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PROPHYLACTIC PHARMACOTHERAPY FOR CHOLESTEROL REDUCTION IN THE CANADIAN MILITARY: POTENTIAL FOR IMPROVED HEALTH AND COST-EFFECTIVE HEALTH CARE

by

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ABSTRACT

Introduction: Statins may be under-prescribed in clinical settings. This study was undertaken to determine if the same is true in the military. The cost-effectiveness of statin therapy in patients identified by current Canadian cholesterol guidelines was also explored.

Methods: Charts of 1424 Canadian military personnel (age≥45) were reviewed at eleven Canadian bases. Risk factors and cholesterol values were used to identify drug therapy candidates and patients not being treated to target values. Cost-effectiveness ratios were estimated based on a systematic review of the literature.

Results: 53/111 patients on therapy were not being treated to target cholesterol levels, while 172/1313 not on therapy were drug therapy candidates. An average of 2.89 years of life saved (YOLS) in drug therapy candidates was forecasted, costing less than $10,000/YOLS.

Conclusion: The health benefits of statin therapy in this population are substantial and the cost-effectiveness is acceptable. Statin therapy warrants greater attention as a preventive strategy.

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1.0 INTRODUCTION

1.1 Background

Cardiovascular disease (CVD) is the leading cause of death in North America and in 1995 accounted for 37% of all deaths in Canada.[1] This disease, in addition to being responsible for a substantial number of lost years of life, is also the leading health care expenditure in Canada. [2] A large portion of CVD deaths are the result of coronary heart disease (CHD).[1] The total annual cost of CHD in Canada has recently been estimated to be 6.5 billion dollars. [3]

Coronary heart disease causation is multi-factorial. Factors which have been shown to independently contribute to the risk of future coronary events include elevated cholesterol[4,5], a personal history of CHD[6], premature heart disease in a first degree relative[7], left ventricular hypertrophy[8] , age[9] and smoking[7] , among others. People with medical conditions such as diabetes[10] and hypertension[7] are also at an increased risk of developing CHD.

Elevated cholesterol appears to hold a special status among risk factors for CHD. [I] Specifically, studies have shown that despite the presence of a number of CHD risk factors in many countries, only countries with elevated cholesterol levels have elevated rates of CHD, suggesting that elevated cholesterol promotes CHD progression. Furthermore, there is a strong interaction of elevated serum cholesterol levels with other risk factors for CHD, such as diabetes and hypertension. [II] The link that exists between elevated cholesterol and CHD has received support from both observational and intervention studies. These studies, in addition to showing

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I The relationship between cholesterol and coronary heart disease is examined by the Working Group on Hypercholesterolemia and Other Dyslipidemias in Detection and Management of Hypercholesterolemia, Health Canada, March 1997.

II For a more comprehensive discussion, readers are referred to the section "Interaction with other risk factors" in the Detection and Management of Hypercholesterolemia Health Canada, March 1997.

that people with elevated cholesterol are more likely to develop CHD[4,5], have proven that cholesterol reduction in this population results in a subsequent reduction in coronary events.[12,13]

Many pharmaceutical agents are available to patients with abnormal cholesterol levels, the most recent class of drug to be developed being the statin drugs, also known as HMG-CoA reductase inhibitors. Other classes of drug therapy that are available include bile acid sequestrants (cholestyramine and colestipol), fibric acid derivatives (clofibrate) and nicotinic acid (niacin). The benefits in terms of cholesterol reduction with drug therapy are usually seen after as few as three months of therapy[14] and the new statin drugs are associated with very few negative side effects.[15]

Drug trials have repeatedly and consistently shown significant decreases in the levels of total cholesterol and low density lipoprotein with the use of lipid lowering pharmacotherapy in both primary[16,17] and secondary prevention.[18,19] Such studies have also shown an increase in the protective lipoprotein fraction, high density lipoprotein cholesterol (HDL-c), to varying degrees. More importantly, the results of all but one of the seven major primary prevention randomized drug trials conducted prior to 1995 [12,16,17,20,21,22,23] that considered coronary event clinical endpoints demonstrated a reduction in the relative risk of non fatal myocardial infarction (MI) with the use of drug therapy to reduce cholesterol. The results of four of these studies [12,16,17,21] were statistically significant. The West of Scotland study (WOSCOPS), as an example, found relative risk reductions in both coronary events and coronary deaths of 29% and 33%, respectively over the course of the five year trial with the use of Pravastatin.[12] More recently, the benefits of lipid lowering medication in terms of coronary event risk reduction have been

demonstrated in patient populations with only moderate cholesterol levels in primary prevention.[24]

