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Date Oct. 10, 2000
ABSTRACT

Cardiovascular disease is the leading cause of death in British Columbia and Canada, with the majority of cases being the result of coronary artery disease (CAD). CAD is a result of the interaction between genetic background and environmental influence. Several modifiable and non-modifiable risk factors contribute to the development and progression of atherosclerosis - the major cause of CAD. Numerous studies have shown that treatment of CAD risk factors, and dyslipidaemia in particular, reduces the incidence of CAD morbidity and mortality. Based on this evidence, national guidelines have been published for the treatment of dyslipidaemia and management of other risk factors of CAD. However, examination of treatment practices in Canada, the US, and Europe has shown sub-optimal adherence to these guidelines.

This thesis describes a questionnaire-based follow-up of consecutive patients referred for selective coronary angiography (SCA) between 1993 and 1995 at two tertiary Vancouver hospitals. Lipid measurements, risk factor prevalence, and medication use at the time of SCA were available for all patients. The follow-up assessed changes in risk factors and medications, incidence of CAD morbidity, access to risk factor counseling, patient awareness of risk factors, and, in the case of deceased patients, cause of death. The 1988 Canadian Consensus Conference on Cholesterol (CCCC) and 1993 National Cholesterol Education Program (NCEP) guidelines were used to determine the appropriate treatment of dyslipidaemia in those who responded to the questionnaire.

Respondents were more likely to have CAD, less likely to smoke, and more likely to live in rural areas than non-respondents. The prevalence of most risk factors was comparable to previous reports, however respondents were more obese and had a greater number of risk factors than the Canadian population. Between 1993 and 1997, 150 patients died, with cause of death available for 102. Of these, 70% died of cardiovascular causes.
Awareness of risk factors was less than ideal among respondents. Only half were able to correctly judge their change in weight and exercise. Just over half knew their blood pressure, while only two-fifths could report their cholesterol level. Counseling for lifestyle risk factors was under-utilised in general, although appeared well targeted to patients requiring intervention.

While the number of patients who would have required cholesterol monitoring, dietary therapy, or drug intervention differed between guidelines, the prevalence of appropriate dyslipidaemia treatment was equivalent regardless of the guideline employed. Three-quarters of respondents requiring cholesterol monitoring had their lipids checked during the follow-up period. Dietary therapy was appropriately administered in approximately 70% of patients requiring treatment. However, counseling by dieticians, which is explicitly required by CCCC guidelines, was seen in only 38%. Lipid lowering drugs (LLD) were not prescribed for over 40% of respondents requiring drug therapy.

While the number of patients being treated appropriately for their dyslipidaemia was found to be slightly higher in the study population than in other studies published in the literature, the level of treatment was still sub-optimal, particularly with respect to utilisation of allied health professionals. With cardiovascular disease being the leading cause of death in British Columbia, more effort must be made to follow established guidelines using well-proven methods of treatment.
TABLE OF CONTENTS

ABSTRACT ............................................................................................................................... ii
TABLE OF CONTENTS ........................................................................................................ iv
ABBREVIATIONS ................................................................................................................ viii
LIST OF TABLES .................................................................................................................. x
LIST OF FIGURES ............................................................................................................... xii
ACKNOWLEDGEMENTS ........................................................................................................ xiii
1 INTRODUCTION .................................................................................................................. 1
1.1 CORONARY ARTERY DISEASE .......................................................................................... 1
  1.1.1 Etiology ......................................................................................................................... 1
  1.1.2 Incidence and Costs ...................................................................................................... 4
  1.1.3 Risk Factors ................................................................................................................... 5
    1.1.3.1 Major Risk Factors ................................................................................................. 6
    1.1.3.2 Conditional Risk Factors ....................................................................................... 8
    1.1.3.3 Predisposing Risk Factors ..................................................................................... 11
  1.1.4 Treatment ..................................................................................................................... 12
    1.1.4.1 Lifestyle Interventions ........................................................................................... 12
    1.1.4.2 Drug Therapies for CAD Event Reduction ............................................................. 13
    1.1.4.3 Lipid Lowering ......................................................................................................... 15
1.2 PUBLISHED GUIDELINES FOR TREATMENT OF DYSLIPIDAEIA ...................... 17
  1.2.1 Canadian Consensus Conference on Cholesterol Guidelines ................................ 17
    1.2.1.1 Lipid Risk Factors and Testing Priorities ............................................................... 17
    1.2.1.2 Dietary Therapy .................................................................................................... 18
    1.2.1.3 Drug Therapy .......................................................................................................... 19
    1.2.1.4 Other Risk Factors ................................................................................................. 19
    1.2.1.5 Canadian Guidelines 2000 ..................................................................................... 19
  1.2.2 National Cholesterol Education Program Guidelines ........................................... 22
1.3 PATIENT AWARENESS OF HEALTH ......................................................................... 25
1.4 APPROPRIATE TREATMENT OF DYSLIPIDAEIA .................................................. 27
1.5 RATIONALE ..................................................................................................................... 30
1.6 HYPOTHESIS .................................................................................................................. 31
1.7 SPECIFIC AIMS .............................................................................................................. 31
2 METHODS

2.1 ORIGINAL COHORT SELECTION

2.2 QUESTIONNAIRE DESIGN

2.2.1 Ethics Approval

2.3 MAIL-OUT

2.4 VITAL STATISTICS INFORMATION

2.5 MEDICAL RECORDS

2.6 STATISTICAL ANALYSIS

3 RESULTS

3.1 RESPONSE RATE

3.2 BASELINE CHARACTERISTICS

3.2.1 Demographics

3.2.2 Lipid Profile

3.2.3 Risk Factor Prevalence

3.2.3.1 Subgroup analyses

3.2.4 Medication Usage

3.3 FOLLOW-UP CHARACTERISTICS

3.3.1 Changes in Risk Factor Prevalence

3.3.2 Changes in Medication Usage

3.3.3 Morbidity

3.3.4 Mortality

3.4 PREDICTORS OF MORBIDITY AND MORTALITY

3.4.1 Morbidity

3.4.2 Mortality

3.5 PATIENT AWARENESS OF HEALTH

3.5.1 Changes in Health Measures

3.5.1.1 Weight

3.5.1.2 Exercise habit

3.5.1.3 Alcohol intake

3.5.2 Risk Markers

3.5.2.1 Hypertension

3.5.2.2 Cholesterol
3.5.3 Instillation of Awareness by Others ........................................... 53
  3.5.3.1 Risk factor counseling ......................................................... 53
  3.5.3.2 Health professionals and laypersons ..................................... 54
3.5.4 Comparison with Hospital Records ........................................... 54

3.6 APPROPRIATE TREATMENT ...................................................... 55
  3.6.1 CCCC Guidelines ............................................................... 55
    3.6.1.1 Lipid Testing .............................................................. 55
    3.6.1.2 Dietary Therapy ......................................................... 55
    3.6.1.3 Drug Therapy ............................................................. 56
    3.6.1.4 Canadian Guidelines 2000 .............................................. 57
  3.6.2 NCEP Guidelines ............................................................... 57
    3.6.2.1 Annual cholesterol measurement ..................................... 57
    3.6.2.2 Dietary therapy .......................................................... 58
    3.6.2.3 Drug therapy .............................................................. 58

3.7 PREDICTORS OF APPROPRIATE TREATMENT ............................... 59
  3.7.1 CCCC Guidelines ............................................................... 59
  3.7.2 NCEP Guidelines ............................................................... 60

3.8 REGIONAL VARIATIONS IN APPROPRIATE TREATMENT ..................... 60

4 DISCUSSION ................................................................................. 62
  4.1 LIMITATIONS OF THE STUDY .................................................. 62
    4.1.1 Methodology ................................................................. 62
    4.1.2 Response Rate and Bias ................................................... 63
  4.2 PATIENT CHARACTERISTICS ................................................... 64
    4.2.1 Demographics and Risk Factor Prevalence .............................. 64
    4.2.2 Baseline Subgroup Analyses .............................................. 68
    4.2.2.1 ApoAI in Low Risk Patients ......................................... 68
    4.2.2.2 Predictors of CAD in Younger versus Older Women ............. 69
    4.2.3 Morbidity ................................................................. 71
    4.2.4 Mortality ................................................................. 72
  4.3 ANALYSIS OF TREATMENT ..................................................... 74
    4.3.1 Awareness and Counseling of Risk Factors ............................. 74
    4.3.2 Pharmacological Interventions ......................................... 76
ABBREVIATIONS

4S ........................................... Scandinavian Simvastatin Survival Study
ACE ....................................... angiotensin converting enzyme
AFCAPS/TexCAPS ........................... Air Force/Texas Coronary Atherosclerosis Prevention Study
AHA ........................................ American Heart Association
apo ........................................... apolipoprotein
ASA ........................................ acetylsalicylic acid
BMI ........................................... body mass index
Ca-channel blocker ...................... calcium channel blocker
CABG ....................................... coronary artery bypass graft
CAD .......................................... coronary artery disease
CARE ....................................... Cholesterol and Recurrent Events
CBS ........................................... cystathionine β-synthase
CCCC ......................................... Canadian Consensus Conference on Cholesterol
CHF .......................................... congestive heart failure
CQIN ......................................... Clinical Quality Improvement Network
CRP ........................................... C-reactive protein
CVD .......................................... cardiovascular disease
DBP .......................................... diastolic blood pressure
DVA-HIT ..................................... Department of Veterans Affairs HDL Intervention Trial
EDTA ......................................... ethylenediaminetetraacetic acid
FATS .......................................... Familial Atherosclerosis Treatment Study
FER_{HDL} .................................. fractional esterification rate of cholesterol in HDL
FPG ........................................... fasting plasma glucose
Hey ......................................... homocyst(e)ine
HDL ................................. high density lipoprotein
HDL-C ............................... high density lipoprotein cholesterol
HERS .................................. Heart and Estrogen/progestin Replacement Study
HMG-CoA ...................... 3-hydroxy-3-methylglutaryl coenzyme A
HRT .................................. hormone replacement therapy
ICD .................................... International Classification of Diseases
IL-1 ................................. interleukin-1
LDL ................................. low density lipoprotein
LDL-C ............................... low density lipoprotein cholesterol
LIPID ................................. Long-term Intervention with Pravastatin in Ischemic Disease
LLD .................................. lipid lowering drugs
Lp(a) ................................. lipoprotein(a)
MI ..................................... myocardial infarction
MTHFR ............................. methylenetetrahydrofolate reductase
NCEP ................................. National Cholesterol Education Program
OxLDL ............................... oxidised LDL
PDGF ................................ platelet-derived growth factor
PTCA ................................. percutaneous transluminal coronary angioplasty
SBP .................................. systolic blood pressure
SCA ................................. selective coronary angiography
SMC ................................ smooth muscle cell
TC ................................. total cholesterol
TG ................................. triglycerides
VLDL ................................. very low density lipoprotein
WOSCOPS .......................... West of Scotland Coronary Prevention Study
LIST OF TABLES

Table 1. AHA classification of major, conditional, and predisposing risk factors ........ 5
Table 2. Risk assessment algorithm of the Canadian 2000 Guidelines.......................... 21
Table 3. Canadian 2000 Guidelines risk assignment for treatment decisions................ 22
Table 4. NCEP Guideline LDL-C thresholds for dietary and drug therapy.................... 25
Table 5. Mean lipid levels for respondent and deceased patient groups, separated by LLD use at baseline............................................................... 38
Table 6. Prevalence of baseline risk factors for non-respondent, respondent, and deceased patient groups.................................................................... 40
Table 7. Univariate analysis of lifestyle risk factors for CAD- and CAD+ groups......... 41
Table 8. Univariate analysis of lipid risk factors for CAD- and CAD+ groups.............. 42
Table 9. Multivariate logistic regression of CAD predictors........................................ 42
Table 10. Univariate analysis of CAD risk factors in women < 60 years...................... 43
Table 11. Univariate analysis of CAD risk factors in women ≥ 60 years....................... 44
Table 12. Multivariate analysis of CAD predictors in women < 60 and ≥ 60 .......... 44
Table 13. Proportion of non-respondents, respondents, and deceased patients taking medications at baseline................................................................. 45
Table 14. Self-reported medication usage of respondents at follow-up, with comparison to baseline prevalence ................................................................. 46
Table 15. Self-reported revascularization procedures and MI of respondents at follow-up ........................................................................................................... 47
Table 16. Variables predictive of all-cause mortality based on multivariate logistic regression........................................................................................................ 49
Table 17. Predictors of CV mortality based on multivariate logistic regression.......... 49
Table 18. Pearson's $\chi^2$ associations between risk factor counseling and reported change in risk factor behaviour................................................................. 54
Table 19. Proportion of respondents receiving appropriate dietary therapy with comparison between patients with high TC versus those with borderline high TC ....... 55
Table 20. Proportion of respondents receiving appropriate drug therapy with comparison between patients with high TC versus those with borderline high TC .............. 56

Table 21. Proportion of respondents receiving appropriate treatment according to CCCC guidelines .................................................................................................................. 56

Table 22. Proportion of respondents receiving appropriate treatment according to Canadian 2000 guidelines .................................................................................................................. 57

Table 23. Proportion of respondents receiving appropriate treatment according to NCEP guidelines .................................................................................................................. 59

Table 24. Variables predictive of appropriate treatment according to CCCC Guidelines .................................................................................................................. 59

Table 25. Variables predictive of appropriate treatment according to NCEP Guidelines .................................................................................................................. 60

Table 26. Variables showing regional variation on univariate analysis .............. 61

Table 27. Regional crossover effect of dietician counseling on self-reported low fat diet intake .................................................................................................................. 61

Table 28. Comparison of the prevalence of lipid risk factors found in CAD+ male respondents with the DVA-HIT cohort .................................................................................................. 67

Table 29. Comparison of type of anti-hypertensive reported at follow-up with baseline use .................................................................................................................. 77
LIST OF FIGURES

Figure 1. Response to injury hypothesis of atherogenesis ........................................ 3
Figure 2. Leading causes of death in British Columbia in 1998 ................................. 4
Figure 3. NCEP Guideline treatment algorithm for primary prevention .................. 24
Figure 4. NCEP Guideline treatment algorithm for secondary prevention ............ 25
Figure 5. Post-MI discharge medications in Canada in 1998 ................................. 27
Figure 6. Causes of death for 102 deceased cohort patients ................................. 48
Figure 7. Comparison of patient-reported weight change with actual weight change...... 51
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1 INTRODUCTION

1.1 CORONARY ARTERY DISEASE

1.1.1 Etiology

The major pathological process underlying coronary artery disease (CAD) is atherosclerosis. The pathogenesis of the atherosclerotic process leading to CAD is a complex interplay of both genetic factors, which define the limit under which atherosclerosis develops, and environmental influences, which impact a person's risk within the limit. These factors set in motion a process described by Russell Ross as the "response-to-injury hypothesis".

According to this theory, illustrated in Figure (1), the steps in atherosclerotic development begin with a mechanical or functional injury to the vascular endothelium, which leads to increased permeability to blood cells, lipoproteins, and certain hormones. Platelet aggregation occurs, with subsequent release of growth factors, such as platelet-derived growth factor (PDGF), and chemoattractants. This stimulates smooth muscle cell (SMC) proliferation and their migration, along with macrophages, into the subintima region where the fatty streaks and plaques of atherosclerosis develop. The SMC's form a fibrous cap over a lipid core. This core contains macrophages that have taken up oxidised low density lipoprotein (LDL) through an unregulated scavenger-receptor mediated process, at which point they are called foam cells. Rupture of the fibrous cap may occur, leading to thrombosis and partial or complete occlusion of the lumen. The clinical manifestation of this process may be unstable angina or non-fatal or fatal myocardial infarction (MI).

The presence of macrophages, together with T-lymphocytes, in the atherosclerotic plaque suggests an inflammatory reaction underlying the atherogenic process. Indeed, pathological as well as clinical evidence has demonstrated a link between inflammation and CAD morbidity and mortality. The concentration of inflammatory markers such as C-reactive protein (CRP)
have been shown to increase in active coronary syndromes such as unstable angina, thus leading to the conclusion that inflammation plays a central role in plaque development and progression\textsuperscript{4}.

In addition to plaque formation, vascular tone also modulates the pathology of atherosclerosis. In particular, endothelium-dependent vasodilation, a normal response to agonists such as acetylcholine, has been shown to be paradoxically altered to vasoconstriction in atherosclerotic coronary arteries\textsuperscript{6}. This endothelial dysfunction, which may be measured using brachial ultrasound, is thought to result from a reduction in the bioavailability of the vasodilator nitric oxide\textsuperscript{7}. 
Figure 1. Response to injury hypothesis of atherogenesis. A schematic of the steps of atherosclerotic plaque formation and subsequent rupture.²
1.1.2 Incidence and Costs

Coronary heart disease made up the greatest portion of all cardiovascular diseases (CVD) at 71%, and was the second leading cause of death in British Columbia in 1998, accounting for 25% of all deaths. Overall, diseases of the circulatory system were responsible for the greatest proportion of deaths in British Columbia in 1998 – 36% in total (Figure 2).

![Figure 2. Leading causes of death in British Columbia in 1998.](image)

The financial burden of CAD on society is felt through diagnostic procedures, medical interventions, lost work hours, and premature death. In 1993, CVD accounted for 15.3% of the total cost of all illnesses in Canada, or $19.7 billion. CAD accounted for $7.8 billion. Indirect costs such as mortality, short, and long-term disability made up two thirds of the economic impact of CAD. Mortality alone was responsible for $4.6 billion (59% of total cost of CAD). Of the direct costs, including hospital care, drugs, physician care expenditures, and research, hospital care made up 75.7% of the total, or $1.6 billion.
1.1.3 Risk Factors

CAD is a multi-factorial disease linked to several modifiable and non-modifiable "risk factors" – a term coined by the long-running Framingham Heart Study. These risk factors may be genetic, metabolic, or psychosocial in nature, and can be divided into three categories. Those risk factors that have a demonstrated independent relationship with CAD are "major" risk factors. Risk factors which have been shown to be associated with CAD, but the causal relationship has not been determined are known as "conditional". And finally, characteristics that worsen the impact of the major risk factors have been called "predisposing" risk factors.

Table (1) outlines the risk factors in each category.

| Table 1. AHA classification of major, conditional, and predisposing risk factors. |
|---------------------------------|---------------------------------|---------------------------------|
| **Major Risk Factors**          | **Conditional Risk Factors**    | **Predisposing Risk Factors**   |
| Cigarette smoking               | Elevated serum triglycerides    | Abdominal obesity               |
| Hypertension                    | Small LDL particles             | Family history of premature CAD |
| Obesity                         | Elevated serum homocysteine     | Ethnic characteristics          |
| Physical inactivity             | Elevated serum lipoprotein(a)   | Psychosocial factors (eg. depression) |
| Elevated serum total cholesterol and LDL-cholesterol | Prothrombotic factors (eg. fibrinogen) |                         |
| Low serum HDL-cholesterol       | Inflammatory markers (eg. C-reactive protein) |                      |
| Diabetes mellitus               |                                 |                                |
| Advancing age                   |                                 |                                |
The Canada Heart Health surveys, completed between 1985 and 1990 found that 33% of women and 41% of men between the ages of 18 and 74 had two or more major risk factors for CAD\textsuperscript{11}.

1.1.3.1 Major Risk Factors

The important role of several key risk factors in the development and progression of CAD has been supported by numerous studies. Smoking tobacco has been linked to profound alterations in vasomotion and platelet adhesion. It has been shown to substantially increase fibrinogen and carboxyhaemoglobin levels, while decreasing high density lipoprotein-cholesterol (HDL-C)\textsuperscript{12}. In Canada, it is responsible for more deaths due to cardiovascular disease than cancer. In 1996/97, 29% of individuals over the age of 15 smoked cigarettes, although the proportion of daily smokers decreased significantly beyond the age of 55\textsuperscript{8}.

The Framingham Study\textsuperscript{9} brought to light the significant impact of hypertension on CAD incidence rates. Individuals with isolated systolic hypertension were more than twice as likely to suffer acute MI than those with a blood pressure <160 mmHg/<95 mmHg. High blood pressure increases overall cardiovascular risk by 2 to 3 times\textsuperscript{13}. In Canada, 22% of individuals (26% of men and 18% of women) had high blood pressure in 1985-90, and diagnosis of hypertension increases with advancing age\textsuperscript{8}. Hypertension has been described as the most useful single factor in characterising CAD risk\textsuperscript{14}.

Diabetes not only increases the risk of developing CAD, but also adversely affects the outcome, with mortality rates significantly higher for individuals with diabetes\textsuperscript{8}. Men with diabetes were 56% more likely to manifest signs of CAD within a 24 year follow-up period than men without diabetes, while women with diabetes were over twice as likely to develop CAD over the same time period than disease-free females\textsuperscript{9}. In addition, Haffner et al\textsuperscript{15} showed that patients with diabetes and no previous evidence of CAD were at an equally high risk for CAD
morbidity and mortality as patients with previous MI, and thus required similarly aggressive treatment.

Obesity is yet another modifiable lifestyle risk factor for CAD. The relationship between obesity and CAD risk is most likely mediated through associations with increased blood pressure, hypertriglyceridaemia, impaired glucose tolerance, and lower levels of HDL-C\cite{16}. Obesity often results from a combination of high saturated fat intake and lack of physical activity.

