%)	20 (2%)
Loop Diuretic	10 (2%)	28 (4%)	38 (3%)
Low-Ceiling Diuretic	119 (24%)	202 (28%)	321 (27%)
Meglitinide	1	0	1
Metformin	58 (12%)	99 (14%)	157 (13%)
Nitrate	1	27 (4%)	28 (2%)
Potassium Sparing Diuretic	21 (4%)	24 (3%)	45 (4%)
Sulphonylurea	31 (6%)	55 (8%)	86 (7%)
Thiazolidinediones	1	4 (1%)	5
Thyroxine	64 (13%)	35 (5%)	99 (8%)
Vardenafil	1	0	1

APPENDIX I

Frequency and mean table for diabetic patients

Diabetics (n=244)	Female (n=86)	Male (n=158)	Total (n=244)
<i>Age Mean (SD)</i>	58.7 (11.5)	57.3 (10.4)	57.8 (10.8)
<i>Weight (Kg) Mean (SD)</i>	77.8 (15)	91.7 (21.5)	86.8 (20.5)
<i>Height (cm) Mean (SD)</i>	159.3 (10.8)	172 (12.2)	167.5 (13.2)
<i>Waist (cm) Mean (SD)</i>	99.3 (11.7)	106.4 (13.8)	103.9 (13.5)
<i>BMI Mean (SD)</i>	30.4 (5.3)	30.2 (5.6)	30.2 (5.5)
<i>Overweight no. (%)</i>	28 (33%)	47 (30%)	75 (31%)
<i>Obese no. (%)</i>	45 (52%)	83 (53%)	128 (52%)
<i>Smoking no. (%)</i>	7 (8%)	30 (19%)	37 (15%)
<i>Hb_{A1c} > 7% no. (%)</i>	32 (37%)	66 (42%)	98 (40%)
<i>Hb_{A1c} > 7% Mean (SD)</i>	8.1 (0.7)	8.1 (0.8)	7.1 (1.1)
<i>Hb_{A1c} diabetics (%) Mean (SD)</i>	7 (1.1)	7.2 (1.1)	8.1 (0.8)
<i>FBG > 6 mmol/L no. (%)</i>	45 (52%)	116 (73%)	161 (66%)
<i>FBG > 6 mmol/L Mean (SD)</i>	8.2 (1.9)	8.4 (1.7)	8.4 (1.7)
<i>Blood Glucose Diabetics (mmol/l) Mean (SD)</i>	6.7 (2.1)	7.6 (2.1)	7.3 (2.1)
<i>Tot Cholesterol Mean (SD)</i>	5.1 (1.1)	5 (1)	5 (1)
<i>LDL Cholesterol Mean (SD)</i>	2.9 (0.9)	2.9 (0.8)	2.9 (0.8)
<i>HDL Cholesterol Mean (SD)</i>	1.3 (0.4)	1.2 (0.2)	1.2 (0.3)
<i>Triglycerides Mean (SD)</i>	1.9 (1.2)	2 (1.2)	1.9 (1.1)
<i>Hypertensives no.</i>	66 (77%)	113 (72%)	179 (73%)
<i>SBP (mmHg) Mean (SD)</i>	130.5 (11.8)	131.2 (14.1)	131 (15.1)
<i>SBP (mmHg) Hypertensives Mean (SD)</i>	134.7 (15.6)	134 (14)	134.3 (14.5)
<i>SBP (mmHg) Non-Hypertensives Mean (SD)</i>	116.8 (13.4)	124.4 (0.1)	122.1 (12.9)
<i>DBP (mmHg) Mean (SD)</i>	79 (10.1)	80.6 (9.5)	80.1 (9.7)
<i>DBP (mmHg) Hypertensives Mean (SD)</i>	80.2 (9.4)	81.1 (9.6)	80.8 (9.6)
<i>DBP (mmHg) Non-Hypertensives Mean (SD)</i>	75.1 (11.5)	79.4 (9.1)	78.1 (10)
<i>MI no. (%)</i>	12 (14%)	25 (16%)	37 (15%)
<i>Stroke no. (%)</i>	5 (6%)	5 (3%)	10 (4%)
<i>PVD no. (%)</i>	1 (1%)	3 (2%)	4 (2%)
<i>Angina no. (%)</i>	16 (19%)	24 (15%)	40 (16%)
<i>Family History no. (%)</i>	24 (28%)	50 (32%)	74 (30%)
<i>MS no. (%)</i>	74 (86%)	134 (85%)	208 (85%)
<i>Insulin no. (%)</i>	13 (15%)	44 (28%)	57 (23%)
<i>Metformin no. (%)</i>	58 (67%)	99 (63%)	157 (64%)
<i>Sulphonylurea no. (%)</i>	31 (36%)	55 (35%)	86 (35%)
<i>Thiazolidinediones no. (%)</i>	1 (1%)	4 (3%)	5 (2%)
<i>Meglitinide no. (%)</i>	1 (1%)	0	1
<i>Acarbose no. (%)</i>	0	1 (1%)	1
<i>NAG LDL no. (%)</i>	56 (65%)	111 (70%)	167 (68%)
<i>NAG LDL (mmol/l) Mean (SD)</i>	3.3 (0.7)	3.3 (0.6)	3.3 (0.7)
<i>mmol/L away from goal</i>	0.8	0.8	0.8
<i>% away from goal</i>	24%	24%	24%