Secondary prevention randomized drug trials have also recently shown a clear benefit of pharmacotherapy, specifically statin therapy, on rates of both fatal and non-fatal CHD.[13,18] For example, the 4S study which examined the effect of simvastatin on CHD over 5.4 years of follow-up found a 30% relative risk reduction of coronary events and death. [13] As with primary prevention, the benefits of pharmacotherapy for CHD prevention have been demonstrated in people with only moderate levels of cholesterol.[19,25]

The lack of a relative risk reduction in all cause mortality, specifically in primary prevention drug studies, was initially an obstacle to the acceptance of drug therapy as a prevention strategy for CHD in people with elevated cholesterol. Initial clinical trials of patients free of CHD showed that while the cholesterol reducing pharmaceutical agents were often effective in reducing the risk of CHD events, patients on drug therapy were often found to have higher rates of other diseases such as cancer.[16,17,22]

Results from recent randomized trials of statin therapy have been instrumental in redefining the role of drug therapy in the primary prevention of CHD. Specifically, an overview of sixteen randomized trials carried out by Hebert and colleagues[26], which specifically examined the risk of stroke and increased mortality due to the use of statin drugs, found no significant difference in non-CVD deaths between treatment and placebo groups. Furthermore, the results of this analysis provided clear evidence of a reduction in stroke with the use of statin therapy in both primary and secondary trials, with the combined results of the secondary trials reaching statistical significance.[26] Lastly, this study also found an overall reduction in total mortality in

patients assigned to statin therapy when the results of the clinical studies were considered together.[26]

Given their impressive effect on CHD and stroke risk reduction and their recently proven lack of negative effect on overall mortality, the use of statin drugs for *both* primary and secondary prevention of heart disease is now encouraged. The results of recent clinical trials of statin therapy have played an important role in guiding policy for the use of statins in the prevention of coronary disease and stroke in the clinical setting. Recent changes in our understanding of the beneficial effect of statin therapy on CHD is reflected in the revised Canadian cholesterol guidelines[27] published in the June 1998 supplemental issue of the Canadian Journal of Cardiology, by the Working Group on Hypercholesterolemia and other Dyslipidemias (hereafter called The Working Group). The Working Group, composed of lipidologists, cardiologists, epidemiologists, nutritionists and general practitioners, among others, used an evidence-based approach in developing the revised Canadian cholesterol guidelines. These guidelines, which are similar in many respects to other guidelines developed in the United States and Europe[28-30], have the added benefit of simplicity for easy use in the clinical setting and a greater emphasis on multiple types of cholesterol levels, including the ratio of total cholesterol to high density lipoprotein and triglyceride levels.

1.2 The Revised Canadian Cholesterol Guidelines

The recommendations of the Working Group for the appropriate cholesterol management of patients at risk for CHD comprise an eight step process. Briefly, the guidelines recommend a total risk assessment, which includes a medical history and a physical as well as a fasting lipid

profile every five years for men over 40 and women over 50 years old. When multiple risk factors for CHD are present, more frequent cholesterol assessments are recommended.

After the appropriate diagnosis and treatment of medical conditions such as diabetes, obesity and hypothyroidism, it is recommended by the guidelines that the ten-year risk of coronary events be assessed for each patient, based on the number of non-lipid risk factors. Non-lipid risk factors identified by the guidelines include: age (>45 for men, >55 for women), family history of premature CHD in a first-degree relative, smoking, hypertension (≥140 mmHg systolic or ≥90 mmHg diastolic) or using antihypertension medication, diabetes and left ventricular hypertrophy. By summing the number of non-lipid risk factors, the risk level is estimated using the table provided in the guidelines in which four risk levels are identified, ranging from low to very high. A copy of this table appears in the following section (p. 19). According to the guidelines, patients with a personal history of CHD are automatically at a very high risk of future coronary events.