Physical inactivity is detrimental not only through its role in promoting obesity, but also as an independent risk factor for CAD. Habitual sedentarianism has been linked to an increased risk of MI\cite{17}. Physical inactivity has been suggested to be as strong a risk factor for atherosclerosis as cigarette smoking, and has been linked to an increase in all-cause mortality\cite{18}.

A large number of both case-control\cite{19,20} and prospective epidemiological studies\cite{21} have shown that plasma lipids and lipoproteins play an important role in CAD development. In particular, elevated levels of total cholesterol (TC) and LDL-cholesterol (LDL-C), along with low levels of HDL-C represent major risk factors for the development of atherosclerosis\cite{22}, and thus form the basis of clinical guidelines aimed at reducing disease incidence and preventing cardiovascular morbidity and mortality\cite{23}. According to a Canadian health survey between 1985 and 1990, 45% of men and 43% of women had a TC greater than the desirable level of 5.2 mmol/L, with 18% and 17%, respectively, in the highest risk group with a TC > 6.2 mmol/L\cite{8}.

Elevated TC has been correlated with CAD morbidity and mortality, but not all patients who suffer from CAD events have high TC levels. The Framingham Study provided evidence to support the importance of employing the ratio of TC to HDL-C as a better marker of risk\cite{24}. The significance of depressed HDL-C levels even at moderate TC concentrations has important
implications for CAD prevention. A TC/HDL-C ratio greater than 5.0 for women and 5.5 for men was recommended as a prompt for lipid lowering therapy.

Non-modifiable risk factors for CAD include age and gender. As all major forms of cardiovascular disease increase with advancing age, it is the dominant risk factor for heart disease. Males have a higher risk of developing CAD, particularly at a younger age, although the incidence of CAD becomes equal between men and women in the sixth and seventh decade.

1.1.3.2 Conditional Risk Factors

The role of triglyceride (TG) levels in the development of atherosclerosis has been controversial for a number of years. While several studies have shown an association between CAD and TG, adjustment for HDL-C tends to attenuate the relationship. However, Stampfer et al showed TG levels to be independently predictive of MI in the Physicians' Health Study. The National Institutes of Health released a consensus statement acknowledging the variability of data and the lack of a causal link between elevated TG and disease. TG levels have been shown to carry more weight in certain populations of patients, particularly women and individuals with a high LDL-C/HDL-C ratio.

The fractional esterification rate of cholesterol in HDL, or FER_{HDL}, has been shown to reflect both LDL and HDL particle size. It is a measure of the ratio of cholesteryl esters produced by endogenous lecithin cholesterol acyltransferase to the amount of cholesterol remaining after incubation of radiolabeled plasma. The greater the FER_{HDL}, the higher the preponderance of small HDL and small, dense LDL particles - both conditional risk factors for CAD.

Homocysteine (Hcy) is an intermediate in the metabolic processing of methionine. This pathway requires the enzymes methylenetetrahydrofolate reductase (MTHFR) and cystathionine...
β-synthase (CBS) along with cofactors folate, vitamin B₆, and vitamin B₁₂. Mutations in the MTHFR or CBS genes have been shown to lead to increased plasma levels of Hcy, as have nutritional deficiencies in folate or the B vitamins³². Hcy levels over the norm of 10 μmol/L have been associated with CAD, peripheral vascular disease, and cerebrovascular disease³³. Proposed mechanisms by which elevated plasma Hcy levels may lead to premature atherosclerosis are a) endothelial injury, particularly through the formation of reactive oxygen species, b) association with coagulation factors, and c) interaction with LDL particles leading to internalisation of LDL by macrophages and the oxidation of lipids by subsequently released Hcy³².

Lipoprotein(a) (Lp(a)) particles consist of an LDL particle with a disulfide linkage between apolipoprotein B-100 (apoB) and apo(a)³³. Apo(a) has been demonstrated to have sequence homology to plasminogen, a precursor of the anticoagulant plasmin. As such, the association between elevated Lp(a) concentration and CAD may be related to competitive inhibition of plasminogen binding at the site of intravascular injury, and thus the loss of beneficial anticoagulation. Conversely, apo(a) binds to fibrin, which is found at the site of injury. This attraction of Lp(a) may serve to bring LDL cholesterol to the injured site, which is then taken up by macrophages to form foam cells³⁴. Lp(a) levels are genetically determined, and may vary between individuals over 1000-fold³⁵. However, levels greater than 0.20g/L have been associated with significantly increased risk of CAD³⁴. There is no treatment known to reduce Lp(a) levels, and thus it has been suggested that reduction of other CAD risk factors take precedence in patients with elevated Lp(a) concentration¹⁰.

Fibrinogen influences platelet aggregation and is a substrate for fibrin formation³⁶. A significant correlation between increased fibrinogen and CAD morbidity and mortality has been found in several studies³³. Plasma viscosity is increased by fibrinogen, and this has been
associated with a negative prognosis from acute MI and unstable angina\textsuperscript{36}. While no specific method to reduce fibrinogen has been discovered, it is known that smoking raises fibrinogen levels, but this can be reversed following smoking cessation\textsuperscript{10}.

The link between inflammation and atherosclerosis is believed to be through the macrophage-derived inflammatory mediator interleukin-1 (IL-1). The presence of IL-1 at the site of endothelial injury may generate procoagulation activity, thus transforming the typically nonthrombotic endothelium into a thrombogenic surface. C-reactive protein is an acute phase reactant induced by IL-1, and has been used as a marker of inflammation\textsuperscript{4}. Elevations of CRP have been found in patients with unstable angina, and like fibrinogen, are believed to indicate a poor prognosis\textsuperscript{36}.

While not specifically stated in the American Heart Association (AHA) classification of conditional risk factors, apolipoproteins have also been shown to be independently associated with CAD, although the causative relationship is unclear. The combination of lipid levels and lifestyle risk factors has only been able to explain half of the CAD incidence\textsuperscript{37}. As a result, researchers have examined the role of apolipoproteins - the protein moieties of lipoproteins - in CAD. ApoB, found on the surface of very low density lipoprotein (VLDL) and LDL particles, has been elevated in both men and women with CAD\textsuperscript{38,37}. Also, reduction of apo B through lipid lowering medications was independently correlated with angiographic regression in the Familial Atherosclerosis Treatment Study (FATS)\textsuperscript{39}. Small, dense LDL particles (pattern B) have been shown to be more atherogenic than large, buoyant LDL because they are more readily taken up by macrophages following oxidation\textsuperscript{24}. Because apo B concentration is believed to be a reflection of the LDL particle number, and the ratio of LDL-apoB/C has been shown to increase with the presence of the pattern B phenotype\textsuperscript{40}, determination of apoB level may represent a more accurate measurement of atherogenicity than LDL cholesterol content.
Reduced plasma concentrations of apolipoprotein AI (apo AI), the principal protein component of HDL molecules, have also been associated with CAD\textsuperscript{41,42}. Whether the predictive power of apo AI level on disease is greater than traditional lipid measurements remains controversial. However, studies have shown that HDL particles containing only apo AI on the surface (LpAI) are selectively reduced in normolipaemic patients with CAD\textsuperscript{43}. In addition, a preponderance of smaller HDL\textsubscript{3} particles, with fewer associated apo AI molecules, has been linked to CAD presence\textsuperscript{44}.

1.1.3.3 Predisposing Risk Factors

Predisposing lifestyle risk factors that contribute to the incidence of CAD include consuming a high saturated fat diet, abdominal obesity, and excessive alcohol intake. Animal studies of dietary effects on cholesterol levels were an early indicator that consuming saturated fats and cholesterol lead to elevated levels of TC and LDL-C\textsuperscript{45}. Epidemiological studies in humans have consistently demonstrated that CAD mortality is directly correlated with saturated fat intake\textsuperscript{46} and that reducing dietary consumption of saturated fats leads to a decrease in blood cholesterol levels\textsuperscript{16}. A diet high in saturated fats also contributes to the insulin resistance syndrome, a predisposing factor to both Type II diabetes and CAD\textsuperscript{47}.

The combination of a high fat diet and sedentarianism has lead to an increasing rate of obesity in North America. These metabolic effects are seen primarily with a pattern of fat distribution known as android obesity, which is characterised by central adiposity\textsuperscript{48}. Abdominal obesity, defined as a waist circumference in men $\geq 102$ cm or $\geq 88$ cm in women, has been linked to disturbances in lipoprotein metabolism and to insulin resistance, and heightens the risk of CAD in obese individuals\textsuperscript{49}.

The association between alcohol intake and CAD is complex. Some studies have shown that moderate alcohol intake, on the order of one to two drinks per day, reduces CAD morbidity
and mortality\textsuperscript{50-51}. Alcohol has been shown to raise HDL-C levels and lower LDL-C\textsuperscript{52} by increasing the synthesis and/or the secretion of apolipoproteins, lipids, and HDL molecules\textsuperscript{53}. However, it appears that excessive consumption of alcohol increases risk of CAD and all-cause mortality\textsuperscript{16}.

Non-modifiable risk factors also play a role in predisposing individuals to atherogenesis. Having a family history of premature heart disease in a first-degree relative (parent, sibling, aunt/uncle) confers increased risk for developing CAD\textsuperscript{54}. This association may be through either genetic or environmental effects, as lifestyle influences such as diet and level of physical activity may be imposed on all household members\textsuperscript{8}.

1.1.4 Treatment

Much of the medical research over the past decades has focussed on identification and treatment of CAD risk factors. Many benefits have been gained from these efforts, with a death rate in 1997 from cardiovascular disease that was half the rate in 1969\textsuperscript{8}. It has been suggested that the decline in CAD mortality may be attributed to lifestyle changes including low fat diets, exercise, and smoking cessation, as well as improved medical and surgical care for pre-existing disease.

1.1.4.1 Lifestyle Interventions

Meta-analysis of several research trials has demonstrated that exercise rehabilitation programs reduce CAD events, cardiac mortality, and overall mortality\textsuperscript{55}. Regular exercise lowers body weight and blood pressure, and can improve serum lipids and diabetes\textsuperscript{8}. Equally important, studies have shown that exercise counseling improves perceived quality of life, reduces depression, and leads to increased psychosocial adjustment\textsuperscript{56}.

Smoking cessation has been shown to reduce cardiovascular events in both primary and secondary prevention\textsuperscript{12}. While mechanisms of this positive effect have not been studied, it has
been proposed that the cessation of smoking returns previously perturbed proatherogenic factors to normal levels.

Several studies have shown that controlling hypertension with angiotensin converting enzyme (ACE) inhibitors, beta-blockers, or diuretics significantly reduces CAD mortality. Hypertension management also has an important role to play in the reduction of overall mortality and stroke. Treatment of hypertension has also been demonstrated to be of particular benefit to reducing CAD risk in patients with diabetes.

While no trials have shown definitive evidence that the appropriate control of blood sugar in patients with diabetes reduces CAD events, lipid lowering in these patients is important in preventing CAD complications.

1.1.4.2 Drug Therapies for CAD Event Reduction

A variety of non-lipid lowering medications have been linked to beneficial outcomes in primary and secondary prevention of CAD morbidity and mortality. Meta-analysis of several aspirin (ASA) trials demonstrated an overall reduction in stroke and MI of 30%, and a decrease of 24% in new vascular events with the administration of 300-325mg of ASA per day. The Physician's Health Study found a 44% reduction in MI with a low dose of 325mg ASA every other day. There are several proposed mechanisms for the beneficial role of ASA in primary and secondary prevention of CAD. Most significant is believed to be the antiplatelet effects of aspirin - the irreversible inhibition of platelet-dependent cyclooxygenase. In addition, ASA may impact on such contributory factors as haemostasis, atherogenesis, and fibrinolysis. As inflammation emerges as an important factor in atherosclerosis, the ability of ASA to modify this process also serves as a possible mechanism of action.

The incidence of CAD in women approaches that in men after menopause. The proposed theories for this increase have centred around the protective effects of oestrogen on
heart disease. Prospective and clinical trials into the efficacy of hormone replacement therapy (HRT) for reducing CAD risk have given contradictory results. Many observational and prospective studies, including one by Nabulsi et al\textsuperscript{67} have shown a strong association between HRT use and a favourable cardiovascular risk profile. HRT users were shown to have higher HDL-C, lower LDL-C, and lower levels of coagulation and thrombogenic factors associated with atherosclerotic disease. However, data from the Heart and Estrogen/progestin Replacement Study (HERS) randomised clinical trial\textsuperscript{68} contradict these results. While lipid changes observed in HERS patients were comparable to other studies, a similar association with fewer CAD events was not seen. This secondary prevention trial using conjugated equine oestrogen and progestin showed an increase in CAD and venous thromboembolic events in the first year, with a significant trend towards a subsequent reduction CAD risk over an additional three years. However, the overall reduction in cardiovascular risk with HRT never achieved significance.

Due to the significance of oxidised LDL in the development of atherosclerosis, much attention has turned to the role that antioxidants may play in preventing CAD. Oxidised LDL has many negative effects on the atherogenic process. It acts as a chemoattractant for circulating monocytes and leads to cytotoxic damage of endothelial cells. This endothelial damage results in aggregation of platelets and subsequent growth factor release\textsuperscript{2}. In addition, oxidised LDL is more readily taken up by macrophages than native LDL, leading to foam cell formation\textsuperscript{1}. Antioxidants such as vitamins E and C, as well as beta-carotene, have been studied to assess their ability to reduce CAD morbidity and mortality. While observational studies show an independent relationship between antioxidant use and lower CAD event risk\textsuperscript{69}, randomised clinical trials, including the HOPE study\textsuperscript{70} have not demonstrated a significant benefit for antioxidants\textsuperscript{71-72}. 

In addition to controlling hypertension, beta-blockers have been shown to reduce morbidity and mortality from CAD. The greatest benefit appears to be for patients who have survived the acute phase of a MI, with positive effects for lower risk individuals as well\textsuperscript{73}.

1.1.4.3 Lipid Lowering

Lipid lowering may be accomplished by many different treatment modalities, from diet, to drug, to surgical means. Results from diet intervention trials vary, and suggest that dietary modification of serum lipids are less potent than lipid lowering medications. The range of serum cholesterol lowering has been generally found on the order of 0\% to 13\%\textsuperscript{12,74}. The addition of exercise to diet modification has been shown to reduce TC and LDL-C by 23\%, and TG by 33\%\textsuperscript{75}. The possibility has been raised that the beneficial effect of reductions in fat consumption may extend beyond simply lowering blood cholesterol levels. For example, one study by Lorgeril et al\textsuperscript{76}, where dietary fat was reduced to 30\% of total caloric intake and mirrored a Mediterranean diet, showed no mean change in cholesterol levels but demonstrated a 63\% reduction in CAD events, along with significant reductions in cardiac and all-cause mortality.

Medications commonly used for reducing total and LDL cholesterol include niacin, bile acid binding resins, fibrates, and 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors, or "statins". Several large epidemiological studies have demonstrated a clear reduction in cardiovascular morbidity and mortality with drugs aimed at decreasing both TC and LDL-C, and benefits appear to be independent of initial TC levels\textsuperscript{12}. In addition to studies with dichotomous outcome variables, angiographic regression studies have also demonstrated the positive effect to lowering cholesterol levels\textsuperscript{39,77}, albeit with lesion regression measures seemingly out of proportion to cardiac event reduction. A very small level of plaque regression was associated with large reductions in CAD event rates.
The Coronary Drug Project trial\textsuperscript{78} was the first to demonstrate a beneficial effect of niacin on overall mortality in patients with previous MI, following a 15 year follow-up. Niacin was also shown to significantly reduce the incidence of nonfatal MI compared to the placebo group. However, due to a number of dermatological and gastrointestinal side effects, there was a higher dropout rate for study patients taking niacin compared to placebo\textsuperscript{79}.

Bile acid binding resins such as cholestyramine have been shown to lower cholesterol levels by preventing the reabsorption of cholesterol-derived bile acids in the small intestine. This leads to a subsequent upregulation of LDL receptors and increased uptake of LDL-C from the blood. The Lipid Research Clinics Coronary Primary Prevention Trial observed the effect of cholestyramine on lowering cholesterol in men and its role in primary prevention of CAD\textsuperscript{80}. Mean reductions in LDL-C of 13\% and in TC of 20\% lead to a 30\% reduction in CAD death.

Fibrates have been shown not only to lower LDL-C, but also raise HDL-C\textsuperscript{81}, and are the drug of choice in patients with hypertriglyceridaemia. The Helsinki Heart Study, which compared 600mg of gemfibrozil twice daily to placebo, showed a 34\% reduction in cardiac endpoints with a 10\% decrease in LDL-C and 10\% increase in HDL-C\textsuperscript{82}.

Statin trials in particular have shown significant reductions in cardiovascular events and mortality with concurrent decreases in all-cause mortality as well\textsuperscript{83}. Primary prevention trials such as West of Scotland Coronary Prevention Study (WOSCOPS)\textsuperscript{84} and Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS)\textsuperscript{85} have demonstrated reductions in risk of CAD events of 31-37\% with a TC lowering of approximately 20\% and LDL-C decrease of 25\%.

Preventing CAD morbidity and mortality with lipid lowering in patients with established CAD has been shown in such studies as Scandinavian Simvastatin Survival Study (4S)\textsuperscript{86}, Cholesterol and Recurrent Events (CARE)\textsuperscript{87}, and Long-term Intervention with Pravastatin in
Ischemic Disease (LIPID)\textsuperscript{88}. Reductions of 34\% in major coronary events and 30\% reduction in all-cause mortality were found with a 25\% decrease in total cholesterol and 35\% decrease in LDL-cholesterol in the 4S study\textsuperscript{86}. As a result of the overwhelming evidence for the superior efficacy, potency, and low incidence of side effects, statins have largely supplanted the other major lipid lowering medications as the drug of first choice\textsuperscript{89}.

While many of the lipid lowering medications have been proven effective in monotherapy, there is increasing evidence that combination therapy is a safe and practical method of treating dyslipidaemia in patients who do not respond as well to single drugs. Combinations of statins and fibrates\textsuperscript{90}, statins and niacin\textsuperscript{91}, as well as concurrent use of three or more different lipid lowering drugs have been shown to reduce TC, LDL-C, TG, and apoB while increasing HDL-C at a compound level greater than predicted for each individual medication\textsuperscript{92}.

1.2 PUBLISHED GUIDELINES FOR TREATMENT OF DYSLIPIDAEMIA

1.2.1 Canadian Consensus Conference on Cholesterol Guidelines

The Canadian Consensus Conference on Cholesterol (CCCC) Guidelines\textsuperscript{93} were released in a final report in 1988 as a response to strong evidence that treatment of dyslipidaemia decreased cardiovascular morbidity and mortality. The recommendations of the panel extended to who should be screened for lipid levels, what risk factors were important to consider, at what point diet and drug therapy should be initiated, and how these therapies should be properly administered.

1.2.1.1 Lipid Risk Factors and Testing Priorities

Based on evidence from a wide range of scientific studies, the CCCC concluded that high TC and LDL-C, along with low HDL-C and an elevated TC/HDL-C ratio were strong independent risk factors for atherosclerosis. They also stipulated that TG be measured both as an important risk factor in certain groups, and to allow calculation of LDL-C.
According to the CCCC Guidelines, the following patients should have lipid screening. Those with:

- Clinical evidence of CAD.
- Family history of premature CAD or hyperlipidaemia in a parent, grandparent, or sibling.
- Pre-existing conditions such as hypertension, diabetes, renal failure, and obesity, particularly abdominal obesity.

1.2.1.2 Dietary Therapy

Recommendations for intensive dietary therapy were made for two different age groups based primarily on TC levels, with consideration given to other lipid levels when TC was within a borderline elevated range.

The guiding principles of diet modification include reducing total fat intake to no more than 30% of total calories, with saturated fats not exceeding 10%. Intensive dietary therapy, as set out by the CCCC, must include dietician counseling. The following lipid levels necessitate diet intervention:

1. Adults ≥ 30 years
   - TC > 6.2mmol/L
   - TC = 5.2-6.2mmol/L +
     - LDL-C > 3.4mmol/L or
     - HDL-C < 0.9mmol/L or
     - TG > 2.3mmol/L

2. Adults 18-29 years
   - TC > 5.7mmol/L
   - TC = 4.6-5.7mmol/L +
     - LDL-C > 3.0mmol/L or
• HDL-C < 0.9mmol/L or
• TG > 2.3mmol/L

The desired treatment goal of the CCCC was to lower TC to 5.2mmol/L or less.

1.2.1.3 Drug Therapy

CCCC Guidelines stipulated that drug therapy should be implemented only after six months of dietary therapy fails to reduce TC to the target level. Many potential lipid-lowering drugs (LLD) were recommended, including combination therapies. All drug therapy was to be accompanied by continuation of dietary therapy. Studies have since shown that combining medication with a low fat diet enhanced favourable lipid changes, and in particular resulted in a significant increase in HDL-C levels\(^94\). It should be noted that the CCCC Guidelines were released prior to the favourable conclusions of the large clinical trials of HMG-CoA reductase inhibitors\(^84\)\(^-\)\(^86\). As such, drug therapy was viewed with more caution due to the failed reduction in all-cause mortality seen in fibrate, resin, and niacin trials\(^78\)\(^-\)\(^80\). More recent revisions to the Canadian guidelines have designated specific cholesterol levels for administration of drug treatment that are similar to those in the National Cholesterol Education Program guidelines.