BMI, body mass index; **Hb_{A1c}**, glycosylated haemoglobin; **FBG**, fasting blood glucose; **tot**, total; **SBP**, systolic blood pressure; **DBP**, diastolic blood pressure; **MI**, myocardial infarction; **PVD**, peripheral venous disease; **MS**, metabolic syndrome; **NAG**, not at goal.

Frequency and mean table for hypertensive patients

Hypertensives (n=729)	Female (n=321)	Male (n=408)	Total (n=729)
Age Mean (SD)	62.6 (9.5)	59.6 (11.2)	60.9 (10.6)
Weight (Kg)Mean (SD)	76.6 (16.5)	90.2 (17.6)	84.1 (18.4)
Height (cm)Mean (SD)	160.4 (9.5)	175.5 (8.6)	168.8 (11.7)
Waist (cm)Mean (SD)	94.9 (13.3)	103.2 (12.5)	99.5 (13.5)
BMI Mean (SD)	29.3 (5.6)	29 (4.8)	29.1 (5.2)
Overweight no. (%)	99 (31%)	153 (38%)	252 (35%)
Obese no. (%)	141 (44%)	165 (40%)	306 (42%)
Smoking no. (%)	40 (12%)	71 (17%)	111 (15%)
Diabetic no. (%)	66 (21%)	114 (28%)	180 (25%)
Hb_{A1c} > 7% (no.)	25 (8%)	51 (13%)	76 (10%)
Hb_{A1c} > 7% Mean (SD)	8.1 (0.7)	8.1 (0.8)	8.1 (0.8)
Hb_{A1c} diabetics Mean (SD)	7 (1.1)	7.1 (1.2)	7 (1.1)
FBG > 6 mmol/L (no.)	79 (25%)	158 (39%)	237 (33%)
FBG > 6mmol/L Mean (SD)	7.7 (1.7)	8 (2)	7.9 (1.9)
Blood Glucose Diabetics Mean (SD)	5.7 (1.5)	6.3 (1.8)	6.1 (1.7)
Tot Cholesterol Mean (SD)	5.5 (1.1)	5.1 (1)	5.3 (1.1)
LDL Cholesterol Mean (SD)	3.3 (1)	3 (0.9)	3.2 (0.9)
HDL Cholesterol Mean (SD)	1.5 (0.4)	1.3 (0.3)	1.4 (0.4)
Triglycerides Mean (SD)	1.7 (0.9)	1.9 (1.3)	1.8 (1.1)
SBP (mmHg) Hypertensives Mean (SD)	136.4 (16.9)	133.5 (13.4)	134.7 (15.1)
DBP (mmHg) Hypertensives Mean (SD)	80.1 (9.6)	81.3 (8.7)	80.8 (9.2)
MI no. (%)	25 (8%)	82 (20%)	107 (15%)
Stroke no. (%)	16 (5%)	21 (5%)	37 (5%)
PVD no. (%)	6 (2%)	8 (2%)	14 (2%)
Angina no. (%)	50 (16%)	73 (18%)	123 (17%)
Family History no. (%)	121 (38%)	155 (38%)	276 (38%)
MS no. (%)	202 (63%)	298 (73%)	500 (69%)
NAG LDL no. (%)	224 (70%)	280 (69%)	504 (69%)

BMI, body mass index; **Hb_{A1c}**, glycosylated haemoglobin; **FBG**, fasting blood glucose; **tot**, total; **SBP**, systolic blood pressure; **DBP**, diastolic blood pressure; **MI**, myocardial infarction; **PVD**, peripheral venous disease; **MS**, metabolic syndrome; **NAG**, not at goal.