Target values for three lipid parameters, namely low density lipoprotein cholesterol (LDL-c), triglycerides (TG) and the ratio of total cholesterol (TC) to high density lipoprotein cholesterol (HLD-c) are presented for each risk category to help physicians identify patients whose lipid levels put them at an increased risk of developing CHD. In consideration of the fact that CHD is a multi-factorial disease, the target value for each lipid parameter decreases with increasing levels of risk, thus promoting lower cholesterol levels among those patients most at risk for CHD based on their non-lipid risk factors.

A stepped care approach is recommended for the management of patients whose lipid profiles exceed the target values identified in the guidelines. Lifestyle modifications, including

smoking cessation, diet therapy and exercise are recommended as the initial approach to cholesterol reduction, the effectiveness of which should be assessed within three months of initiation of the modifications according to the guidelines.[27] Patients whose lipid profile exceeds the target value of the LDL-c by at least 1 mmol/L or exceed the target TC to HLD-c ratio by more than one, despite attempts to reduce their risk of CHD through lifestyle modifications, are considered as candidates for drug therapy. Recommendations for the type of drug therapy to be initiated based on the lipid imbalances are also presented in the guidelines.

In the revised cholesterol guidelines triglyceride target values are also identified for each risk level. This is a reflection of the fact that an elevated triglyceride level has recently been identified as an independent risk factor for CHD.[7] There is, however, no current evidence that lowering triglyceride levels lowers the risk of developing CHD. Because of this fact, an elevated triglyceride level alone, in the absence of other lipid imbalances, does not warrant initiation of lipid lowering pharmacotherapy. This will likely remain so until evidence is provided which clearly demonstrates that lowering the level of triglyceride reduces the risk of developing CHD.

While future modifications and revisions to the current Canadian cholesterol guidelines are likely as we continue to understand better the effects of cholesterol on heart disease, these cholesterol guidelines represent an important contribution to promoting the appropriate management of cholesterol in the clinical setting. In these guidelines, important clinical findings of the last decade in the area of cholesterol and heart disease have been distilled using scientific methodology and are presented in a comprehensive and easy to use format. Managing patients based on the best available evidence will ensure the best possible outcomes and the best possible patient care.

1.3 Pharmacotherapy as a CHD Risk Reduction Strategy in People with Elevated Cholesterol

Based on the revised cholesterol guidelines[27], pharmacotherapy for cholesterol reduction is only one component of the overall CHD risk management strategy for patients with elevated cholesterol. The importance of this component must, however, not be underestimated given what is known about the other components of the overall risk management strategy. In the management of patients at risk for heart disease, three steps prior to pharmacotherapy are identified in the guidelines. These are: 1) the management of concurrent medical conditions, such as diabetes, that increase the risk of heart disease; 2) elimination of modifiable risk factors such as smoking from the risk factor profile and; 3) advise on how to improve diet and exercise to reduce cholesterol levels. Each of these steps, while intuitively appealing as a risk reduction strategy does not eliminate the excess risk of heart disease. With respect to the management of concurrent medical conditions such as diabetes and hypertenstion for example, it has been shown that the appropriate medical management of these diseases, while reducing the risk of CHD, does not eliminate the excess risk. Specifically, both insulin dependent and non-insulin dependent diabetics have been shown to develop CHD with greater frequency than non diabetics, even when well controlled. [31] The same is true for patients with high blood pressure, with treated hypertensives exhibiting higher rates of CHD than normotensives.[32] Given these findings, patients with concurrent medical conditions will have a higher risk of developing CHD despite having these medical conditions managed appropriately.