1.2.1.4 Other Risk Factors

Based on epidemiological studies, the CCCC panel recommended counseling for several other CAD risk factors. They stipulated intervention on both an individual and population basis for cigarette smoking, hypertension, diabetes, obesity, and sedentary behaviour.

1.2.1.5 Canadian Guidelines 2000

In 2000, the Working Group on Hypercholesterolemia and Other Dyslipidemias published an updated series of recommendations for the treatment of dyslipidaemia\(^95\). In comparison to the 1988 CCCC Guidelines, the decision to treat is based on a multi-factorial risk
assessment, and target levels of LDL-C, TG, or the ratio of TC/HDL-C. A patient's risk of CAD is classified according to the algorithm shown in Table (2).
Table 2. Risk assessment algorithm of the Canadian 2000 Guidelines.95

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Risk points</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Men</td>
<td>Women</td>
<td></td>
</tr>
<tr>
<td>Age (yrs)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>30-34</td>
<td>-1</td>
<td>-9</td>
<td></td>
</tr>
<tr>
<td>35-39</td>
<td>0</td>
<td>-4</td>
<td></td>
</tr>
<tr>
<td>40-44</td>
<td>1</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>45-49</td>
<td>2</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>50-54</td>
<td>3</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>55-59</td>
<td>4</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>60-64</td>
<td>5</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>65-69</td>
<td>6</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>70-74</td>
<td>7</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>TC (mmol/L)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 4.14</td>
<td>-3</td>
<td>-2</td>
<td></td>
</tr>
<tr>
<td>4.15-5.17</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>5.18-6.21</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>6.22-7.24</td>
<td>2</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>≥ 7.25</td>
<td>3</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>HDL-C (mmol/L)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 0.90</td>
<td>2</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>0.91-1.16</td>
<td>1</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>1.17-1.29</td>
<td>0</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>1.30-1.55</td>
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<td>0</td>
<td></td>
</tr>
<tr>
<td>≥ 1.56</td>
<td>-2</td>
<td>-3</td>
<td></td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 120</td>
<td>0</td>
<td>-3</td>
<td></td>
</tr>
<tr>
<td>120-129</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>130-139</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>140-159</td>
<td>2</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>≥ 160</td>
<td>3</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Smoker</td>
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<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>2</td>
<td>2</td>
<td></td>
</tr>
</tbody>
</table>

**Add total risk points**

<table>
<thead>
<tr>
<th>Risk</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 10%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10%-20%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>20%-30%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;30%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Calculate 10 year risk**

<table>
<thead>
<tr>
<th>Risk</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 10%</td>
<td>≤ 5 points</td>
<td>≤ 9 points</td>
</tr>
<tr>
<td>10%-20%</td>
<td>≤ 8 points</td>
<td>≤ 14 points</td>
</tr>
<tr>
<td>20%-30%</td>
<td>≤ 10 points</td>
<td>≤ 17 points</td>
</tr>
<tr>
<td>&gt;30%</td>
<td>&gt; 10 points</td>
<td>&gt; 17 points</td>
</tr>
</tbody>
</table>
Treatment with lifestyle modifications or LLD is then based on the levels of certain important lipid parameters, given in Table (3). For patients at moderate or low risk, if lipid parameters are not lowered below treatment thresholds within a specific time frame, then LLD should be added to the regimen.

**Table 3. Canadian 2000 Guidelines risk assignment for treatment decisions.**

<table>
<thead>
<tr>
<th>Level of Risk</th>
<th>Treatment</th>
<th>LDL-C mmol/L</th>
<th>TC/HDL-C</th>
<th>TG mmol/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very High &gt; 30% or CAD+ or DM</td>
<td>LLD + diet</td>
<td>≥ 2.5</td>
<td>≥ 4</td>
<td>≥ 2.0</td>
</tr>
<tr>
<td>High 20%-30%</td>
<td>LLD + diet</td>
<td>≥ 3.0</td>
<td>≥ 5</td>
<td>≥ 2.0</td>
</tr>
<tr>
<td>Moderate 10%-20%</td>
<td>diet</td>
<td>≥ 4.0</td>
<td>≥ 6</td>
<td>≥ 2.0</td>
</tr>
<tr>
<td>Low &lt; 10%</td>
<td>LLD @ 3mos</td>
<td>≥ 5.0</td>
<td>≥ 7</td>
<td>≥ 3.0</td>
</tr>
</tbody>
</table>

Significant changes from the CCCC Guidelines include the classification of patients with diabetes as very high risk for the development of CAD, and the early initiation of LLD in high risk individuals. In addition, risk classification is made more relevant by taking into account gender differences in many of the risk factors.

1.2.2 **National Cholesterol Education Program Guidelines**

The American National Cholesterol Education Program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults released its second edition of recommendations for dyslipidaemia screening and treatment in JAMA in 1993. These guidelines took a more specific and strict stance on treatment of lipid risk factors for CAD.

Algorithms for diagnosis of hyperlipidaemia utilised multiple lipid measurements and risk factor assessment, and were different for primary and secondary prevention of CAD.
Classification of risk was based on TC, HDL-C, and number of other risk factors. Treatment decisions were then based on LDL-C levels.

The algorithm for primary prevention is found in Figure (3). CAD risk factors considered in the initial classification include:

- Men ≥ 45 years of age.
- Women ≥ 55 years of age or with premature menopause and no HRT.
- Family history of premature CAD in first degree relative.
- Smoking
- Hypertension
- Diabetes
- HDL-C < 0.9mmol/L

Negative risk factor: HDL-C ≥ 1.6mmol/L
Nonfasting Total Cholesterol and HDL Cholesterol
Assess Nonlipid Risk Factors

<table>
<thead>
<tr>
<th>TC &lt; 5.2 mmol/L</th>
<th>TC 5.2-6.2 mmol/L</th>
<th>TC ≥ 6.2 mmol/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>HDL-C ≥ 0.9 mmol/L</td>
<td>HDL-C &lt; 0.9 mmol/L</td>
<td>HDL ≥ 0.9 mmol/L &lt; 2RF</td>
</tr>
<tr>
<td>HDL &lt; 0.9 mmol/L ≥ 2RF</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Repeat TC &amp; HDL 5 yrs RF education</td>
<td>Diet &amp; Exercise counseling Repeat TC &amp; HDL 1 yr RF education</td>
<td>Fasting Lipid Analysis</td>
</tr>
</tbody>
</table>

Fasting LDL Cholesterol

<table>
<thead>
<tr>
<th>LDL-C &lt; 3.4 mmol/L</th>
<th>LDL-C 3.4-4.1 mmol/L &lt; 2RF</th>
<th>LDL-C 3.4-4.1 mmol/L ≥ 2RF</th>
<th>LDL-C ≥ 4.1 mmol/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>Repeat TC &amp; HDL 5 yrs RF education</td>
<td>Diet &amp; Exercise counseling Repeat TC &amp; HDL 1 yr RF education</td>
<td>Initiate appropriate therapy</td>
<td></td>
</tr>
</tbody>
</table>

Figure 3. NCEP Guideline treatment algorithm for primary prevention.23
The secondary prevention treatment guidelines are outlined in Figure (4). In the case of patients with clinical evidence of CAD, TC and HDL-C levels are not used to classify risk. High risk is initially assumed and a much stricter LDL-C is used to determine appropriate treatment.

<table>
<thead>
<tr>
<th>Fasting LDL Cholesterol</th>
<th>LDL-C ≤ 2.6mmol/L</th>
<th>LDL-C &gt; 2.6mmol/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diet &amp; Exercise counseling</td>
<td>Repeat TC &amp; HDL 1 yr</td>
<td>RF education</td>
</tr>
<tr>
<td>Initiate appropriate therapy</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Figure 4. NCEP Guideline treatment algorithm for secondary prevention.**

The appropriate therapy required by the NCEP Guidelines for primary and secondary prevention of CAD is listed in Table (4). Initiation levels for dietary and drug therapy are based on LDL-C levels.

**Table 4. NCEP Guideline LDL-C thresholds for dietary and drug therapy**

<table>
<thead>
<tr>
<th>Risk Classification</th>
<th>Dietary Therapy</th>
<th>Drug Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>No CAD + &lt; 2RF</td>
<td>≥ 4.1mmol/L</td>
<td>≥ 4.9mmol/L</td>
</tr>
<tr>
<td>No CAD + ≥ 2RF</td>
<td>≥ 3.4mmol/L</td>
<td>≥ 4.1mmol/L</td>
</tr>
<tr>
<td>CAD</td>
<td>&gt; 2.6mmol/L</td>
<td>≥ 3.4mmol/L</td>
</tr>
</tbody>
</table>

**1.3 PATIENT AWARENESS OF HEALTH**

The prevention and management of heart disease requires not only the intervention of health professionals and administration of medical treatments, but also the involvement of patients in their own care. Patients who are aware of their health risks and understand the
behaviours that place them in danger of suffering from CAD are more likely to take an active role in modifying such factors as diet, physical activity, smoking habits.

One important indication of patient health awareness is the accuracy with which individuals can report various physical measures. Self-reported anthropometric measurements such as weight and waist circumference have often been shown to deviate from reality\textsuperscript{96}. It has been suggested that patient awareness of weight and other measures of obesity may reflect a cultural bias and can be differentiated by gender\textsuperscript{97}. Some studies have demonstrated a tendency for obese individuals, particularly women, to underestimate their true weight\textsuperscript{98-99}, while others have concluded that self-reported weight is a reliable and accurate indicator of actual weight\textsuperscript{100}.

Along a similar vein, self-reporting of exercise and diet habits may be skewed towards perceived cultural ideals. A study by Lichtman et al\textsuperscript{101} showed that obese individuals were much more likely to under-report their caloric intake and overestimate their energy expenditure during physical activity. Adherence to an exercise program may be affected by such health beliefs as self-efficacy, perceived severity of disease, benefits of the exercise, and barriers that must be overcome\textsuperscript{102}, as well as physical characteristics such as high body fat and weight, smoking, and CAD symptom level\textsuperscript{103}.

Knowledge of CAD risk factors is an important determinant of patient health awareness. While knowledge of cardiovascular risk factors has improved in recent years\textsuperscript{104}, there are indications that women\textsuperscript{105} and less educated people\textsuperscript{106} may be uninformed regarding mortality and risk characteristics of CAD. One study examining the ability of participants drawn from active duty military personnel to identify important CAD risk factors showed that awareness ranged from 99\% for being overweight, to 73\% for elevated cholesterol levels, and 53.3\% for diabetes\textsuperscript{107}.
Awareness of personal risk for CAD is also vital in measuring health status. Of 1471 high risk individuals in a community-based cardiovascular risk reduction program, 73% knew their blood pressure, while only 15% knew their cholesterol level. However, an encouraging finding was that lack of risk status awareness did not correlate with self-initiated changes in lifestyle behaviours such as exercise and cholesterol reduction.

1.4 APPROPRIATE TREATMENT OF DYSLIPIDAEMIA

Except for age, dyslipidaemia is the most important predictor of CAD. The overwhelming evidence that lowering cholesterol levels prevents both primary and secondary CAD events, coupled with identification and treatment strategies for concurrent risk factors has led to the development of national guidelines for dyslipidaemia management. However, there is widespread evidence that treatment practices for CAD have been sub-optimal in Canada and around the world. Data from FastTrakII, a standardised quality assurance program implemented in over 100 hospitals in Canada, is shown in Figure (5). The gap between evidence-based recommendations and actual practice is seen in post-MI discharge medications.

![Discharge medications graph](image)

**Figure 5. Post-MI discharge medications in Canada in 1998.**
A study by the Clinical Quality Improvement Network (CQIN) investigators at four Canadian hospitals revealed drastic under-treatment of patients with a high one year risk for CAD events. Only 22% were prescribed diet therapy, and only 8% received lipid lowering medications. Moreover, only 28% had had a lipid assessment performed in the five years prior to their index hospitalisation.

A survey of Ontario physician practices with regard to CAD primary prevention showed that only one quarter started patients on drug therapy with a TC less than 6.22 mmol/L. This was by far less aggressive than seen in US physicians. But despite having stronger stated attitudes towards dyslipidaemia treatment, along with stricter guidelines, American physicians fare no better in treating their patients appropriately. Several studies show rates of only 28% to 50% compliance with NCEP guidelines. And of those patients prescribed the appropriate treatment, studies have shown that only one quarter to one third met the recommended LDL-C target. Additional data from Britain demonstrated an 82% rate of appropriate treatment for hypertension according to guidelines, compared to only 17% for dyslipidaemia. Finally, data from the HERS study revealed that only one-third of women with LDL-C levels over 4.1 mmol/L were receiving lipid lowering medications.

An additional problem in the treatment of dyslipidaemia is patient non-compliance with taking cholesterol-lowering medications as prescribed. While LLD must be taken for at least two years to show a reduction in CAD mortality, a study of the Saskatchewan Prescription Drug Plan showed that only 25% of patients were still taking their medication after one year. Factors such as side effects, rapport with doctors, and cost all decrease the chance of patient adherence.

Neither physicians nor patients have demonstrated adequate compliance to guidelines and recommendations for appropriate treatment. Public health information regarding the role of
cholesterol in heart disease has created confusion for both doctors and patients\textsuperscript{119}, which in turn has contributed to sub-optimal management of dyslipidaemia in BC and Canada.
1.5 **RATIONALE**

Death and disability from CAD is a major concern in Canada. Not only does atherosclerosis cost society a great deal financially, it also represents a significant burden on the emotional and psychological health of the people. As such, the prevention and treatment of this disease should be paramount in national health practices.

The evidence that treatment of dyslipidaemia and other risk factors for CAD reduces both morbidity and mortality is clear. Based on observational and prospective studies, basic science and clinical trials, guidelines for the diagnosis and management of dyslipidaemia and CAD risk have been drawn up and disseminated throughout North America. Despite all of this, numerous studies have indicated that appropriate treatment of patients with CAD or at risk of developing the disease is not given. Sub-optimal management of lipids using diet and medications is common. Interventions for other important risk factors such as smoking, exercise, diabetes, and hypertension are not being employed to the fullest potential.

The aim of this study was to determine the level of appropriate treatment in a population of British Columbians who have angiographic documentation as to the presence and severity of CAD. Furthermore, information was gathered on the prevalence of adjuvant therapies, risk factor counseling, and anthropometric measures to assess what characteristics impact morbidity and mortality, as well to predict appropriate management according to guidelines. The design of the study also allowed assessment of patient awareness of health status, often a crucial element of successful outcomes.

The knowledge gained from this research will provide insight into the treatment practices of British Columbia physicians. It will provide a basis for the education of patients and health professionals into better prevention strategies and management of cardiovascular health risks.
1.6 HYPOTHESIS

The majority of patients seen for angiography at St. Paul's and Vancouver General hospitals between 1993 and 1994 who required dyslipidaemia treatment and risk factor modification for the purpose of primary or secondary CAD prevention will not have received appropriate treatment according to published guidelines of the time.

1.7 SPECIFIC AIMS

1. To determine the appropriateness of treatment according to CCCC and NCEP guidelines in a population of angiographically defined British Columbians.

2. To establish the prevalence of CAD drug therapies such as ASA, anti-hypertensives, and HRT.

3. To ascertain the availability of risk factor counseling, including exercise, smoking cessation, and dietician interventions.

4. To assess patient awareness of health and health markers such as weight, change in exercise habits, and cholesterol levels.

5. To determine what lipid and lifestyle risk factors independently predict CAD morbidity and mortality.

6. To determine what lipid and lifestyle risk factors independently predict appropriate treatment.
2 METHODS

2.1 ORIGINAL COHORT SELECTION

A total of 1109 consecutive individuals, referred to two Vancouver teaching hospitals for selective coronary angiography (SCA), were recruited for the study between 1993 and 1995. At the time of their SCA, fasting blood samples were collected in ethylenediaminetetraacetic acid (EDTA), centrifuged, and the plasma aliquoted and stored at -70°C. On each sample, TC\textsuperscript{120}, TG\textsuperscript{121}, HDL-C\textsuperscript{122}, and apoB\textsuperscript{123} were measured as previously described. FER\textsubscript{HDL} was determined using an isotopic assay method\textsuperscript{124}. LDL-C was calculated using the Friedewald equation\textsuperscript{125} for individuals with TG less than 4.5 mmol/L.

Each angiogram was assessed semi-quantitatively by a cardiologist and scored as a) no evidence of narrowing in any vessel, or b) narrowing of either <50% or >50% in one, two, or three vessels. Patients in this study were considered to be angiographically positive for CAD whether they had less than or greater than 50% narrowing in at least one vessel. While this definition differs from that typically found in the literature, the reasoning behind it was that increasing evidence has shown that small plaques may contribute to cardiovascular morbidity and mortality more than large plaques\textsuperscript{126}. Additionally, by including patients with any degree of narrowing in the CAD positive group, it was hoped that misclassification due to subjective differences in diagnosis around the 50% mark could be avoided.

A two-page questionnaire (Appendix 1) regarding clinical and lifestyle variables was administered to every patient by a nurse or attending cardiologist. Questions were asked regarding smoking, drinking, and exercise habits. Measurements of height, weight, sitting blood pressure, and waist circumference were obtained. Previous history of cardiovascular disease, diabetes, hypertension, and renal insufficiency in both the patient and other family members was determined. Current medications were recorded from the patient's chart. This information was
entered into a database and double-checked for accuracy. All participants in this study signed a consent form approved by both university and hospital ethical review boards.

2.2 QUESTIONNAIRE DESIGN

The follow-up questionnaire (Appendix 2) was based closely on the original questionnaire given to patients at the time of angiography. Questions regarding smoking, exercise, and alcohol habits were taken word for word to ensure accurate comparison on these risk factor changes. Patients were asked to provide height and weight data, as well as an indication of whether their weight had changed in the intervening four years, in which direction, and by how much. Although waist circumference was measured at the original visit using the outdated World Health Organisation method of measuring maximum girth with the patient in the supine position, it was decided to have the patients repeat this form of measurement on follow-up. In this manner, determining the change in abdominal circumference would be more appropriate.

In order to assess appropriateness of treatment as well as patient awareness and involvement in their health care, individuals were asked if cholesterol had been measured in the past four years, the date of most recent measurement, and what the value was, if known. A similar question was asked regarding blood pressure and previous diagnosis of hypertension.

The prevalence of cardiovascular events and procedures was ascertained. Specifically, individuals were asked whether they had experienced percutaneous transluminal coronary angioplasty, coronary artery bypass graft, or myocardial infarction within the past four years since angiography.

It was felt to be important that the prevalence of risk factor counseling and the utilisation of paramedical staff in treatment practices be assessed. Thus, patients were asked whether they had been counseled on various lifestyle risk factors including smoking, cholesterol, diet, and
exercise. Additionally, the person who served as counselor - doctor, nurse, dietician, exercise or physical therapist, or family and friends was requested. The last choice was intended to learn of societal and community involvement in patient health care.

Medication information was requested. Patients were asked to supply type of medication, name, dose, and start date if known. Having this information self-reported caused concern regarding incomplete information, but this in itself would provide data on patient understanding of their illness and treatment.

Clinical and research scientists reviewed the questionnaire and provided feedback on its design, wording, and appropriateness. A group of volunteers filled out several questions on the questionnaire to assess readability and clarity, and modifications were made accordingly.

2.2.1 Ethics Approval

A cover letter introducing the study and an informed consent form were drafted according to guidelines set out by St. Paul's Hospital and the University of British Columbia. These were sent, along with the finalised questionnaire and a research proposal, to the Ethics Committees from both institutions. Approval was granted by the University of British Columbia Behavioural Research Services review board and the St. Paul's Hospital Ethics Committee. Additional ethics approval was obtained from Vancouver General Hospital to allow access to health records for data acquisition and confirmation.

2.3 MAIL-OUT

Record matching was attempted through the British Columbia Cardiac Registry to obtain vital status and most recent mailing addresses. Matches were made for 1027 individuals. Ninety-seven were known to be deceased as of December 31, 1997. The remaining individuals were mailed a questionnaire accompanied by a cover letter explaining the nature of the study, and two copies of an ethics board approved informed consent. Potential participants were to sign
both copies of the informed consent, and return one copy along with the completed questionnaire. A self-addressed, stamped envelope was provided for this purpose. Patients who had not responded within two weeks of mail-out were contacted by phone. Any concerns they had about the questionnaire were addressed, and they were encouraged to complete and return the forms. Envelopes returned unopened and incorrect phone numbers were checked using hospital databases and Internet search engines to find a current address. A second mail-out was sent to non-responders in August 1999. Again, follow-up phone calls were made after two weeks to encourage participation.

Patient returns were matched with the original information based on name, date of birth, and PHN number. They were assigned the same lab identification given to their original blood sample. Eight returns matched for name, but not for birth date or personal health number. These patients were considered lost to follow-up and the questionnaires were destroyed. An Access 97 database was designed to capture the data from the returned questionnaires. Data was entered as questionnaires were returned and hard copies of the consent form and questionnaire were collated and filed.

2.4 VITAL STATISTICS INFORMATION

Once the mail-out was complete, and all responders had returned their questionnaires, the British Columbia Vital Statistics Agency was contacted. Patient identifying information was sent for all individuals, including those known to be deceased. Matches were made for 102 individuals for whom we obtained cause of death, indicated by International Classification of Diseases (ICD)-9 codes. There was some concern that 35 of the patients listed as deceased on the BCCR did not match with the Vital Statistics database. However, the BCCR information was assumed to be correct, given the possibility that there may have been a problem with the
linkage to the Vital Statistics database because PHN numbers were not available for those patients.