Research has shown that diet and exercise for cholesterol reduction as a risk reduction strategy is also of limited value in reducing the risk of heart disease on a long-term basis. While

the short-term effects of improved diet and exercise are compelling in terms of cholesterol reduction, the long-term effectiveness of these lifestyle modifications is disappointing. For example, an overview of sixteen clinical trials designed to evaluate the effectiveness of diets in lowering serum cholesterol in free living subjects found a reduction in serum cholesterol of only 0-4% in the trials which used a Step 1 diet as the intervention, and showed no overall benefit in terms of CHD mortality.[33] More recently, a systematic review conducted by Guyatt and colleagues [34] has reached similar conclusions. Specifically, in their review, the weighted-average risk ratio for both coronary heart disease mortality and overall mortality showed a small and insignificant reduction in the level of risk with diet therapy.[34] Based on these results and those of others it has now been realized that the impressive short-term results of dietary modification often obtained in institutional settings, cannot be extrapolated across time or to the population at large.

The unimpressive long-term outcomes of dietary interventions are believed to be the result of poor long-term compliance to diet interventions and the less controlled "real world" setting. Recently, the Canadian Task Force on Periodic Health Examination[35] stated that "There is no strong evidence that the dietary changes currently being advocated as the initial therapeutic intervention will reduce the risk of CHD in the general population or in high-risk groups". (p.658) For similar reasons of poor compliance, the long-term positive effect of exercise strategies in reducing the risk of CHD are being questioned.[36,37] Lastly, smoking cessation as a risk management strategy, while having notable health benefits for those who successfully quit[38], is a risk management strategy obviously limited to smokers. Furthermore, the quitting success rate in asymptomatic smokers is low, specifically in long-time smokers.[39]

Lastly, multiple risk factor interventions, which attempt to reduce the risk of CHD by eliminating or reducing several risk factors simultaneously, have also not proven to be effective long-term risk management strategies. In a recent systematic review of randomized controlled trials of multiple risk factor interventions[40], the authors concluded that "The pooled effects of multiple risk factor intervention on mortality were insignificant and small....."(p 1666). Only two of the fourteen trials included in this review used cholesterol lowering drugs as part of the intervention. The authors further reported that "changes in risk factors were modest, were related to the amount of pharmacological treatment..." (P 1666).

The poor long term compliance with lifestyle changes and dietary modifications, combined with the excess risk of heart disease that remains in patients with other concurrent medical conditions, makes second line therapy with lipid lowering medication an integral part of the overall risk management strategy in CHD risk reduction in patients with elevated cholesterol. Based on the available evidence on long-term compliance with lifestyle risk modification strategies, the majority of patients with elevated cholesterol levels will remain at risk, despite attempts to eliminate modifiable risk factors from their overall risk profile. For this reason, the degree to which cholesterol is being managed appropriately with lipid lowering pharmaceutical agents can be considered as a good indicator of how well cholesterol is being managed in the clinical setting. Risk reduction strategies which focus on improved pharmacologic management of patients with elevated cholesterol have the potential to yield large benefits. This is due to the number of patients in the clinical setting with elevated cholesterol, the poor long-term compliance of patients to lifestyle modifications, and the efficacy of the new statin agents in reducing coronary events, stroke and overall mortality.

The revised Canadian cholesterol guidelines[27] identify patients most likely to benefit from pharmacotherapy for CHD prevention. Unfortunately, we do not know how well cholesterol is being managed in the clinical setting with lipid lowering medication. The results of some studies would suggest that a gap exists in certain clinical settings between current practice and optimal cholesterol management [41-43] as defined by evidence-based cholesterol guidelines. This gap appears to be the result of inappropriate screening *and* management of cholesterol with lipid lowering agents. Specifically, results obtained in a recent Canadian survey of primary care practice, which collected data on the clinical management of 21,470 adults with respect to their risk for heart disease, found that less than half of the patients with diagnosed CHD had ever had their cholesterol checked.[41] McCormick and colleagues[42], in their study of drug prescription in people with previous myocardial infarction (MI), found a high degree of sub-optimal cholesterol management. In their study of 1710 patients with a previous MI they found that only 11.7% of the sample were on lipid lowering pharmacotherapy.[42] This was despite the fact that over 36% of the patients had elevated cholesterol levels.[42] Lastly, cholesterol management among patients who are receiving statin therapy also appears to be poor. Marcelino and Feingold [43] found that only 30 of the 90 patients in their study had successfully reached the treatment LDL-c goal after one year of drug therapy.