2.5 MEDICAL RECORDS

Permission was obtained from both St. Paul's Hospital and Vancouver General Hospital to review health records on the cohort. A random sample of records were requested and reviewed at the respective hospitals every week. In total, 129 patients with 223 discharges since 1994 were reviewed at St. Paul's Hospital and 95 patients with 165 discharges at Vancouver General Hospital.

The information collected from the medical chart included history of diabetes, smoking, renal insufficiency, peripheral vascular disease, or stroke. Incidence of percutaneous transluminal coronary angioplasty (PTCA), coronary artery bypass graft (CABG), MI, unstable angina, congestive heart failure, and other cardiovascular morbidities was recorded in order to confirm information given by patient report. Frequency of measurement and value was obtained for blood pressure and lab measurements, including TC, LDL-C, HDL-C, TG, and glucose where available. Evidence of counseling by dieticians or physiotherapists was also noted.

2.6 STATISTICAL ANALYSIS

Statistical analysis was performed using SPSS 8.0 software. Differences between categorical variables, given as percentages, were determined using a Chi-square test. In the case of multiple comparisons between three groups - non-respondents, respondents, and deceased - a Bonferroni correction was applied. Continuous variables were assessed using Student's t-test and results are given as means ± standard error of the mean. Analysis of changes in medication usage was assessed using the McNemar test for change. Predictors of morbidity, mortality, and appropriate treatment were determined using stepwise Logistic Regression. Significance for all tests was defined as p ≤ 0.05, and all analyses were two-tailed.
3 RESULTS

3.1 RESPONSE RATE

A total of 1109 patients were recruited in the initial angiography study. Using original questionnaires and hospital databases, addresses were found for 1027 individuals. Linkage with the British Columbia Cardiac Registry database revealed that 97 of the 1027 patients were deceased as of December 31, 1997. Thus, 930 questionnaires were mailed out in two mailings with follow-up phone calls to encourage response.

One hundred and thirty-eight questionnaires were returned unopened, and correct addresses could not be found using every means available. Ultimately, 314 completed questionnaires were returned. Either through returned letters, telephone calls, or subsequent Vital Statistics record linkage, an additional 53 subjects were determined to have died since December 1997. However, five of the patients listed by Vital Statistics as deceased had died after responding to the questionnaire. Thus in total, there were 314 respondents, 430 non-respondents, and 150 deceased patients from the original cohort, with 220 lost to follow-up.

Response rate = \frac{\text{respondents}}{\text{original cohort} - \text{lost to follow-up} - (\text{deceased} - \text{prior respondents})}

Response rate = \frac{314}{1109-220-(150-5)} = \frac{314}{744} = 42\%

3.2 BASELINE CHARACTERISTICS

3.2.1 Demographics

Of the 314 respondents, 237 were males (75%). Males made up 73% of the deceased group. This was not significantly different from the proportion of males among non-responders (72%). Eighty-one percent of follow-up patients had positive angiograms at their initial visit (CAD+), compared with 87% of deceased patients. There was a significantly smaller proportion
of non-responders with CAD than among responders (75%; p≤0.05). This may be explained by the possibility that CAD- individuals may not have seen the need to participate in the study. Patients with negative SCA were included, however, in order to determine risk factor prevalence and treatment in the context of primary prevention as well as secondary prevention. The average age of male respondents was 60.9±0.6 years, of females was 64.4±1.1 years (p≤0.01).

3.2.2 Lipid Profile

The mean lipid levels at baseline for respondents and deceased patients are given in Table (5). There were no significant differences in the initial lipid parameters comparing non-respondents to deceased or respondents. Means are separated for those taking LLD at baseline and those not on medications.

Table 5. Mean lipid levels for respondent and deceased patient groups, separated by LLD use at baseline.

<table>
<thead>
<tr>
<th></th>
<th>Respondents</th>
<th></th>
<th>Deceased</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>LLD- (n=256)</td>
<td>LLD+ (n=58)</td>
<td>LLD- (n=131)</td>
<td>LLD+ (n=15)</td>
</tr>
<tr>
<td>TC (mmol/L)</td>
<td>5.19±0.08</td>
<td>4.96±0.12</td>
<td>5.15±0.10</td>
<td>4.99±0.30</td>
</tr>
<tr>
<td>TG (mmol/L)</td>
<td>1.82±0.08</td>
<td>2.13±0.18</td>
<td>1.76±0.09</td>
<td>1.47±0.16</td>
</tr>
<tr>
<td>LDL-C (mmol/L)</td>
<td>3.63±0.07</td>
<td>3.20±0.11*</td>
<td>3.70±0.09</td>
<td>3.56±0.26</td>
</tr>
<tr>
<td>HDL-C (mmol/L)</td>
<td>0.96±0.02</td>
<td>0.97±0.03</td>
<td>0.95±0.02</td>
<td>0.97±0.09</td>
</tr>
<tr>
<td>TC/HDL</td>
<td>5.70±0.13</td>
<td>5.41±0.21</td>
<td>5.71±0.16</td>
<td>5.54±0.50</td>
</tr>
<tr>
<td>FERHDL</td>
<td>23.76±0.53</td>
<td>25.11±1.05</td>
<td>22.60±0.75</td>
<td>22.91±2.00</td>
</tr>
<tr>
<td>ApoB (g/L)</td>
<td>0.97±0.02</td>
<td>0.92±0.03</td>
<td>0.98±0.02</td>
<td>0.95±0.06</td>
</tr>
</tbody>
</table>

Values given as mean ± standard error of the mean. Comparison between groups for TG was based on logarithmically transformed values.
* Significantly lower than LLD- respondents (p≤0.005)
3.2.3 **Risk Factor Prevalence**

Table (6) outlines the prevalence of risk factors at baseline for non-respondents, respondents, and deceased patients. It should be noted that five of the respondents subsequently died, and these patients have been included in both the respondent and deceased groups.

Advanced age as a risk factor reflected men ≥ 45 years or women ≥ 55 years\(^{23}\). Hypertension was defined as a systolic blood pressure (SBP) ≥ 140mmHg and a diastolic blood pressure (DBP) ≥ 90mmHg, or taking anti-hypertensive medications\(^ {127}\). Overall obesity reflected a body mass index (BMI) greater than or equal to 30 kg/m\(^2\) or an abdominal girth greater than 102cm in men or 88cm in women\(^ {10}\). Elevated TC was defined as TC > 5.2 mmol/L, elevated LDL-C was > 3.4 mmol/L, and low HDL-C was < 0.9 mmol/L\(^ {23}\). Elevated TG reflected the CCCC guideline level of risk of ≥ 2.3 mmol/L\(^ {93}\). FER\(_{HDL}\) was used as a marker of small, dense LDL particles. Individuals with an FER\(_{HDL}\) greater than the 95th percentile (> 17.97 for women, > 25.80 for men) were designated as having this conditional risk factor\(^ {128}\). Abdominal obesity as a predisposing risk factor was defined as a waist circumference of greater than 102cm in men or greater than 88cm in women\(^ {129}\).
Table 6. Prevalence of baseline risk factors for non-respondent, respondent, and deceased patient groups.

<table>
<thead>
<tr>
<th>Classification</th>
<th>Risk Factor</th>
<th>Non-respondents (n=430)</th>
<th>Respondents (n=314)</th>
<th>Deceased (n=150)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major</td>
<td>Men ≥ 45</td>
<td>88% (n=310)</td>
<td>93% (n=237)</td>
<td>94% (n=109)</td>
</tr>
<tr>
<td></td>
<td>Women ≥ 55</td>
<td>78% (n=120)</td>
<td>88% (n=77)</td>
<td>83% (n=41)</td>
</tr>
<tr>
<td></td>
<td>Current smokers</td>
<td>18% (n=425)</td>
<td>7%(^a) (n=307)</td>
<td>21% (n=145)</td>
</tr>
<tr>
<td></td>
<td>Former smokers</td>
<td>51%(^b) (n=425)</td>
<td>64% (n=307)</td>
<td>57% (n=145)</td>
</tr>
<tr>
<td></td>
<td>Hypertension</td>
<td>38%</td>
<td>37%</td>
<td>35%</td>
</tr>
<tr>
<td></td>
<td>Diabetes</td>
<td>17%</td>
<td>16%</td>
<td>18%</td>
</tr>
<tr>
<td></td>
<td>Obesity</td>
<td>51% (n=429)</td>
<td>49% (n=311)</td>
<td>48% (n=145)</td>
</tr>
<tr>
<td></td>
<td>Physical inactivity</td>
<td>10% (n=420)</td>
<td>8% (n=305)</td>
<td>15% (n=142)</td>
</tr>
<tr>
<td></td>
<td>Elevated TC</td>
<td>44% (n=423)</td>
<td>43%</td>
<td>40% (n=146)</td>
</tr>
<tr>
<td></td>
<td>Elevated LDL-C</td>
<td>55% (n=418)</td>
<td>56% (n=312)</td>
<td>54% (n=146)</td>
</tr>
<tr>
<td></td>
<td>Low HDL-C</td>
<td>45% (n=423)</td>
<td>42% (n=313)</td>
<td>45% (n=146)</td>
</tr>
<tr>
<td>Conditional</td>
<td>Elevated TG</td>
<td>23% (n=423)</td>
<td>21%</td>
<td>19% (n=146)</td>
</tr>
<tr>
<td></td>
<td>Elevated FER(_{HDL})</td>
<td>45% (n=423)</td>
<td>45% (n=313)</td>
<td>41% (n=146)</td>
</tr>
<tr>
<td>Predisposing</td>
<td>Abdominal obesity</td>
<td>48% (n=403)</td>
<td>44% (n=294)</td>
<td>50% (n=127)</td>
</tr>
<tr>
<td></td>
<td>Family history</td>
<td>44%</td>
<td>48%</td>
<td>41%</td>
</tr>
</tbody>
</table>

For variables with missing data, the total number of individuals is given in brackets and the prevalence is a percentage of this number.

\(^a\) Significantly lower than non-respondents and deceased (p<0.001)

\(^b\) Significantly lower than respondents (p<0.001)

3.2.3.1 Subgroup analyses

(The first set of results makes up a portion of the paper: Francis MC, Frohlich JJ.)

Coronary artery disease in patients at low risk - apolipoprotein AI as an independent risk factor. Atherosclerosis. In press.)\(^{130}\)

Two subgroup analyses were performed on the original cohort. The first was to determine the lipid and lifestyle risk factors that predicted CAD in those patients without any of the major risk factors. Individuals with TC < 5.2 mmol/L, HDL-C > 0.9 mmol/L, SBP < 140 mmHg and DBP < 90 mmHg, no diabetes, and no family history of premature CAD in first degree relatives were selected. Preliminary analysis indicated that apo AI was significantly
lower in patients with positive angiograms. Fifty-four patients met the selection criteria, 29 having positive evidence of CAD (CAD+) and 25 with no SCA evidence of disease (CAD-).

Chi-square analysis of gender in CAD+ and CAD- patients revealed a significantly greater number of females in the control group. Therefore, all further univariate analyses of risk factors included an adjustment for gender. Because apoAI concentration is known to vary with age in females but not in males, and since we were adjusting for gender, we felt it important to adjust for age as well.

Table (7) shows the results of logistic regression analysis for all lifestyle risk factors. The only variable showing a significant difference between patients with CAD and those without was gender, as expected.

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>CAD- (n=25)</th>
<th>CAD+ (n=29)</th>
<th>Univariate p</th>
<th>Adjusted p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td>≤0.001</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>44%</td>
<td>86%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>56%</td>
<td>14%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (yr)</td>
<td>58.9±2.22</td>
<td>63.8±2.49</td>
<td>ns</td>
<td></td>
</tr>
<tr>
<td>Waist (cm)</td>
<td>76.1±7.3</td>
<td>82.9±5.6</td>
<td>ns</td>
<td>ns</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>25.2±0.9</td>
<td>25.9±0.9</td>
<td>ns</td>
<td>ns</td>
</tr>
<tr>
<td>Smoking</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>52%</td>
<td>21%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Past</td>
<td>40%</td>
<td>62%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current</td>
<td>8%</td>
<td>14%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Logistic regression of each lipid variable with adjustment for age and gender is shown in Table (8). A lower apoAI concentration in CAD+ individuals was the strongest factor associated with CAD (p ≤ 0.001), while a lower LDL-C and higher FERHDL were also significant. Higher TG concentration in CAD+ patients was of borderline significance. Of the parameter ratios examined, the ratio of apoB/apoAI showed a significant relationship with the presence of disease.
Table 8. Univariate analysis of lipid risk factors for CAD- and CAD+ groups.

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>CAD- (n=25)</th>
<th>CAD+ (n=29)</th>
<th>Univariate p</th>
<th>Adjusted p</th>
</tr>
</thead>
<tbody>
<tr>
<td>TC (mmol/L)</td>
<td>4.67±0.08</td>
<td>4.39±0.09</td>
<td>≤0.05</td>
<td>ns</td>
</tr>
<tr>
<td>TG (mmol/L)</td>
<td>1.30±0.11</td>
<td>1.63±0.15</td>
<td>ns</td>
<td>≤0.05</td>
</tr>
<tr>
<td>HDL-C (mmol/L)</td>
<td>1.21±0.05</td>
<td>1.10±0.03</td>
<td>≤0.05</td>
<td>ns</td>
</tr>
<tr>
<td>LDL-C (mmol/L)</td>
<td>3.48±0.09</td>
<td>3.07±0.12</td>
<td>≤0.01</td>
<td>≤0.05</td>
</tr>
<tr>
<td>Apo B (mg/dL)</td>
<td>83.8±3.2</td>
<td>83.4±2.9</td>
<td>ns</td>
<td>ns</td>
</tr>
<tr>
<td>Apo AI (mg/dL)</td>
<td>135.4±6.5</td>
<td>111.1±3.0</td>
<td>≤0.002</td>
<td>≤0.001</td>
</tr>
<tr>
<td>FER_{HDL}</td>
<td>15.56±1.24</td>
<td>19.08±1.10</td>
<td>≤0.05</td>
<td>≤0.01</td>
</tr>
<tr>
<td>TC/HDL-C</td>
<td>3.97±0.14</td>
<td>4.09±0.14</td>
<td>ns</td>
<td>ns</td>
</tr>
<tr>
<td>Apo B/Apo AI</td>
<td>0.66±0.05</td>
<td>0.77±0.04</td>
<td>ns</td>
<td>≤0.05</td>
</tr>
</tbody>
</table>

Forward stepwise logistic regression was used to build a model of predictors for CAD in this cohort of patients free from major risk factors. Results are shown in Table (9). The only variables found to associate with disease presence were gender, age, and apoAI concentration. Risk factors believed to be potential confounders for the effect of apoAI were also tested using logistic regression.

Table 9. Multivariate logistic regression of CAD predictors.

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>OR</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender*</td>
<td>0.14</td>
<td>≤0.02</td>
</tr>
<tr>
<td>Age</td>
<td>1.14</td>
<td>≤0.01</td>
</tr>
<tr>
<td>Apo AI</td>
<td>0.94</td>
<td>≤0.002</td>
</tr>
</tbody>
</table>

* Males coded as 0, females coded as 1.

The association of reduced levels of apoAI with CAD presence remained significant after adjusting for FER_{HDL}, HDL-C, TG, LDL-C, and use of medications such as beta-blockers or LLD (data not shown). Insulin/glucose ratio did not confound the effect of apoAI concentration, nor did waist circumference, BMI, or smoking (data not shown).
The second subgroup analysis was undertaken to test the hypothesis that different risk factors would be associated with CAD in women $\geq 60$ compared to women younger than 60.

From the original cohort, all women who had been referred for their first angiography and had no history of taking LLD were selected. Of these 203 women, 76 were $< 60$ years of age, and 127 were $\geq 60$ (62%).

Univariate analysis of CAD risk factors for younger women is presented in Table (10). Some lipid parameters were significantly associated with CAD when analysed individually. However, when adjustment was made for the contribution of smoking, the effects were eliminated.

### Table 10. Univariate analysis of CAD risk factors in women $< 60$ years.

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>CAD- (n=43)</th>
<th>CAD+ (n=33)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>50.4±1.1</td>
<td>52.2±1.4</td>
<td>ns</td>
</tr>
<tr>
<td>Menopause</td>
<td>47%</td>
<td>64%</td>
<td>ns</td>
</tr>
<tr>
<td>Family history</td>
<td>47%</td>
<td>64%</td>
<td>ns</td>
</tr>
<tr>
<td>Hypertension</td>
<td>26%</td>
<td>21%</td>
<td>ns</td>
</tr>
<tr>
<td>Diabetes</td>
<td>5%</td>
<td>24%</td>
<td>$\leq 0.01$</td>
</tr>
<tr>
<td>Waist (cm)</td>
<td>80.4±4.4</td>
<td>82.5±5.4</td>
<td>ns</td>
</tr>
<tr>
<td>BMI (kg/m$^2$)</td>
<td>27.2±0.8</td>
<td>27.2±1.1</td>
<td>ns</td>
</tr>
<tr>
<td>Smoking</td>
<td>(n=41)</td>
<td>(n=32)</td>
<td>$\leq 0.01$</td>
</tr>
<tr>
<td>Never</td>
<td>54%</td>
<td>22%</td>
<td></td>
</tr>
<tr>
<td>Former</td>
<td>34%</td>
<td>34%</td>
<td></td>
</tr>
<tr>
<td>Current</td>
<td>12%</td>
<td>38%</td>
<td></td>
</tr>
</tbody>
</table>

Univariate analysis of CAD predictors in women $\geq 60$ years showed that no lifestyle risk factors were associated with positive SCA, other than age. However, several lipid risk factors were related to CAD in older women, even after adjustment for smoking. These results are shown in Table (11).
Table 11. Univariate analysis of CAD risk factors in women ≥ 60 years.

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>CAD- (n=62)</th>
<th>CAD+ (n=63)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>67.8±0.7</td>
<td>70.6±0.7</td>
<td>≤0.01</td>
</tr>
<tr>
<td>TC (mmol/L)</td>
<td>5.20±0.12</td>
<td>5.56±0.11</td>
<td>≤0.05</td>
</tr>
<tr>
<td>TG (mmol/L)*</td>
<td>1.39±0.08</td>
<td>1.87±0.12</td>
<td>≤0.0001</td>
</tr>
<tr>
<td>LDL-C (mmol/L)</td>
<td>3.72±0.12</td>
<td>3.97±0.10</td>
<td>ns</td>
</tr>
<tr>
<td>HDL-C (mmol/L)</td>
<td>1.17±0.04</td>
<td>1.11±0.04</td>
<td>ns</td>
</tr>
<tr>
<td>TC/HDL-C</td>
<td>4.69±0.18</td>
<td>5.35±0.20</td>
<td>≤0.05</td>
</tr>
<tr>
<td>Apo B (g/L)†</td>
<td>0.94±0.03</td>
<td>1.03±0.03</td>
<td>≤0.05</td>
</tr>
<tr>
<td>FERHDL</td>
<td>17.27±0.87</td>
<td>19.03±0.89</td>
<td>ns</td>
</tr>
</tbody>
</table>

* All analyses performed on logarithmically transformed values.
† n=60 for CAD- group, n=62 for CAD+ group.

Multivariate analysis of predictors (Table 12) revealed that diabetes and smoking were the sole variables associated with CAD presence in younger women. In older women, stepwise logistic regression of all variables showed that only advancing age and elevated triglycerides predicted disease.

Table 12. Multivariate analysis of CAD predictors in women < 60 and ≥ 60.

<table>
<thead>
<tr>
<th>Predictor</th>
<th>WOMEN &lt; 60</th>
<th>OR</th>
<th>p value</th>
<th>WOMEN ≥ 60</th>
<th>Predictor</th>
<th>OR</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes</td>
<td></td>
<td>26.7</td>
<td>≤0.001</td>
<td>TG</td>
<td>15.7</td>
<td>≤0.01</td>
<td></td>
</tr>
<tr>
<td>Smoking</td>
<td></td>
<td></td>
<td></td>
<td>Age</td>
<td>1.1</td>
<td>≤0.05</td>
<td></td>
</tr>
<tr>
<td>Former vs never</td>
<td>3.4</td>
<td>ns</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current vs never</td>
<td>16.4</td>
<td>≤0.001</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

3.2.4 Medication Usage

Table (13) details the baseline medications of the cohort. HRT prevalence is given as a percentage of women, while cholesterol medication types are shown as a percentage of those taking LLD.
Table 13. Proportion of non-respondents, respondents, and deceased patients taking medications at baseline.

<table>
<thead>
<tr>
<th>Medication</th>
<th>Non-Respondents (n=430)</th>
<th>Respondents (n=314)</th>
<th>Deceased (n=150)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin</td>
<td>65%</td>
<td>71%</td>
<td>61%</td>
</tr>
<tr>
<td>HRT</td>
<td>23% (n=120)</td>
<td>18% (n=77)</td>
<td>17% (n=41)</td>
</tr>
<tr>
<td>Antioxidants</td>
<td>3%&lt;sup&gt;a&lt;/sup&gt;</td>
<td>9%</td>
<td>5%</td>
</tr>
<tr>
<td>Beta-blockers</td>
<td>47%</td>
<td>49%</td>
<td>47%</td>
</tr>
<tr>
<td>ACE inhibitors</td>
<td>16%</td>
<td>18%</td>
<td>29%&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Ca-channel blockers</td>
<td>37%</td>
<td>39%</td>
<td>36%</td>
</tr>
<tr>
<td>LLD</td>
<td>17%</td>
<td>18%</td>
<td>11%</td>
</tr>
<tr>
<td>Statins</td>
<td>73% (n=71)</td>
<td>82% (n=51)</td>
<td>85% (n=13)</td>
</tr>
<tr>
<td>Fibrates</td>
<td>18% (n=71)</td>
<td>16% (n=51)</td>
<td>15% (n=13)</td>
</tr>
<tr>
<td>Combination Rx</td>
<td>4% (n=71)</td>
<td>2% (n=51)</td>
<td>--</td>
</tr>
</tbody>
</table>

<sup>a</sup> Significantly lower than respondents (p≤0.002)  
<sup>b</sup> Significantly lower than non-respondents and respondents (p≤0.005)

3.3 FOLLOW-UP CHARACTERISTICS

3.3.1 Changes in Risk Factor Prevalence

Fifty percent of respondents had hypertension at follow-up, either because they acknowledged taking anti-hypertensives, or reported that their SBP was ≥ 140mmHg and their DBP was ≥ 90mmHg. This is a significant increase over the number of respondents with hypertension at baseline (37%; p≤0.001).

There were significantly fewer obese individuals at follow-up (39% vs 49%; p≤0.025). Obesity could not be assessed in one respondent due to missing information about waist circumference and weight on the returned questionnaire. It is important to note that both abdominal girth and weight were self-reported at follow-up, and thus there may be underestimation errors in the given values (see section 1.3). This may partially explain the significant decrease in the number of obese individuals at follow-up. There was no significant
difference in the number of respondents who reported being abdominally obese on the questionnaire compared to baseline prevalence.

The only other lifestyle risk factor to change significantly over the intermediary four years was incidence of diabetes. Twenty-three percent (72) of respondents had diabetes at follow-up, compared to 16% (51) at baseline ($p \leq 0.05$).

3.3.2 Changes in Medication Usage

Self-reported medications at follow-up are given in Table (14), with baseline percentages provided for reference. The McNemar test for change was used to compare proportions to baseline values, and $p$-values can be found in the table. This test analyses the change in medication usage for those patients with information available at both baseline and follow-up. The number of available subjects for each drug is given in parentheses, and the prevalence is a percentage of this total.

<table>
<thead>
<tr>
<th>Medication</th>
<th>Baseline</th>
<th>Follow-up</th>
<th>$p$-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASA (n=314)</td>
<td>71%</td>
<td>86%</td>
<td>$\leq 0.001$</td>
</tr>
<tr>
<td>HRT (n=77)</td>
<td>14%</td>
<td>17%</td>
<td>ns</td>
</tr>
<tr>
<td>Antioxidants (n=220)</td>
<td>9%</td>
<td>45%</td>
<td>$\leq 0.001$</td>
</tr>
<tr>
<td>Beta-blockers (n=189)</td>
<td>50%</td>
<td>58%</td>
<td>$\leq 0.05$</td>
</tr>
<tr>
<td>ACE inhibitors (n=189)</td>
<td>23%</td>
<td>39%</td>
<td>$\leq 0.001$</td>
</tr>
<tr>
<td>Ca-channel blockers (n=189)</td>
<td>39%</td>
<td>46%</td>
<td>ns</td>
</tr>
<tr>
<td>LLD (n=314)</td>
<td>18%</td>
<td>55%</td>
<td>$\leq 0.001$</td>
</tr>
<tr>
<td>Statins (n=40)</td>
<td>83%</td>
<td>80%</td>
<td>ns</td>
</tr>
<tr>
<td>Fibrates (n=40)</td>
<td>15%</td>
<td>8%</td>
<td>ns</td>
</tr>
<tr>
<td>Combination rx (n=40)</td>
<td>3%</td>
<td>13%</td>
<td>ns</td>
</tr>
</tbody>
</table>
3.3.3 Morbidity

Table (15) details the proportion of follow-up patients reporting cardiovascular morbidty events. The first column contains events that occurred prior to angiography, while the second column gives the percentage of events within the intervening years before follow-up. Fifty-one percent of events at follow-up occurred in patients with no prior history of MI or revascularization procedure, while 49% occurred in patients who had already suffered a CAD event.

<table>
<thead>
<tr>
<th>Morbidity</th>
<th>Baseline</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>PTCA</td>
<td>16%</td>
<td>36%</td>
</tr>
<tr>
<td>CABG</td>
<td>8%</td>
<td>24%</td>
</tr>
<tr>
<td>MI</td>
<td>32%</td>
<td>14%</td>
</tr>
</tbody>
</table>

3.3.4 Mortality

Five of the 150 deceased patients died after responding to the questionnaire. Data were obtained on cause of death from the BC Vital Statistics Agency for 102 of the patients. Figure (6) breaks down the causes of death by category. Acute myocardial infarction (AMI) falls under the category of CAD, but has been separated to show that it makes up a substantial proportion of CAD deaths. Overall, the percentage of patients who died of cardiovascular disease in this cohort was 70%. 

47
3.4 PREDICTORS OF MORBIDITY AND MORTALITY

3.4.1 Morbidity

Stepwise logistic regression based on likelihood ratio was performed for 280 respondents with complete data, in order to establish those variables that predicted CAD morbidity during the follow-up period. The only significant predictor of PTCA, CABG, and MI was a positive angiographic finding at baseline. Patients with positive angiograms had nearly a six-fold higher risk of requiring revascularization or suffering from a MI during the intervening four years (RR: 5.59, 95% CI: 2.71-11.56; \( p \leq 0.0001 \)).

3.4.2 Mortality

Variables considered to have a possible association with mortality were tested using stepwise logistic regression for all responders, non-responders, and deceased patients (\( n = 781 \)). One hundred and fourteen patients were removed from the analysis because of missing data. Those individuals that were lost to follow-up were not included in the total because their vital
status could not be ascertained. Table (16) describes the baseline characteristics predictive of all-cause mortality.

**Table 16. Variables predictive of all-cause mortality based on multivariate logistic regression.**

<table>
<thead>
<tr>
<th>Descriptor</th>
<th>Level</th>
<th>OR</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td></td>
<td>1.04</td>
<td>1.02-1.06</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Exercise</td>
<td>Occ (512) vs None (85)</td>
<td>0.56</td>
<td>0.31-0.999</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td></td>
<td>Mod (157) vs None</td>
<td>0.99</td>
<td>0.51-1.93</td>
<td>ns</td>
</tr>
<tr>
<td></td>
<td>Heavy (27) vs None</td>
<td>0.48</td>
<td>0.13-1.84</td>
<td>ns</td>
</tr>
<tr>
<td>Smoking</td>
<td>Ever (559) vs Never (222)</td>
<td>1.77</td>
<td>1.10-2.86</td>
<td>&lt;0.02</td>
</tr>
<tr>
<td>CABG</td>
<td>(69)</td>
<td>2.57</td>
<td>1.41-4.65</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>LLD</td>
<td>(132)</td>
<td>0.44</td>
<td>0.23-0.83</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>TC/HDL-C</td>
<td></td>
<td>1.10</td>
<td>1.01-1.21</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

Numbers in parenthesis represent the number of respondents in each category of risk factor.

Baseline predictors of cardiovascular death are given in Table (17). The total number of patients included in this analysis was 740 because cause of death could not be determined in an additional 41 individuals.

**Table 17. Predictors of CV mortality based on multivariate logistic regression.**

<table>
<thead>
<tr>
<th>Descriptor</th>
<th>Level</th>
<th>OR</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td></td>
<td>1.06</td>
<td>1.03-1.10</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Exercise</td>
<td>Occ (489) vs None (83)</td>
<td>0.41</td>
<td>0.19-0.86</td>
<td>0.05</td>
</tr>
<tr>
<td></td>
<td>Mod (143) vs None</td>
<td>0.82</td>
<td>0.35-1.89</td>
<td>ns</td>
</tr>
<tr>
<td></td>
<td>Heavy (25) vs None</td>
<td>0.32</td>
<td>0.04-2.70</td>
<td>ns</td>
</tr>
<tr>
<td>Smoking</td>
<td>Ever (530) vs Never (210)</td>
<td>2.83</td>
<td>1.32-6.07</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>TGL*</td>
<td></td>
<td>0.23</td>
<td>0.06-0.94</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>TC/HDL-C</td>
<td></td>
<td>1.21</td>
<td>1.06-1.38</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

* Analysis performed on logarithmically transformed values.
3.5 PATIENT AWARENESS OF HEALTH

3.5.1 Changes in Health Measures

3.5.1.1 Weight

Self-reported weight change was separated into three categories: increased, decreased, and no change. The difference between patient-given weight at follow-up and measured baseline weight was calculated. To categorise actual weight change, the category of no change was defined as the follow-up weight being within ± 2 kg of baseline weight. This figure was chosen because it represented an approximate 5 lb change in weight. It was believed that this was a reasonable margin of error for self-assessment of weight change, and it has been used in other studies of self-reported weight accuracy\(^97\). As such, a true increase in weight over the four years had to be an increase by more than 2 kg over baseline weight, and a decrease was a reduction by more than 2 kg. Self-reported weight and change was available for 300 patients. Figure (7) shows the breakdown of correct responses, as well as under- and over-estimation of true weight change.
Figure 7. Comparison of patient-reported weight change with actual weight change.

Weight change as calculated by subtracting baseline measured weight from follow-up recorded weight is represented categorically along the X-axis. The tri-coloured bars indicate the proportion of respondents stating their weight increased (blue), decreased (maroon), or remained the same (yellow) in response to the question "Has your weight changed in the past four years?"

In total, 53% of respondents correctly identified the change in their weight based on reported follow-up weight. There was no significant difference between men and women or CAD+ and CAD- individuals. There was no difference in accuracy of reported weight change for patients in the three BMI classifications – healthy weight, overweight, and obese. However, significantly fewer respondents who were abdominally obese at follow-up were accurate in their assessment of weight change over four years (Non-obese: 58% correct; Obese: 44% correct; p<0.05).
3.5.1.2 Exercise habit

Patients were asked in the original questionnaire to describe their exercise habits. At follow-up, they were asked to state whether their exercise habits had changed in the interim four years, and their current level of participation in physical activity. Of those who said that their exercise levels had not changed, 54% correctly stated that their current exercise was identical to their level at baseline. As for those who said their exercise habits had changed, only 42% reported an exercise level different from that given on the original questionnaire (p<0.05).

3.5.1.3 Alcohol intake

Alcohol intake was assessed at both baseline and follow-up, using an identical question structure. Individuals were also asked whether their drinking habits had changed. Two hundred and sixty-five stated that there had been no change in their drinking pattern, with baseline and follow-up responses available for 250. For these patients, 70% accurately noted that their current alcohol intake was identical to that recorded on the original questionnaire. Only 54% of the 48 patients stating their drinking habit had changed correctly recorded so on the new questionnaire (p<0.05).

3.5.2 Risk Markers

3.5.2.1 Hypertension

Patients were asked if they knew their blood pressure, if they had been diagnosed with hypertension, and if they were taking anti-hypertensive medications. One hundred and seventy-three of the 314 respondents (55%) knew their blood pressure. Of these, 18 reported a SBP ≥ 140 mmHg and a DBP ≥ 90 mmHg. Sixteen (89%) reported having hypertension, and 13 (72%) stated they were on medications to lower their blood pressure.
Anti-hypertension medications were reportedly prescribed to 146 respondents. Ninety-six (66%) of these patients knew their blood pressure, and 71% had been diagnosed with hypertension, according to self-report.

3.5.2.2 **Cholesterol**

Individuals were asked not only if their cholesterol had been measured during the follow-up period, but also if they knew their cholesterol level. Of all respondents, 238 (76%) had had their cholesterol measured within the four years since angiography. However, only 41% of the 314 respondents knew what their cholesterol level was.

3.5.3 **Instillation of Awareness by Others**

3.5.3.1 **Risk factor counseling**

To assess the attention certain risk factors were receiving from health professionals and the general public, we inquired about counseling given to patients. In total, 224 (71%) of respondents reported being counseled regarding cholesterol. Fifty-one of the 58 (88%) patients on LLD at baseline reported receiving counseling, while 87% of those on LLD at follow-up said they were counseled about cholesterol. Blood pressure was reportedly discussed with 61% of all respondents, and with 93 of the 116 (80%) who had hypertension at baseline. Twenty-four percent said they were counseled about smoking; 87% of current smokers at follow-up reported being counseled, 8% of those who reported never smoking on the follow-up questionnaire, and 24% of patients who stated they had quit smoking. The importance of exercise in CAD risk reduction was said to have been addressed with 56% of respondents, diet and weight loss discussed with 62%, and 25% reported receiving counseling on alcohol intake.

Table (18) gives the results of Pearson's $\chi^2$ analyses of the associations between counseling of risk factors and patient-reported change in risk behaviour.
Table 18. Pearson's $\chi^2$ associations between risk factor counseling and reported change in risk factor behaviour.

<table>
<thead>
<tr>
<th>Comparison</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>EtOH counseling vs EtOH change</td>
<td>ns</td>
</tr>
<tr>
<td>Exercise counseling vs Exercise change</td>
<td>≤0.01</td>
</tr>
<tr>
<td>Exercise instructor vs Exercise change</td>
<td>≤0.001</td>
</tr>
<tr>
<td>Diet counseling vs Diet change</td>
<td>≤0.02</td>
</tr>
<tr>
<td>Dietician counselor vs Diet change</td>
<td>≤0.001</td>
</tr>
</tbody>
</table>

3.5.3.2 Health professionals and laypersons

The vast majority of counseling was performed by physicians - 84% of respondents reported being counseled by a doctor. Other health care professionals acted as a source of risk information much less frequently. Nurses reportedly counseled 14% of patients, dieticians 37%, exercise specialists 11%, and physio- or occupational therapists only 5%. Comparably, 15% of patients reported being counseled on cardiovascular risk factors by friends and family.

3.5.4 Comparison with Hospital Records

Medical records were reviewed at Vancouver General Hospital and St. Paul's Hospital to verify patient-reported morbidity. One hundred and twenty-eight charts for respondents were screened for admissions for PTCA, CABG, or MI. Fourteen (11%) patients were unaware that they had either had a revascularization procedure or suffered an acute MI.

Two patients had been diagnosed with diabetes according to their hospital chart, yet did not report this fact on the follow-up questionnaire. In addition, three individuals stated that they did not suffer from diabetes at follow-up although they were noted to have diabetes on the original questionnaire.

Only 22 of the 128 patients whose medical records were assessed had undergone lipid assessment in hospital (17%). In comparison to the TC levels at baseline, the concentration increased in 12 patients and decreased in 10.
3.6 APPROPRIATE TREATMENT

3.6.1 CCCC Guidelines

3.6.1.1 Lipid Testing

CCCC guidelines do not stipulate the frequency of lipid testing that is appropriate, but they do specify which individuals should have their lipids assessed. Patients with previously diagnosed CAD, family history of premature CAD, hypertension, diabetes, renal insufficiency, or obesity should have regular cholesterol measurements. Of the responders who fell into these categories, which included all but four patients, 76% reported having their cholesterol measured in the intervening four years.

3.6.1.2 Dietary Therapy

Using CCCC guideline criteria, 136 of the 314 respondents (43%) required intensive dietary therapy for their dyslipidaemia. Table (19) details the number of patients who reported receiving the necessary treatment. Individuals have been separated into two groups - those with TC > 6.2 mmol/L, and those with TC=5.2-6.2 mmol/L who also met the other lipid cut-offs for treatment. These groups are based on CCCC guidelines for treatment, which also separate patients based on the two categories of TC level. P-values for $\chi^2$ tests comparing the proportions are also given.

**Table 19. Proportion of respondents receiving appropriate dietary therapy with comparison between patients with high TC versus those with borderline high TC.**

<table>
<thead>
<tr>
<th></th>
<th>TC &gt; 6.2 mmol/L (n=45)</th>
<th>TC=5.2-6.2 mmol/L (n=91)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diet counseling</td>
<td>62%</td>
<td>64%</td>
<td>ns</td>
</tr>
<tr>
<td>Dietician counselor</td>
<td>40%</td>
<td>35%</td>
<td>ns</td>
</tr>
<tr>
<td>Low fat diet</td>
<td>86% (n=44)</td>
<td>66% (n=86)</td>
<td>$\leq 0.025$</td>
</tr>
</tbody>
</table>
3.6.1.3 Drug Therapy

Lowering TC below 5.2 mmol/L was the stated goal of the 1988 CCCC guidelines. If this goal was not met after six months of dietary therapy, commencement of drug therapy was recommended. Forty-one percent of respondents were able to provide a recent cholesterol level. Of the 136 who should have received dietary therapy, 101 either had a current TC > 5.2 mmol/L, or their cholesterol level was unknown. Table (20) gives the proportions being managed appropriately with medications.

Table 20. Proportion of respondents receiving appropriate drug therapy with comparison between patients with high TC versus those with borderline high TC.

<table>
<thead>
<tr>
<th></th>
<th>TC &gt; 6.2 mmol/L (n=35)</th>
<th>TC=5.2-6.2 mmol/L (n=66)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cholesterol counseling</td>
<td>89%</td>
<td>70%</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Lipid lowering drug</td>
<td>74%</td>
<td>45%</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

Examining only those individuals known not to have met the TC target (n=32), only 53% were taking a LLD at follow-up. For those patients who reported meeting the target of TC < 5.2 mmol/L (n=35), 83% were prescribed a LLD.

Table (21) outlines the total percentage of respondents receiving appropriate dyslipidaemia treatment according to CCCC guidelines.

Table 21. Proportion of respondents receiving appropriate treatment according to CCCC guidelines.

<table>
<thead>
<tr>
<th>Appropriate treatment</th>
<th>N</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cholesterol check</td>
<td>311</td>
<td>76%</td>
</tr>
<tr>
<td>Diet counseling</td>
<td>136</td>
<td>63%</td>
</tr>
<tr>
<td>Dietician counselor</td>
<td>136</td>
<td>38%</td>
</tr>
<tr>
<td>Low fat diet</td>
<td>130</td>
<td>73%</td>
</tr>
<tr>
<td>Cholesterol counseling</td>
<td>136</td>
<td>79%</td>
</tr>
<tr>
<td>LLD</td>
<td>101</td>
<td>55%</td>
</tr>
</tbody>
</table>
3.6.1.4 **Canadian Guidelines 2000**

While appropriate treatment of patients assessed in 1993 and 1994 cannot be judged using guidelines published in 2000, a useful comparison may be made. Table (22) illustrates the percentage of patients who would be considered to have received proper treatment according to the 2000 Guidelines if they were assessed today.

**Table 22. Proportion of respondents receiving appropriate treatment according to Canadian 2000 guidelines.**

<table>
<thead>
<tr>
<th>Appropriate treatment</th>
<th>N</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cholesterol check</td>
<td>313</td>
<td>76%</td>
</tr>
<tr>
<td>Diet counseling</td>
<td>274</td>
<td>64%</td>
</tr>
<tr>
<td>Low fat diet</td>
<td>268</td>
<td>72%</td>
</tr>
<tr>
<td>Cholesterol counseling</td>
<td>274</td>
<td>75%</td>
</tr>
<tr>
<td>LLD</td>
<td>274</td>
<td>59%</td>
</tr>
</tbody>
</table>

3.6.2 **NCEP Guidelines**

3.6.2.1 **Annual cholesterol measurement**

According to NCEP guidelines, 285 of the respondents (91%) should have had their cholesterol monitored on a yearly basis. However, based on questionnaire responses, only 220 reported having their cholesterol checked at any time in the *four* years following their initial visit and SCA. Thus, 23% of these patients were not being followed appropriately regarding regular lipid assessment. When the respondents are separated into those with angiographic evidence of CAD compared to those without, significantly more of the CAD+ patients had their cholesterol checked within the follow-up period (79% vs 62%, p<0.025). Of note, because we asked simply if cholesterol had been checked since SCA, we cannot ascertain if lipid analysis was, in fact, performed annually, as is stipulated by NCEP guidelines.
3.6.2.2 Dietary therapy

In patients with pre-existing CAD, a fasting LDL-C measurement greater than or equal to 2.6 mmol/L is an indication for dietary therapy. Using these criteria, 211 of the CAD+ respondents (67% of the total, 83% of CAD+ individuals) should have received dietary counselling and been placed on a low-fat diet. Sixty-six percent reported receiving counselling on their diet, while 71% indicated that they were on a low-fat/low-cholesterol diet.

For the purposes of primary prevention, the number of risk factors in combination with a LDL-C cutoff determines the need for dietary therapy. Seventeen of the CAD- respondents met the criteria for dietary therapy. Of these, 59% had received dietary counselling, and 71% of them were on a low-fat/low-cholesterol diet.

In summary, 228 patients should have been placed on dietary therapy, based on NCEP guidelines for treatment. However, only 70% of these individuals reported being on a low-fat/low cholesterol diet. Thus, 30% of respondents were not being treated appropriately according to accepted guidelines for CAD prevention.

3.6.2.3 Drug therapy

As for dietary therapy, initiation of drug therapy is based on presence of CAD, number of risk factors, and LDL-C levels. For those patients requiring secondary prevention, 57% (144) had LDL-C levels greater than 3.4 mmol/L, necessitating drug therapy. Sixty-three percent reported taking a lipid-lowering agent at follow-up. Only nine CAD- patients had LDL-C levels indicative of drug therapy. Of these, only 44% were prescribed a lipid-lowering drug.

Thus of the 153 respondents (49%) requiring medications to manage their dyslipidaemia according to guidelines, only 62% were receiving appropriate treatment. Table (23) shows the percentage of respondents receiving appropriate treatment according to NCEP guidelines.
Table 23. Proportion of respondents receiving appropriate treatment according to NCEP guidelines.

<table>
<thead>
<tr>
<th>Appropriate treatment</th>
<th>N</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cholesterol check</td>
<td>285</td>
<td>77%</td>
</tr>
<tr>
<td>Diet counseling</td>
<td>227</td>
<td>65%</td>
</tr>
<tr>
<td>Low fat diet</td>
<td>227</td>
<td>70%</td>
</tr>
<tr>
<td>Cholesterol counseling</td>
<td>153</td>
<td>75%</td>
</tr>
<tr>
<td>LLD</td>
<td>153</td>
<td>62%</td>
</tr>
</tbody>
</table>

3.7 PREDICTORS OF APPROPRIATE TREATMENT

3.7.1 CCCC Guidelines

Baseline risk factors thought to be associated with appropriate treatment were tested using stepwise logistic regression. Table (24) provides the results of multivariate analysis for four critical characteristics of appropriate dyslipidaemia management according to CCCC guidelines.

Table 24. Variables predictive of appropriate treatment according to CCCC Guidelines.

<table>
<thead>
<tr>
<th>Guideline</th>
<th>Predictor</th>
<th>Odds Ratio</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cholesterol checking</td>
<td>Age</td>
<td>0.95</td>
<td>0.92-0.98</td>
<td>≤0.002</td>
</tr>
<tr>
<td>(n=277)</td>
<td>CAD+</td>
<td>3.28</td>
<td>1.61-6.68</td>
<td>≤0.001</td>
</tr>
<tr>
<td></td>
<td>HDL-C</td>
<td>7.75</td>
<td>2.02-29.77</td>
<td>&lt;0.002</td>
</tr>
<tr>
<td>Dietician counselor</td>
<td>Diabetes</td>
<td>4.05</td>
<td>1.29-12.69</td>
<td>≤0.01</td>
</tr>
<tr>
<td>(n=112)</td>
<td>Rural vs urban*</td>
<td>0.39</td>
<td>0.17-0.89</td>
<td>&lt;0.02</td>
</tr>
<tr>
<td>Low fat diet</td>
<td>Obese</td>
<td>0.24</td>
<td>0.08-0.66</td>
<td>≤0.005</td>
</tr>
<tr>
<td>(n=108)</td>
<td>PTCA</td>
<td>0.04</td>
<td>0.003-0.38</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>TC</td>
<td>4.70</td>
<td>1.63-13.57</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>Rural vs urban*</td>
<td>2.84</td>
<td>1.03-7.81</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Drug Therapy</td>
<td>LLD</td>
<td>unestim.</td>
<td>unestim.</td>
<td>≤0.0005</td>
</tr>
<tr>
<td>(n=85)</td>
<td>TC</td>
<td>3.23</td>
<td>1.20-8.66</td>
<td>≤0.01</td>
</tr>
</tbody>
</table>

*Urban coded as 1, rural coded as 0. See section 3.8 for definition of rural and urban.
3.7.2 NCEP Guidelines

Baseline characteristics predictive of appropriate treatment according to American guidelines are given in Table (25).

Table 25. Variables predictive of appropriate treatment according to NCEP Guidelines.

<table>
<thead>
<tr>
<th>Guideline</th>
<th>Predictor</th>
<th>Odds ratio</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cholesterol checking</td>
<td>Age</td>
<td>0.95</td>
<td>0.92-0.99</td>
<td>≤0.005</td>
</tr>
<tr>
<td>(n=257)</td>
<td>CAD+</td>
<td>2.87</td>
<td>1.20-6.87</td>
<td>≤0.02</td>
</tr>
<tr>
<td></td>
<td>HDL-C</td>
<td>7.37</td>
<td>1.77-30.70</td>
<td>≤0.005</td>
</tr>
<tr>
<td>Low fat diet</td>
<td>Obese</td>
<td>0.49</td>
<td>0.25-0.98</td>
<td>≤0.05</td>
</tr>
<tr>
<td>(n=200)</td>
<td>Alcohol habit</td>
<td>--</td>
<td>--</td>
<td>≤0.05</td>
</tr>
<tr>
<td></td>
<td>occ vs none</td>
<td>0.51</td>
<td>0.19-1.36</td>
<td>ns</td>
</tr>
<tr>
<td></td>
<td>mod vs none</td>
<td>0.25</td>
<td>0.08-0.78</td>
<td>≤0.02</td>
</tr>
<tr>
<td></td>
<td>heavy vs none</td>
<td>0.11</td>
<td>0.01-0.83</td>
<td>≤0.05</td>
</tr>
<tr>
<td></td>
<td>PTCA</td>
<td>0.39</td>
<td>0.16-0.95</td>
<td>≤0.05</td>
</tr>
<tr>
<td></td>
<td>ASA</td>
<td>2.47</td>
<td>1.16-5.25</td>
<td>≤0.02</td>
</tr>
<tr>
<td></td>
<td>Exercise ever vs never</td>
<td>5.20</td>
<td>1.90-14.27</td>
<td>≤0.001</td>
</tr>
<tr>
<td>Drug Therapy</td>
<td>PTCA</td>
<td>13.96</td>
<td>1.67-116.98</td>
<td>≤0.001</td>
</tr>
<tr>
<td>(n=137)</td>
<td>MI</td>
<td>0.21</td>
<td>0.07-0.65</td>
<td>≤0.005</td>
</tr>
<tr>
<td></td>
<td>LLD</td>
<td>23.82</td>
<td>2.53-224.01</td>
<td>≤0.0002</td>
</tr>
<tr>
<td></td>
<td>LDL-C</td>
<td>0.11</td>
<td>0.03-0.37</td>
<td>≤0.0001</td>
</tr>
<tr>
<td></td>
<td>HDL-C</td>
<td>unestim.</td>
<td>unestim.</td>
<td>≤0.0001</td>
</tr>
<tr>
<td></td>
<td>TC/HDL-C</td>
<td>14.69</td>
<td>4.48-48.17</td>
<td>≤0.0001</td>
</tr>
</tbody>
</table>

3.8 REGIONAL VARIATIONS IN APPROPRIATE TREATMENT

Respondents were defined as either rural or urban based on mailing addresses. The British Columbia Government statistics web site (www.bcstats.gov.bc.ca) was used to obtain Health Area categories in order to classify the respondents. Urban dwellers included those living in Kelowna (health area 23), Kamloops (health area 24), the Lower Mainland (health areas 34-45), Prince George (health area 57), Victoria (health area 61), or Nanaimo (health area 68). Table (26) shows those variables that were significantly different between rural and urban
patients. Continuous variables have been analysed with a Student's t-test, categorical with a χ² test.

**Table 26. Variables showing regional variation on univariate analysis.**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Rural (n=99)</th>
<th>Urban (n=206)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>59.6±1.0</td>
<td>62.9±0.7</td>
<td>≤0.01</td>
</tr>
<tr>
<td>BMI</td>
<td>29.0±0.5</td>
<td>27.4±0.3</td>
<td>≤0.005</td>
</tr>
<tr>
<td>Baseline diabetes</td>
<td>5%</td>
<td>21%</td>
<td>≤0.001</td>
</tr>
<tr>
<td>Follow-up diabetes</td>
<td>12%</td>
<td>27%</td>
<td>≤0.005</td>
</tr>
<tr>
<td>Follow-up low fat diet</td>
<td>62% (n=97)</td>
<td>74% (n=201)</td>
<td>≤0.05</td>
</tr>
<tr>
<td>CCCC guidelines - low fat diet</td>
<td>26%</td>
<td>31%</td>
<td>≤0.05</td>
</tr>
<tr>
<td>CCCC guidelines - dietician counselor</td>
<td>21%</td>
<td>12%</td>
<td>≤0.05</td>
</tr>
</tbody>
</table>

Closer examination of the crossover effect seen with respect to patients on a low fat diet and counseled by a dietician in rural and urban areas suggests that dieticians have a stronger influence on patients living in urban centres, despite their less-frequent use. Table (27) shows the results of χ² analysis of low fat diet with adjustment for dietician counseling.

**Table 27. Regional crossover effect of dietician counseling on self-reported low fat diet intake.**

<table>
<thead>
<tr>
<th></th>
<th>Rural Low fat diet</th>
<th>Urban Low fat diet</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No dietician counselor</td>
<td>62% (n=63)</td>
<td>69% (n=126)</td>
<td>ns</td>
</tr>
<tr>
<td>Dietician counselor</td>
<td>62% (n=34)</td>
<td>83% (n=75)</td>
<td>≤0.02</td>
</tr>
</tbody>
</table>

There is also an association between counseling by a dietician and reported diet change for urban dwellers (p≤0.001) but not for rural patients.
4 DISCUSSION

4.1 LIMITATIONS OF THE STUDY

4.1.1 Methodology

The diagnosis of CAD in this cohort was based on semi-quantitative selective coronary angiography (SCA). While SCA has long been the gold standard for the assessment of coronary atherosclerosis presence and severity, there has been increasing evidence that its sensitivity is low. The diagnosis of percent stenosis relies on a comparison with adjacent segments of the artery. Due to the diffuse nature of atherosclerosis, there is a possibility of disease underestimation\textsuperscript{132}. For example, if a section of the lumen is reported to be 50\% narrower than the surrounding vessel, but the entire vessel is already narrowed by 30\%, then the occlusion is in fact 80\%. In addition, new theories of plaque expansion have suggested that the outer wall of the vessel may bulge as the plaque grows, thus leaving the lumenal space unchanged and CAD undetectable by SCA\textsuperscript{133}. However, long-term studies of patients with chest pain and normal angiograms, have shown them to have a good prognosis, with no greater CAD morbidity than individuals not referred for SCA\textsuperscript{134}.

The nature of the follow-up study design has certain limitations. Whereas the baseline data on risk factors, morbidity, and medications was collected from hospital charts, the follow-up information was gathered solely by patient self-report. Thus the chance for inaccuracies is high. Patients may be unclear on what medications they are taking and their intended purpose. Numerous studies have demonstrated that people incorrectly report weight\textsuperscript{97}, exercise, diet\textsuperscript{135}, and other risk behaviours. Random medical record checks revealed that fourteen patients were unaware that they had suffered a heart attack or had a revascularization procedure since their original SCA. Therefore, the validity of the risk factor data acquired through the mail-out questionnaire must be viewed with caution. However, while self-reported data may have been
judged to be a limitation, it did provide important additional information about CAD treatment. The level of understanding and awareness of respondents could be assessed through comparison to "hard" baseline data. This was particularly true when the patients' perceptions of change were obtained along with a self-report of risk level, as was the case with exercise, weight, and alcohol intake - three variables particularly susceptible to misreport. Patient awareness of health and disease risk is invaluable in the prediction of the success of lifestyle modifications, medication compliance, and positive outcomes.

4.1.2 Response Rate and Bias

Every effort was made to maximise response rate. The questionnaire was kept to one page, follow-up phone calls were made to non-responders to encourage response, and a second mail-out was made to those who could not be reached by phone or who stated that they would be willing to complete a new questionnaire. However, despite these efforts, only 42% of those who received a questionnaire responded. While this response rate was less than ideal and endangered the analyses with potential biases, it fell within the range of response rates of 37% to 70% found in similarly designed postal surveys\textsuperscript{136-137-138}.

As anticipated with a low response rate, some biases were found in the data collected. There were significant differences in key baseline characteristics that had to be taken into account when generalising the study findings to wider populations. Significantly more respondents had positive angiographic findings at their initial visit. One possible explanation of this bias may stem from the wording of the consent form. The purpose of the study was described as an assessment of treatment for CAD and dyslipidaemia in British Columbia. This may have misled potential participants with no evidence of CAD that their response was unnecessary, as was borne out by several of the follow-up phone calls.
Responders were biased towards non-smoking, which has been seen in other mail-out lifestyle and heart health surveys\textsuperscript{139-138}. Smokers may have been unwilling to respond to a questionnaire assessing lifestyle modification and disease treatment since they themselves had been resistant or unable to stop smoking. It is also possible that individuals who had quit smoking were particularly interested in calling attention to their efforts to modify their risk behaviours.

The smaller proportion of non-respondents taking antioxidants at baseline may reflect a lower interest in self-health. This would seem to fit with the higher frequency of current smokers among those who did not wish to participate in the follow-up. However, the absolute number of patients taking antioxidants was very small - 12 non-responders versus 28 responders - and so this difference was likely not clinically relevant.

A further bias that appeared in the analysis of the data was the finding that patients living in rural British Columbia were more likely to respond to the questionnaire than urban dwellers (rural: 59\%, urban: 48\%; \( p \leq 0.02 \)). One possible explanation is that individuals living outside of major centres may have been more accustomed to remote communication for health care, and were thus more comfortable returning a mail-out questionnaire regarding their health. This bias must be kept in mind in light of the finding that urbanites were less likely to receive appropriate dietician counseling while rural dwellers were less likely to report a low fat diet if CCCC dietary therapy was indicated. These differences may have been more or less pronounced had there been a greater response rate.

\textbf{4.2 PATIENT CHARACTERISTICS}

\textbf{4.2.1 Demographics and Risk Factor Prevalence}

Not unexpectedly, the vast majority of individuals in the cohort had positive angiograms and males outnumbered females on the order of three to one. The average age of males and
females was similar to other angiographic studies\textsuperscript{140} and was in keeping with the observation that women with CAD are predominantly post-menopausal (84\% of women).

These individuals referred for SCA suffered from a large number of risk factors. Seventy-nine percent (77\% female, 79\% male) had two or more CAD risk factors, compared to 33\% of women and 41\% of men in the Canadian Heart Health Surveys\textsuperscript{11}. Closer examination of the respondent group revealed other similarities and differences in risk factor prevalence compared with published cohorts.

Baseline lipid levels appeared relatively homogenous for the entire cohort, with the only difference being a significantly lower mean LDL-C concentration in respondents who were taking LLD at baseline. Mean TC levels were below 5.2 mmol/L and thus within a desirable range, as were TG (<2.3 mmol/L) and HDL-C (>0.9 mmol/L) levels. However, LDL-C was higher than desired (>3.4 mmol/L) and the mean TC/HDL-C ratio was above the normal of five. This would seem reasonable given that this was a cohort of patients being referred for SCA, and these findings correspond to those from a similar published angiographic cohort\textsuperscript{140}. Comparison with the serum lipid levels of men from the Framingham Heart Study revealed that the men in this cohort had relatively similar LDL-C, HDL-C, and TC levels, along with mean ratio of TC/HDL-C\textsuperscript{24}.

The percentage of current smokers within the non-respondent and deceased groups appeared to be consistent with other study populations\textsuperscript{39,87} and with statistics for BC in 1996/1997\textsuperscript{8}. However, the respondent pool, with only 7\% being current smokers, was far below the 25\% found in the general population. These differences are difficult to interpret in light of the low response rate.

The proportion of British Columbians with high blood pressure in 1996/1997 was 9\%\textsuperscript{8}. The study cohort was distinct from the general population in that it was made up of individuals
with the presence, signs, or potential for CAD. Dividing the cohort into CAD+ and CAD-
revealed that 33% of SCA negative individuals had hypertension, with 38% of CAD+ having a
diagnosis of high blood pressure. There was no significant difference between the proportion of
CAD+ with hypertension in this cohort compared to the LIPID study cohort\textsuperscript{88}. However, the
prevalence of hypertension in this cohort was significantly greater than that found in the
AFCAPS/TexCAPS study for CAD- patients (33% vs 22%; p\leq0.001). This variation is likely
due to discrepancies in selection criteria. Among the noticeable differences, individuals in the
AFCAPS/TexCAPS study had higher lipid levels at baseline, fewer individuals with a family
history of premature CAD, and fewer patients taking anti-hypertensives\textsuperscript{85}.

Diabetes was found less frequently among respondents than was been shown in other
studies (17% vs 24%; p\leq0.05)\textsuperscript{141}. However, the number of CAD+ patients with diabetes (18%)
was identical to the proportion in a review of over 48,000 USA patients\textsuperscript{115}. A regional variation
was found in the prevalence of diabetes. Patients living in urban centres were significantly more
likely to have diabetes both at baseline and on follow-up than those living rurally. This was
despite the fact that the mean BMI of rural patients was significantly higher than urban dwellers,
although there was no difference in the number of obese individuals from each region. One
speculation may be that patients with diabetes needed to live closer to health facilities for
management of their disease. They would require access to dieticians, regular physician
monitoring, and pharmacies for medication, which may be more accessible in a city centre.

The incidence of obesity in the entire cohort was much greater than the 29% found in the
Canadian National Population Health Survey\textsuperscript{8}. And yet, a BMI greater than 27 kg/m\textsuperscript{2} was used
as the guideline for obesity in the 1996/1997 survey - much less stringent than the criterion of \geq
30 kg/m\textsuperscript{2} used for this cohort. Presumably, the proportion of obese subjects would then be even
greater in this cohort than the proportion seen in the Canadian population. This may be due to
the older age of those referred for SCA, as weight increases with age, particularly in women. Indeed, the Canadian National Population Survey was a measure of all individuals between the ages of 15 and 64, while the respondents in this study ranged in age from 37 to 87 at follow-up. Given the association of abdominal obesity with elevated TG, insulin resistance, and increased CAD risk, the observation that almost half of all individuals in the original cohort had waist circumferences well above desirable measurements (<88 cm for women, <102 cm for men) is of great concern.

The proportion of patients with TC levels greater than 5.2 mmol/L at baseline (43%) was comparable to that found in the 1985-1990 Canadian Heart Health Surveys. Comparison of abnormal lipid levels in male CAD+ patients was possible with a study of 8650 men recruited for the Department of Veterans Affairs HDL Intervention Trial. Similarities and discrepancies are outlined in Table (28).

<table>
<thead>
<tr>
<th>Lipid Risk Factor</th>
<th>Respondents</th>
<th>DVA-HIT Cohort</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDL-C &gt; 3.4 mmol/L</td>
<td>53%</td>
<td>56%</td>
<td>ns</td>
</tr>
<tr>
<td>HDL-C &lt; 0.9 mmol/L</td>
<td>45%</td>
<td>38%</td>
<td>≤0.05</td>
</tr>
<tr>
<td>TG &gt; 2.3 mmol/L</td>
<td>24%</td>
<td>33%</td>
<td>≤0.01</td>
</tr>
</tbody>
</table>

The frequency of predisposing family history of CAD in this cohort was higher than proportions found in retrospective hospital studies of CCU patients (45% vs 36%; p≤0.025) and general admissions (45% vs 33%; p≤0.01). The proportion of CAD+ BC patients with family history was, however, significantly lower than those in the Heart Education and Research Trial (46% vs 74%; p≤0.001).
Very few risk factors changed in the intervening years between the original SCA and the follow-up questionnaire. Two that did - hypertension and diabetes - have been shown to be age-dependent\(^1\). Thus, the increase over four years was most likely explained simply by the aging of the population. Although the increases may also be a reflection of the high prevalence of obesity in the cohort, a predisposing factor for both conditions. The significant decrease in obesity at follow-up, combined with the observation that only half of the respondents were able to correctly gauge their weight change, may have been due to errors in self-report of weight and waist circumference. Indeed, many studies have shown that obese individuals in particular are prone to under-representation of their body weight\(^97\).

4.2.2 **Baseline Subgroup Analyses**

The availability of risk factor information, lipid profiles, and angiographic data on a large number of individuals allowed for the analysis of CAD predictors in specific sub-populations. The first study was an attempt to elucidate possible explanations for the occurrence of CAD in patients who were otherwise at very low risk of developing the disease due to their lack of major risk factors. The impetus for the second substudy was that CAD in women, as a whole, has been studied far less than in men, and the variation in incidence between younger and older women may be a result of a different risk profile between the age groups.

4.2.2.1 **ApoAI in Low Risk Patients**

(This discussion makes up a portion of the paper: Francis MC, Frohlich JJ. Coronary artery disease in patients at low risk - apolipoprotein AI as an independent risk factor. Atherosclerosis. In press.)\(^130\)

This study examined the role of plasma apoAI concentration as an independent risk factor for CAD in patients with none of the major risk factors. Several previous studies have shown that apoAI is a stronger predictor of atherosclerosis than the traditional plasma lipids\(^37,143,42\).
However, no prospective studies have supported an association between apoAI and CAD. Thus, current consensus is that apoAI is not a better predictor of atherosclerotic disease than HDL-C. However, this study was unique in that it looked at a select population of individuals in whom the strength of apoAI concentration versus HDL-C levels had not been examined.

After univariate analysis several lipid parameters and ratios were predictive of the presence of CAD after adjustment for age and gender. Significantly lower levels of LDL-cholesterol were seen in CAD+ patients, which would seem counterintuitive given the established link between high LDL-cholesterol and CAD. However, adjusting LDL-C for FER_{HDL}, a marker for small lipoprotein particles, eliminated its association with CAD. This suggested that the relationship between LDL-C and presence of disease was more likely based on the preponderance of small, dense LDL particles.

Multivariate logistic regression analysis revealed that, apart from gender and age, the sole predictive variable for CAD was apoAI concentration. For every increase of 1 mg/dL in apoAI, there was a concomitant 6% decrease in CAD risk. Thus, after taking into account all possible factors that may affect disease presence, it was a reduced level of serum apoAI that distinguished patients with disease from those with normal angiograms. The strong association of apoAI with CAD in low risk patients remained after adjustment for FER_{HDL}, LDL-C, and other potential confounders such as HDL-C and obesity. These findings lend support to the suggestion by Kottke et al that low apoAI concentration may represent a threshold event in the development of CAD, particularly in patients with none of the other traditional risk factors.

4.2.2.2 Predictors of CAD in Younger versus Older Women

Studies of CAD and its associated risk factors in women are less prevalent than research on men. The Framingham Heart Study was one of the first to demonstrate that different risk factors carry different weights in women versus men. While the incidence of atherosclerosis is
much lower in women, there is a sharp increase in CAD after the age of 60. It seemed reasonable to hypothesise that the change in CAD incidence may be due to a change in relevant risk factors in older women.

Univariate analysis of women < 60 revealed strong associations between CAD and both diabetes and smoking. Both of these risk factors have previously been shown to have a greater impact on CAD in women. While several lipid parameters had a significant relationship with CAD when examined alone, in keeping with reports in the literature, adjustment for smoking eliminated the relationships. Multivariate analysis of younger women showed that presence of diabetes and current smoking were the sole variables predictive of CAD. Both of these risk factors showed a strong association with CAD in a Scottish study of women under 60.

The risk profile of CAD women ≥ 60 was very different from that of younger women. With regards to lifestyle risk factors, only age was significantly predictive of positive angiographic findings. This was expected given that CAD incidence increases with age in post-menopausal women. Several lipid parameters were related to CAD after univariate analysis. After adjustment for smoking, to allow comparison between younger and older women, TC (p<0.02), TG (p<0.001), and apoB (p<0.05) were significantly elevated in women with CAD. However, multivariate logistic regression of all possible predictors revealed that only age and TG level were associated with CAD in women ≥ 60. TG levels have previously been linked to CAD in women more so than in men. However, the association has tended to weaken or disappear upon multivariate analysis. Also, none of these studies have looked at CAD risk factors solely in older women.

The variation in risk factors predictive of CAD between younger and older women may be due to a survival effect. Young women who smoke or who have diabetes may be more likely to die before reaching 60. Those that survive into their 7th decade may be more susceptible to
elevated lipids, particularly TG. However, as this was a cross-sectional study, there is no way to ascertain that there was a longitudinal survival effect of smoking or diabetes on CAD in women. This analysis did suggest that risk factors associated with CAD in women < 60 years versus women over ≥ 60 were different.

4.2.3 Morbidity

Two-fifths of respondents who were referred for SCA had a prior history of either a MI or revascularization procedure. Over the intervening four years, there was an increase in the number of angioplasties and bypass grafts, with a concomitant decrease in the number of MI's. The annual rate of hospitalisation for MI in Canada for 1996/1997 was 8.9%. Averaged over four years, the rate of MI among respondents was 3.5%, just over a third of the national rate. Fifty-eight (57%) of those who had suffered a MI at baseline went on to have a revascularization procedure, while one-quarter had another heart attack. The hospitalisation rate for CABG in Canada was 2% in 1996/1997. The average annual rate during the follow-up period for respondents was 6%, presumably much higher due to the high-risk nature of the patients, or perhaps the higher proportion of males in the cohort, who are much more likely to have surgical intervention than females.

The prevalence of MI, PTCA, and CABG as entered in the follow-up questionnaire must be viewed with care. Comparison to medical records revealed that out of 128 randomly reviewed charts, 14 patients (11%) failed to report that they had had a CAD event since the original SCA. Reasons for patient error are unclear. Those who were unaware of revascularization or MI were no older than the other patients were, and thus age-related factors such as dementia or memory loss were probably not at issue. Possible explanations may be that they were not informed by medical staff in the case of silent MI, or that they misunderstood the surgical procedure that they underwent. It is possible that a PTCA was performed during the
course of a planned angiography, and thus the patient may have been unaware or forgotten that
the angioplasty was done. The fact that 11% of the respondents were unaware of having suffered
a significant CAD event highlights a potential problem in patient communication and health
consciousness, and presents an opportunity to enhance patient education.

The finding that only angiographic status predicted future morbidity seemed appropriate.
There were no differences in predictors of each morbidity event taken alone. Presence of CAD
should have had the greatest association with CAD morbidity, overpowering any other
associated factors.

4.2.4 Mortality

One hundred and fifty patients died between 1993 and 1999, indicating an overall
mortality rate of 2.3% per year. With cause of death available for 102 individuals, death due to
cardiovascular disease was established in 71 patients. Thus, the mortality rate from CVD in this
cohort was estimated at 1.1% per year. The mortality rate from CVD in Canada was 0.5% for 19978. Given that the patients in this cohort were selected for either presence of CAD or
suspicion due to a number of risk factors, they were more prone to die from heart disease.

Medical treatment of patients in the deceased groups differed significantly from
respondents. A surprising finding was that deceased individuals were significantly more likely
to have been prescribed ACE inhibitors at baseline. ACE inhibitors have been indicated for
patients with renal insufficiency147, and there were significantly more deceased patients with
this condition. However, the numbers are too small to determine whether this would explain the
difference. The HOPE trial148 has shown that the ACE inhibitor Ramipril had broad-ranging
beneficial effects beyond merely hypertension control. ACE inhibitors are recommended for
treatment of diabetes, as they reduce the incidence of diabetic neuropathy and other
complications. Significantly more patients with diabetes among the deceased group were
receiving ACE inhibitors at baseline than others in the cohort. Also, ACE inhibitors were shown
to be of great benefit to patients with congestive heart failure (CHF). Although there was no
data on the prevalence of CHF in the cohort, it may be reasonable to assume that a greater
number of individuals who died may have suffered from the condition.

Multivariate analysis revealed that the predictors of all-cause mortality and
cardiovascular mortality were quite similar. With increasing age, the chance of death increased.
Mortality was significantly affected by the lifestyle habits of exercise and smoking. All-cause
mortality was 44% less likely for those who exercised occasionally while cardiovascular death
was reduced by 59%. While there was no effect with increased exercise intensity, the number of
individuals partaking in moderate and heavy exercise was much smaller. Current smoking or
any history of smoking cigarettes increased the chance of overall mortality by 77% and
cardiovascular mortality by almost three-fold. An increase by one unit in the TC/HDL-C ratio
increased the likelihood of CVD mortality by 21% and all-cause mortality by 10%

There was some disagreement in predictors of total versus CVD mortality. For each 1
mmol/L increase in TG concentration, there was an associated 77% drop in CVD mortality,
although TG did not predict all-cause mortality. This is an intriguing finding given that, first of
all, the majority of studies in the literature have failed to show an independent relationship
between CVD death and TG upon multivariate analysis26. Secondly, the mean TG concentration
among those who died of cardiovascular causes was 1.49 mmol/L compared to 1.89 mmol/L for
others in the cohort. TG was significantly lower for those dying of CVD (p≤0.05; based on the
logarithmic transformation due to skewed distribution). This finding was contrary to all other
reports in the literature which, when an association between TG and CAD mortality has been
seen, TG levels were elevated26. The reduction in TG at baseline, prior to death from CVD, may
have been an indicator of an insidious process that resulted in the depletion of TG-containing
lipoproteins from the blood. It may have been the result of a low carbohydrate or calorie diet, which has been seen in many elderly individuals. A study by Wei et al demonstrated that low fasting plasma glucose (FPG) was independently associated with CVD mortality. They also showed that patients with low FPG had significantly lower TG levels. It may be possible that the lower TG concentration among patients in this cohort who died of cardiovascular causes may be a reflection of low FPG levels. It should be stressed that the absolute levels of TG were low among the cohort and were, for the most part, within CCCC guidelines.

Overall mortality was further associated with CABG and prescription of LLD at baseline. Both variables had the expected effect on mortality - patients who had undergone bypass had a two and a half fold higher risk of death, while LLD administration at baseline reduced the chance of death by 56%. Why a history of CABG would be associated with overall mortality but not CVD mortality is uncertain. It may be due to the fact that the other predictors of CVD death conveyed higher risks that negated the effect of bypass surgery, or that the number of respondents who had undergone a CABG prior to SCA was quite small. Use of LLD may only have been associated with overall death in part because of the small absolute numbers taking the medications. There may not have been enough patients on LLD to show a significant effect.

4.3 ANALYSIS OF TREATMENT

4.3.1 Awareness and Counseling of Risk Factors

As smoking is a major risk factor for CAD, smoking cessation counseling should be a priority in the prevention of cardiovascular morbidity and mortality. Unfortunately, due to the significant response bias towards non-smokers returning the questionnaire, numbers for respondents were too small for any meaningful analysis. It was discovered that nearly three-quarters of patients who smoked at the time of their SCA were subsequently counseled about the
health risks of smoking. However, with so few respondents in this group (22), assessment of the effectiveness of the counseling on smoking cessation cannot be performed.

Arguably, the first indicator of appropriate lifestyle management of CAD is the level of awareness the patient has regarding a particular risk factor. When asked about their blood pressure, just over half of the respondents were able to provide it. This is considerably lower than the 73% of respondents who knew their blood pressure in a community screening project of heart disease risk\textsuperscript{108}. Of the 115 (37%) who stated that they had been diagnosed with hypertension, only 71% knew their blood pressure. This demonstrates less than optimal awareness of a particularly potent CAD risk factor among respondents.

Additionally, only 71% of those who reported taking medications for high blood pressure stated that they had hypertension. If over one-quarter of the respondents taking anti-hypertensives did not understand that they suffer this medical condition, this may hamper medication compliance, which is particularly difficult in asymptomatic long-term conditions such as hypertension\textsuperscript{152}.

Counseling about the dangers of high blood pressure was relatively low for all respondents as a group (61%) but appeared to be well-targeted to those who had been diagnosed with hypertension at the original assessment (80%). Canadian guidelines\textsuperscript{127} for blood pressure management recommend weight loss, particularly in obese patients. Seventy percent of respondents who were obese and hypertensive (64) at baseline received counseling on diet and weight, with 64% receiving exercise counseling.

Obesity was much more common among respondents than has been seen in the general population\textsuperscript{8}. Compounding this problem was the observation that only half of the patients were able to correctly gauge their weight change over four years. And, as expected based on previous reports\textsuperscript{98}, abdominally obese individuals were significantly worse at judging their weight change
than non-obese individuals. Thus, patient awareness of this risk factor was disappointingly low among respondents.

Treatment of obesity may be accomplished through several different approaches. Counseling patients to adopt a low fat diet, as a means of weight reduction, is important. Encouraging regular physical activity may also promote weight loss. Diet and weight loss were reportedly discussed with 68% of obese patients, and 60% were counseled on increasing their exercise level. The prevalence of counseling in this high-risk population appeared to be suboptimal. Treatment of risk factors such as obesity though counseling and education is widely believed to be an efficacious and cost-effective method of managing CAD\textsuperscript{153}.

While there was a significant correlation between risk factor counseling, particularly by experts in the field of diet and exercise, and changes in risk behaviour, the correlation was quantitatively small. And the effect on reducing obesity was moderate at best. Only 63% of obese respondents counseled on their diet and weight and 55% of those who received exercise counseling reported a decrease in weight compared to baseline. Greater involvement of dieticians and exercise instructors in risk factor counseling may potentially improve the management of obesity.

4.3.2 Pharmacological Interventions

A number of medications have been shown to reduce CAD morbidity and mortality as a peripheral benefit. Aspirin has been found to be particularly important in reducing events\textsuperscript{62} and is recommended for patients without a risk for gastrointestinal bleeding. Aspirin use among respondents increased significantly over the four year follow-up period, and was comparable to 1998 rates of post-MI ASA prescription in Canada\textsuperscript{8}. However, regular aspirin use among CAD+ patients was significantly lower than rates found in both LIPID\textsuperscript{88} and CARE\textsuperscript{87} studies. Given
that meta-analyses of primary and secondary prevention trials have shown that risk reduction is greater in patients with established CAD, targeting to CAD+ individuals should be improved.

Between 1993 and 1997, the use of antioxidants increased dramatically. Despite no conclusive evidence from randomised trials that antioxidants reduce the incidence of CAD and associated complications, many more respondents reported taking these supplements on the questionnaire. Self-medication with vitamins and other supplements has risen sharply over recent years, with Canadians spending almost four billion dollars per year on these medicine alternatives. The desire to take personal control over health may explain the increase, as may the wish to use "natural" ways to treat medical problems.

Prevalence of drug treatment for hypertension did not appear to change over the four years, with medications prescribed to 92% of hypertensives at baseline and 92% of self-reported follow-up hypertensives. The type of medication used to manage hypertension did appear to shift from the early-90's to the late-90's. The prevalence of drugs used specifically for blood pressure control at the time of SCA and as reported on the questionnaire is given in Table (29).

Table 29. Comparison of type of anti-hypertensive reported at follow-up with baseline use.

<table>
<thead>
<tr>
<th>Medication</th>
<th>Baseline</th>
<th>Follow-up</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beta-blocker</td>
<td>53%</td>
<td>44%</td>
<td>ns</td>
</tr>
<tr>
<td>ACE inhibitor</td>
<td>30%</td>
<td>52%</td>
<td>≤0.001</td>
</tr>
<tr>
<td>Ca-channel blocker</td>
<td>50%</td>
<td>26%</td>
<td>≤0.001</td>
</tr>
</tbody>
</table>

It is apparent that prior to 1993, the majority of hypertensive patients were treated with either beta-blockers or Ca-channel blockers. However after 1994, a preference towards ACE inhibitors emerged to the deference of Ca-channel blockers. ACE inhibitors have been touted as the newest generation of drug for optimal management of hypertension, and this may explain the increased use of this class of blood pressure medication.
A total of 111 respondents reported taking beta-blockers on the questionnaire. Over half of these said they were prescribed the drug for reasons other than hypertension. This was equivalent to 20% of all respondents, and represented a significant decrease compared to baseline adjuvant beta-blocker use (30%; \( p \leq 0.025 \)). One possible reason for the decline may have been the reduction in MI frequency in the four-year follow-up period compared to pre-SCA, given that post-MI patients have been shown to derive the greatest benefit from beta-blocker therapy\(^\text{73}\). There is also the possibility, because this data was self-reported, that respondents were not aware that they were taking beta-blockers, or that they were intended for CAD risk reduction rather than blood pressure control. Of note, 26 patients were not able to provide the type of heart drug they were taking, and so the use of beta-blockers for CAD prevention may have been greater at follow-up than reported.

4.3.3 Appropriate Treatment of Dyslipidaemia

The relationship between dyslipidaemia and CAD has been well established in the scientific literature and widely disseminated in the popular media. Public education campaigns such as the American Heart Association's "Cholesterol Low Down" program and the Canadian Heart and Stroke Foundation's "HeartSmart Women" have stressed the benefit of not only maintaining a low cholesterol level but also the importance of simply knowing one's cholesterol level. However, only 41% of respondents were able to give their TC level, despite over three-quarters of them reporting to have had their cholesterol measured within the last four years and 71% stating that they were counseled about their cholesterol level. Reasons for this lack of personal awareness may be attributable to the uncertainty that many patients may have felt about cholesterol - particularly the confusion between "good" cholesterol versus "bad" cholesterol\(^\text{119}\).

Two primary sets of guidelines for the treatment of dyslipidaemia were available to physicians in 1993. The CCCC guidelines were published in CMAJ in 1988\(^\text{93}\), while the second
incarnation of the NCEP guidelines was released in JAMA in 1993\textsuperscript{23}. The CCCC guidelines reflected the Canadian policy of dyslipidaemia treatment, and thus should have been most relevant to physicians treating patients in this cohort. However, the ubiquitous influence of American medicine on Canadian practices must also be considered. References to the NCEP cholesterol limits were found in several SPH and VGH hospital charts. Thus, analysis of appropriate treatment among respondents was performed using both sets of guidelines. The prevalence of appropriate dyslipidaemia management according to the 2000 Canadian guidelines has been included for comparison, but these guidelines cannot be used to judge the treatment practices of British Columbian physicians between 1993 and 1997.

4.3.3.1 **Cholesterol Screening**

The CCCC guidelines\textsuperscript{93} recommended lipid testing for all individuals with a high perceived risk of CAD or prior evidence of the disease. Based on these criteria, all but four of the respondents should have had lipids assessed. The NCEP guidelines\textsuperscript{23} used a combination of TC and HDL-C level with the categorical number of risk factors. On this basis, only 91\% of patients should have had annual screening of cholesterol levels. By comparison, Canadian 2000 criteria\textsuperscript{95} for cholesterol screening were slightly altered from the 1988 CCCC guidelines. An age limit was introduced so that all men over 40 and women over 50 were to be screened. Rather than considering a list of individual risk factors for screening, major risk factors were grouped, with the presence of two or more necessitating lipid assessment. Also, clinical evidence not only of CAD, but also peripheral vascular disease or carotid atherosclerosis was an indication for fasting lipid screening. These criteria were met by all but one respondent.

Despite the wide variation in guidelines for cholesterol screening, there was no difference in the number of respondents who were screened appropriately. Approximately three-quarters of those requiring lipid assessment stated that their cholesterol had been measured within the
previous four years. Of note, the NCEP guidelines for frequency of testing were much stricter than the CCCC. Lipid profiles were required every year according to American recommendations. However, due to the wording of the questionnaire, the appropriate frequency of testing could not be ascertained. No program for repeated measures was given in the 1988 Canadian guidelines\textsuperscript{155}. Nor was there a stipulation for regular cholesterol screening in the recent 2000 Canadian guidelines - the frequency was left to clinical judgement\textsuperscript{95}.

The predictors of appropriate cholesterol screening were identical for both the CCCC and NCEP guidelines. The older the respondents were, the less likely they were to have had their cholesterol checked. Angiographic evidence of disease increased the chances of having cholesterol appropriately measured by approximately three-fold. Unexpectedly, for every 1 mmol/L increase in baseline HDL-C, there was a seven- to eight-fold greater likelihood that patients would have their lipids screened within the follow-up period. It is unclear why the presence of a negative risk factor for CAD would elicit greater vigilance on the part of physicians. Higher HDL-C, which would have been reflected in an elevated TC level, may have served as a risk marker to physicians who considered only TC in lipid risk assessment. Conversely, patients with elevated HDL-C levels, which have been associated with such positive health behaviours as increased exercise\textsuperscript{156}, may have taken a more active interest in their health, and may have requested closer monitoring of lipid levels by their physicians.

4.3.3.2 Dietary Therapy

All guidelines for the management of dyslipidaemia recommended diet as the cornerstone of therapy\textsuperscript{155}. However, only the CCCC guidelines were explicit in the requirement for dietician intervention in the promotion of a suitable low fat diet. Policy makers were concerned about the accessibility of dieticians within the health management team\textsuperscript{93}, and it would appear this was with good reason. Of those respondents requiring intensive dietary therapy according to CCCC.
guidelines, only 38% reported being counseled by a dietician. This also varied regionally, with urban dwellers significantly less likely to have seen a dietician than their rural counterparts.

Analysis of predictors of dietician counseling revealed that patients with diabetes were four times more likely to have been counseled by a dietician as part of their recommended treatment. This was not unexpected given the necessity of dietician intervention for optimal nutritional management of adult-onset diabetes. In addition, respondents living in city centres were 61% less likely to be appropriately counseled by a dietician, in keeping with the previously described regional variation in dietician accessibility.

Despite the sub-optimal use of allied health professionals, 63% of patients reported receiving dietary counseling and 73% stated that they were on a low fat diet. While encouraging, these findings should be viewed with caution. The type of diet was self-reported, and as previously shown in the literature\textsuperscript{101}, individuals, particularly obese individuals, tend to underestimate their dietary fat intake.

Separation of respondents with high TC levels from those with borderline TC in combination with abnormalities in other lipid measures revealed a disparity in the prevalence of patients on a low fat diet. While there was no difference in the frequency of dietary counseling between these two groups, those with borderline high TC were significantly less likely to report being on a low fat diet than those with TC above 6.2 mmol/L. A study involving focus group assessment of patient attitudes towards high cholesterol indicated that there was substantial confusion over "how high is too high" with regards to cholesterol, and a lack of confidence in the effect diet had on lowering cholesterol\textsuperscript{119}. These concerns may explain the lower adherence to a low fat diet in respondents with borderline TC.

The regional difference in dietician counseling was further confounded by a paradoxical variation in low fat diet prevalence among rural and urban respondents. Although patients living
in city centres were less likely to have seen a dietician, they were more likely to report that they were on a low fat diet. This may be an indication that dietician intervention was more effective for urbanites despite its limited use. Or perhaps patients living in a rural setting were successfully counseled to improve their dietary intake of fat, but were aware that the change was not enough to be considered a low fat diet. In effect, rural individuals may have started off with a poorer diet, and despite consulting a dietician, were not able to adequately reduce their fat intake. Unfortunately, there was no way to assess the actual dietary intake of respondents, and all that was available was the self-reported categorisation of their diet.

NCEP guidelines have stricter criteria for dietary management of dyslipidaemia. As such, more respondents would have required dietary therapy under the American guidelines (228 vs 135; p≤0.001). The Canadian 2000 recommendations are even more rigorous than either of the older guidelines. Using the 2000 criteria for dietary therapy, almost 90% of respondents would have required implementation of a low fat diet to control their dyslipidaemia. In spite of these differences, the percentage of patients reporting they were on a low fat diet was nearly identical under all three guidelines, in the range of 70%-73%. This figure appeared to fall within the range of literature studies on adherence to guidelines. McBride et al\textsuperscript{112} showed that only 55% of patients requiring dietary therapy under NCEP guidelines received dietary counseling. At the other end of the spectrum, 79% of patients requiring dietary intervention according to NCEP guidelines in a US-wide survey stated that they had been placed on a low fat diet by their physician\textsuperscript{111}.

While the percentage of respondents on a required low fat diet according to CCCC and NCEP guidelines was equal, the variables associated with appropriate dietary therapy were not all the same. Both obesity and history of PTCA prior to SCA were significantly associated with a reduced likelihood of being on a low fat diet. This was the expected effect of obesity on
appropriate diet; or rather it was logical that obese individuals would be found less likely to subscribe to a low fat diet. However, it seemed counterintuitive that patients undergoing revascularization would not make modifications to their diet in order to decrease their risk of CAD morbidity and mortality. Some studies have shown that post-PTCA patients are reluctant to change their lifestyle following the procedure, and many find the switch to a low fat diet drastic and an impediment to a satisfactory quality of life\textsuperscript{157}.

Other predictors of appropriate dietary therapy according to CCCC guidelines included TC level and regionalisation. Every 1 mmol/L increase in TC was associated with a nearly fivefold higher likelihood of reporting a low fat diet. Rural dwellers were nearly three times less likely to be consuming a diet low in fat, once again reflecting the regional disparity in dietary fat intake.

Lifestyle risk factors appeared to have stronger effect on NCEP-based dietary therapy. For individuals who consumed moderate (1-2 drinks per day) and heavier (> 2 drinks per day) quantities of alcohol, the chance of eating low fat foods decreased by 75% to 90% respectively. Perhaps there was a perceived correlation between regular drinking and high fat intake among respondents requiring dyslipidaemia management. Patients who reported some level of physical activity were five times more likely to eat less fat. This may indicate that advice on weight loss and risk reduction emphasised not only healthier eating habits, but also the need for increased exercise. Or perhaps patients who made exercise a part of their lifestyle were more health-conscious, and thus more likely to reduce their dietary fat intake. The use of ASA by those requiring dietary therapy according to American recommendations was also associated with low fat diet, perhaps also indicative of greater personal interest in health.
4.3.3.3 **Drug Therapy**

One important difference between the CCCC and NCEP guidelines, and a limitation to this study, was the target for cholesterol lowering. CCCC guidelines used a TC ≤ 5.2 mmol/L as the desirable goal for dietary therapy. If this level was not reached after six months, then pharmacologic intervention was indicated\(^93\). NCEP guidelines, on the other hand, used LDL-C to determine the need for continued treatment. The LDL-C cut-off differed depending upon the presence of CAD and number of additional risk factors. If LDL-C remained above the limit for drug therapy after an adequate trial of dietary therapy, then LLDs may need to be prescribed\(^23\).

Self-reported TC levels were available for only 67 of the respondents who required dietary therapy under CCCC guidelines. The need for subsequent drug treatment was assumed for those whose follow-up TC did not meet the goal (n=32) and for those who did not provide a recent TC measurement (n=69). While almost 80% of those requiring drug therapy were counseled on their cholesterol levels, only 55% reported being prescribed a LLD at follow-up. There was also a significant difference in counseling and LLD prescription between respondents with baseline TC > 6.2 mmol/L and those with TC between 5.2 and 6.2 mmol/L. Three-quarters of those with highly elevated TC were appropriately receiving LLD, but only 45% of patients with borderline TC were on drug therapy. Literature reports have indicated that physicians tend to withhold medication for dyslipidaemia treatment until cholesterol levels are well above guideline cut-offs, and prefer to employ only dietary therapy for those with marginally elevated serum lipids\(^158\). Doctors may have been concerned about drug compliance or medicalisation of patients in whom they perceive less risk of CAD morbidity and mortality. Also, for the sake of simplicity in the face of innumerable treatment guidelines, family physicians may have wished to use only TC as the criterion for drug therapy, rather than having to screen for other lipid parameters such as LDL-C and HDL-C\(^159\).
For those respondents requiring drug therapy according to CCCC guidelines who reported meeting TC targets at follow-up (n=35), over 80% were prescribed LLDs. It is unclear as to whether these individuals were more appropriately treated or whether this finding was merely an indication that LLDs were efficacious in lowering TC to the desired goal.

As with dietary therapy, the number of patients who should have been prescribed LLDs according to the 2000 Canadian guidelines was vastly greater than was borne out by the Canadian guidelines of the time (252 vs 101; p≤0.001). The prevalence of respondents who were appropriately managed, however, was once again comparable between the two.

Follow-up LDL-C levels were not available for respondents, and so target achievement could not be assessed according to NCEP guidelines. Therefore, all respondents who required dietary therapy were assumed to have required subsequent drug therapy if their LDL-C levels were above recommended levels. This assumption was less than ideal, as some of these patients may have met LDL-C targets and not required LLDs. Hopefully, however, this was balanced by those whose LDL-C levels may have risen above drug target levels following SCA, but who were not included in the analysis due to the lack of recent lipid levels.

A greater number of respondents required medication management of their dyslipidaemia based on NCEP guidelines compared to CCCC guidelines (153 vs 101). Although it would appear that a greater proportion of respondents was treated appropriately with LLD under the American guidelines (62% vs 55%), this difference did not achieve significance.

There have been no studies looking directly at adherence to CCCC drug therapy guidelines. However, the CQIN investigators did observe that only 8% of high risk patients in an acute care setting received drug intervention for dyslipidaemia. While 55% is certainly a vast improvement over this finding, LLD treatment among respondents was less than optimal. Previous studies on adherence to NCEP guidelines have shown that appropriate drug therapy has
been administered to anywhere from 37% to 52% of patients\textsuperscript{160-113}. The prevalence of appropriate drug therapy in this cohort of respondents appeared to be slightly better than the literature. However, 38% of patients remained inappropriately treated according to NCEP guidelines. This was sub-optimal and increasing efforts should be made to comply with evidence-based recommendations for dyslipidaemia management.

Multivariate models of appropriate drug therapy predictors were somewhat unstable, primarily due to small numbers. However, differences in parameters associated with CCCC appropriate treatment versus NCEP appropriate treatment did emerge. Whether a respondent received LLD in accordance to Canadian guidelines was based solely on the prescription of LLD at baseline, and the initial TC level. While the effect of baseline lipid medications could not be estimated using logistic regression, an increase in TC of 1 mmol/L improved the chances for proper LLD administration by over three-fold.

The predictors of appropriate drug therapy based on NCEP guidelines were more varied and more variable. Having undergone PTCA prior to SCA increased the chances of receiving LLD by almost 14 times, while suffering a MI lowered the chances by almost 80%. That patients with a history of MI would be less likely to be treated appropriately with medications was distressing. Post-MI patients are at high risk for further CAD events, and the Number-Needed-to-Treat (NNT) has been shown to be lower than for patients with no history of atherosclerotic disease\textsuperscript{161}. A possible explanation for this finding may be that angioplasties would have been performed at a tertiary care hospital under the care of cardiologists. On the other hand, diagnosis and treatment of MI may have occurred at a non-tertiary hospital with limited specialist resources. Prescription of LLDs following MI may have been less likely under these circumstances. In addition, studies have shown that lipid levels decrease following an acute event, such as a MI. Although there was no record of the timing of MI's at baseline, if an
event had occurred within 3-6 months of the original SCA, the lipid levels may have been falsely low; potentially below guideline thresholds for LLD treatment.

The observation that respondents with higher LDL-C levels at baseline were less likely to be taking LLD at follow-up was equally disheartening. However, the large confidence intervals for many of the variables may denounce the model as a poor fit for the data. Other lipids associated with appropriate NCEP drug therapy were HDL-C concentration and TC/HDL-C ratio. The effect of HDL-C could not be estimated. However, an observed increase of one unit in TC/HDL-C ratio predicted a 14-fold increase in appropriate LLD use. Finally, baseline prevalence of LLD was highly associated with suitable medication therapy at follow-up.

There are striking differences in the selection criteria for treatment between the three sets of guidelines. Direct comparisons of the ability of CCCC guidelines, NCEP guidelines, and a Framingham multivariate risk equation (a precursor of the Canadian 2000 guidelines) by Grover et al\textsuperscript{162} revealed that the NCEP guidelines were slightly better than CCCC guidelines in discriminating overall CHD risk, while the model based on the Framingham Heart Study showed the greatest ability to predict coronary deaths. However, regardless of number of respondents allocated to treatment groups, there was no difference in the prevalence of appropriate dyslipidaemia treatment using any of the guidelines. And thus it remains that the education of physicians on appropriate management of CAD risk factors along with the promotion of awareness and compliance among patients at risk is of utmost importance for the prevention of cardiovascular disease and death.

4.4 IMPACT ON CLINICAL PRACTICES

The biases created by the low response rate weaken the applicability of the study findings to broader populations. Future studies using a mail-out questionnaire should make every attempt
to maximise the rate of response. Face-to-face and telephone interviews have been shown to have higher response rates, although they require considerably more time and money to carry out\textsuperscript{163}. While obtaining self-reported data allowed for the assessment of patient awareness of CAD risk factors, the accuracy of information about medication usage, morbidity, and diet must be viewed with a degree of suspicion. Future researchers may wish to have the patients fill out the questionnaire with their physician or cardiologist. Money could be saved and data made more reliable by simply conducting a retrospective chart review. However, hospital charts often lack data about lifestyle risk factors, and patient awareness can not be assessed.

This study was unique both in the population that was examined and the results that were obtained. Although there were limitations associated with a less-than-ideal response rate and self-reported data, the findings from this research can be used to inform CAD and dyslipidaemia treatment practices in British Columbia in the context of both primary and secondary prevention.

Opportunities for lipid screening were missed in one-quarter of respondents. The use of dietary therapy, regardless of the guidelines used to judge the need for intervention, was appropriate in about 70\% of respondents. While this was on par with literature reports, treatment of dyslipidaemia through diet must be improved in order to decrease health costs to society. Administration of LLD according to published recommendations was certainly sub-optimal. Not even two-thirds of patients who returned the questionnaire were receiving appropriate drug therapy.

Although the Canadian 2000 guidelines could not be used to judge the treatment practices of physicians between 1993 and 1997, they most certainly provide a fresh opportunity to improve current practice. Using the criteria outlined for dietary and drug therapy, a significant number of British Columbians referred for SCA would require intervention to manage their dyslipidaemia. Physicians' compliance to guidelines may have been poor due to confusion or
misinformation regarding diagnostic and treatment recommendations. The simplified risk assessment algorithm of the recent Canadian guidelines may improve their ability to target patients for appropriate treatment.

Along with guidelines for dyslipidaemia, the need to manage other CAD risk factors must be emphasised. This study revealed a disappointing lack of patient awareness regarding obesity, physical activity, high blood pressure, cholesterol, and CAD morbidity. Patient understanding of health behaviours and risk factors should be improved. In this way, increased compliance with medication and lifestyle modification, along with a reduction in morbidity and mortality may be achieved. The consistent use of "experts" to counsel patients on behaviour changes should be encouraged. Dieticians, exercise instructors, and smoking cessation nurses have an important role to play in educating patients about health risks, and providing them with new strategies to ensure that alteration of diet and exercise habits remains a lifelong priority.

The treatment of CAD and dyslipidaemia in study respondents was not ideal. These results are from two university-affiliated tertiary care hospitals. Presumably, the appropriate management of patients may be worse at other hospitals without the support of highly trained specialists and access to the latest research. There have been changes in practice since this cohort was examined. St. Paul's Hospital now has a drug therapy discharge sheet (Appendix 3). Medications that have a significant impact on lowering CAD morbidity and mortality must be considered for all patients following MI or revascularization procedures, with reasons given if the drug is not prescribed.

CAD is the leading cause of death and disability in British Columbia and Canada. Many years of research have contributed to the understanding of risk factors and treatments for morbidity and mortality due to heart disease. Appropriate primary and secondary prevention of
CAD according to evidence-based guidelines is imperative in order to reduce health costs and improve the quality and length of life of British Columbians.
5 REFERENCES


24. Kannel W. Range of serum cholesterol values in the population developing coronary artery disease. Am J Cardiol, 1995; 76: 69C-77C.


29. Assmann G and Schulte H. Relation of high-density lipoprotein cholesterol and triglycerides to incidence of atherosclerotic coronary artery disease (the PROCAM experience). Am J Cardiol, 1992; 70: 733-737.


35. Ridker P, Hennekens C, and Stampfer M. A prospective study of lipoprotein(a) and the risk of myocardial infarction. JAMA, 1993; 270(18): 2195-2199.


Appendix A

Study of Cholesterol Esterification and Coronary Artery Disease

Coordinated by: Drs J Frohlich and H Pritchard
Department of Pathology and Laboratory Medicine
University of British Columbia

Funded by: Medical Research Council of Canada

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Personal Information

To be completed by the patient:

- What is your name? ________________ ________________
- Date of Birth (d/m/y) ________ ________ ________
- Sex M ☐ F ☐
  - If female, have you passed menopause? Y ☐ N ☐
  - If yes, do you take hormone replacement therapy? Y ☐ N ☐
- What is your ethnic background?
- Have any of your close relatives (parent, brother, sister, uncle, etc) had significant heart disease (MI or angina) before the age of 60? Y ☐ N ☐
  - If yes, how many relatives? ______
- Which category best describes your exercise habits? ☐ none ☐ occasional (slow walks several times a week) ☐ moderate (active, ie: jogging twice a week) ☐ heavy (daily vigorous exercise)
- What category best describes your smoking habits? ☐ I have never smoked ☐ occasional (less than 10 cigarettes a week) ☐ moderate (approximately one pack a day) ☐ heavy (more than one pack a day)
  - If you smoked in the past, how many years ago did you stop? ______, and how much did you smoke (pks/day)? ______
- What category best describes your drinking habits? ☐ never ☐ occasional (less than 1 drink a day) ☐ moderate (1 to 2 drinks a day) ☐ heavy (more than 3 drinks a day)
- Are you a vegetarian? Y ☐ N ☐
  - If yes, for how many years have you been a vegetarian? ______

---

Patient ID# __________ Apo B __________ HDL TC __________
TC __________ APO AI __________ HDL FC __________
FC __________ APO AII __________ HDL TG __________
TG __________ LpAI __________ Plasma LCAT __________

FER HDL __________ MER HDL __________
HDL 2b __________ HDL 3a __________
HDL 3b __________

Comment

Atherosclerosis Specialty Laboratory

Phone: (604)875-3087
Fax: (604)875-2787
Clinical Information

to be completed by the physician/designate

1 Weight
   Height
   Waist circumference

   - Any significant weight gain/loss over last 3 months (± 3kg (7lb))?

2 Documented history of disease:

A Personal history

- CAD
- PVD
- CVD
- Diabetes Mellitus
- Renal Insufficiency
- Hypertension

   → If previous CAD present:

   - Angiography
   - Angioplasty
   - Bypass surgery
   - MI

B Family history

- CAD
- PVD
- CVD
- Diabetes Mellitus
- Hypertension

3 Indicate all current medications and specify:

- ASA
- ACE inhibitors
- Beta blockers
- Calcium channel blockers
- Antioxidants (vitamin E, carotene)
- Lipid lowering drugs
- Other

4 Result of current angiography:

- How many vessels affected?
  - None
  - 1
  - 2
  - 3

- What is the percentage obstruction?
  - <50%
  - >50%
This form should take approximately 10-15 minutes to complete. Please try to answer all of the questions to the best of your ability.

Today's date: __________________________ dd/mm/yy

What is your Personal Health Number? __________________________ (On the front of your CareCard)

Name: ___________________________________________ Birthdate: __________________________ dd/mm/yy

How tall are you? _______________ in/cm How much do you weigh? _______________ lbs/kg

Has your weight changed in the past four years? □ Increased □ Decreased □ Stayed the same

If your weight has changed, by how much approximately? _______________ lbs/kg

With a tape measure, lie on your back, relax, and measure around your waist at the level of your belly button. What is the measurement? _______________ in/cm

SMOKING
Have you ever regularly smoked tobacco? □ Yes □ No If yes, how many years? _______________

□ I don't smoke anymore

When did you quit? __________________________

□ Occasional (less than 10 cigs/week)

□ Moderate (approx. 1 pack/day)

□ Heavy (more than 1 pack/day)

EXERCISE
Has there been any change in your exercise habits in the past 4 years? □ Yes □ No

□ Don't exercise

□ Occasional (slow walks many times/week)

□ Moderate (active, ie: jogging 2x/week)

□ Heavy (daily vigorous exercise)

ALCOHOL
Has there been any change in your drinking habits in the past 4 years? □ Yes □ No

□ Don't drink

□ Occasional (Less than one drink/day)

□ Moderate (1 to 2 drinks/day)

□ Heavy (more than 3 drinks/day)

NUTRITION
Have you made any changes to your diet in the past 4 years? □ Yes □ No

□ Traditional North American diet

□ Low fat/cholesterol diet

□ Calorie-reduced diet

□ Vegetarian

□ Other (eg. Jenny Craig) __________________________
CHOLESTEROL
Has your cholesterol been checked in the past four years?  □ Yes  □ No
When was it last measured? ________________________
What was the most recent measurement? _______________  □ Don’t know

HYPERTENSION
Do you have high blood pressure?  □ Yes  □ No  When was it last measured? ________________
What was the measurement? _______________  □ Don’t know

DIABETES
Do you have diabetes?  □ Yes  □ No
If yes, do you take insulin?  □ Yes  □ No

DOCTOR/HOSPITAL VISITS
In the past four years, have you been seen for heart trouble or blood vessel disease? □ Yes  □ No
In the past four years, have you had any of the following:
- Angioplasty  □ Yes  □ No
- Bypass surgery  □ Yes  □ No
- Heart attack  □ Yes  □ No

What is your family doctor’s name? ________________________
When was the last time you visited a heart specialist? ________________

LIFESTYLE COUNSELLING
Has anyone discussed any of the following issues with you? □ Yes  □ No
If yes, which ones were discussed? □ Yes  □ No
Who discussed it/them with you?
- Doctor
- Nurse
- Dietician/nutritionist
- Exercise instructor
- Physical/occupational therapist
- Family/friend

MEDICATIONS
Which of the following types of medications do you take regularly? (check all that apply)
- Cholesterol medication  □ Yes  □ No
- Blood pressure medication  □ Yes  □ No
- Heart medication  □ Yes  □ No
- Diabetic medication  □ Yes  □ No
- Aspirin/Blood thinners  □ Yes  □ No
- Hormone Replacement Therapy  □ Yes  □ No
- Anti-depressants  □ Yes  □ No
- Vitamins  □ Yes  □ No
- Natural medicines  □ Yes  □ No
- Other  ________________

If possible, please include a list of the medications you take including name of drug, dose, and date started.

Thank you for filling out this questionnaire. Your help with this research is appreciated.
**St. Paul's Hospital**

**CARDIAC DISCHARGE ORDERS**

**Discharge Prescription Order Form**

**Name:** ____________________________

**Allergy:** ____________________________

- [ ] Computer-generated medication profile (prepared by a pharmacist & reviewed with patient) requested. *(NOTE: Complete 24 hrs prior to discharge)*

<table>
<thead>
<tr>
<th>DRUG</th>
<th>DOSE/FREQUENCY</th>
<th>QUANTITY/REFILL</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ACE INHIBITORS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Enalapril</td>
<td>[ ] Not indicated</td>
<td>[ ] Contraindicated</td>
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<tr>
<td>Ramipril</td>
<td></td>
<td></td>
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<tr>
<td>Other</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>ANTICOAGULANTS/ANTIPLATELETS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ASA</td>
<td>[ ] Not indicated</td>
<td>[ ] Contraindicated</td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>[ ] Not indicated</td>
<td>[ ] Contraindicated</td>
</tr>
<tr>
<td>Warfarin</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>BETA-BLOCKERS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acebutolol</td>
<td>[ ] Not indicated</td>
<td>[ ] Contraindicated</td>
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<tr>
<td>Metoprolol</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>CALCIUM CHANNEL BLOCKERS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amlodipine</td>
<td>[ ] Not indicated</td>
<td>[ ] Contraindicated</td>
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<tr>
<td>Diltiazem CD</td>
<td></td>
<td></td>
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<tr>
<td>Verapamil SR</td>
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<td></td>
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<tr>
<td><strong>DIURETICS</strong></td>
<td></td>
<td></td>
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<tr>
<td>Furosemide</td>
<td></td>
<td></td>
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<tr>
<td>Spironolactone</td>
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<tr>
<td>Hydrochlorothiazide</td>
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<tr>
<td><strong>LIPID-LOWERING MEDICATIONS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atorvastatin</td>
<td>[ ] Not indicated</td>
<td>[ ] Contraindicated</td>
</tr>
<tr>
<td>Pravastatin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>NITRATES</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nitroglycerin patch</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Isosorbide dinitrate</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>OTHER MEDICATIONS:</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- Discontinue all other medications if not listed on this sheet.

**Distribution:**
- White copy: Give to patient on discharge.
- Canary Copy: Fax copy of this form to Dr. ____________________________ and place back on chart
- Pink copy: St. Paul's Hospital Pharmacy

**Form No. NF180T (09/99)**

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**Signature/MSC #** ____________________________ **Date** ____________________________