Because there are both financial and health-related consequences of not providing appropriate care with respect to elevated cholesterol in the clinical setting, determining any discrepancies which exist between current practice and the guideline recommendations is paramount. Also, quantifying the health benefits of improved cholesterol management in terms of life years saved and identifying the financial resources required to achieve these benefits

could provide the impetus for a greater investment into preventive pharmacotherapeutic strategies for CHD prevention.

Appropriate cholesterol management in certain occupational settings, such as the military, is of particular concern because of the potentially negative impact that heart disease can have not only on the military member themselves but also on those people under their care. The added responsibility and importance of closely medically monitoring people who are responsible for the well-being of others has long been realized by the aviation industry, which subjects its pilots to medical testing every six months. Similarly, the military performs routine medical exams on its personnel to ensure that they are fit for duty. Given the extra investment that these industries devote to the health of their employees, it could be expected that a gap might not exist between current and optimal cholesterol management. Specific to the military however, the results of a small study carried out at the National Defence Medical Centre (NDMC) in Ottawa[44] indicate that a discrepancy does exist between current practice and optimal cholesterol management with pharmacotherapy in at least one military medical establishment in Canada. It is not known whether the results of this study are indicative of systemic sub-optimal cholesterol management of military personnel with elevated cholesterol at risk for CHD. Identifying any discrepancies and improving cholesterol management in the military is also important given that most military personnel retire from the Canadian Forces by age fifty-five. Since the risk of heart disease increases with age, any financial burden of sub-optimal cholesterol management in the military will thus be borne by the civilian sector. Lastly, the existence of poor cholesterol management in closely medically monitored populations, such as the military, has implications for the feasibility

of appropriate cholesterol management in routine clinical care in the less structured and less well monitored civilian sector.

1.4 Aims and Objectives

The aims and objectives of the present study were as follows:

1) To determine the extent of any discrepancy that exists between current practice and optimal cholesterol management (as defined by revised Canadian cholesterol guidelines) with lipid lowering pharmaceutical agents in the Canadian military population.

2) To quantify the potential years of life saved by improved cholesterol management with cholesterol lowering pharmaceutical agents in personnel identified as candidates for drug therapy.

3) To quantify the financial resources required, from a Department of National Defence (DND) perspective, to improve the management of cholesterol in the military and further, to determine the cost-effectiveness of this risk management strategy in the identified population based on lifetime drug therapy.

To address objective one, non-lipid risk factor data and lipid measurements were collected from the medical charts of military personnel. Patients qualifying for cholesterol reducing drug therapy, based on the guideline recommendations, or patients on drug therapy but not being treated to target cholesterol levels were identified. To address the last two objectives, a systematic review of the existing literature on the cost-effectiveness of pharmacotherapy in the prevention of CHD was undertaken. Based on this review, high quality economic analyses were identified. The relevance of the estimates of these analyses to the current clinical population was

then assessed. Objectives two and three were then answered by applying the results of the most appropriate analysis(es) to the study sample.

2.0 METHODS

2.1 Sample Selection

A cross-sectional chart review of regular force personnel posted to eleven military bases across Canada was undertaken between July and November 1998. The sample was a convenience sample based on all charts available for military personnel over the age of forty-five, during a site visit at each of the eleven bases. Age was the only eligibility criteria for inclusion into the study. Age forty-five was chosen since it is at this time that age itself becomes a risk factor for CHD in men. Chart reviews of this population are particularly attractive because the military has a vested interest in the health of its employees and therefore has complete and comprehensive medical records. Specifically, all military personnel are required to have routine medical exams, which occur on a bi-yearly basis starting at age forty-five. Personnel for whom charts were not available, and who were thus not eligible for inclusion in the present investigation, were those personnel who were on an international posting (United Nations, foreign), navy personnel who were at sea, recently posted personnel or personnel not posted to one of the eleven major military bases in Canada.

2.2 Data Abstraction and Risk Estimation

Values of lipid parameters (TC, TG, LDL-c, HDL-c), as well as data on major non-lipid risk factors identified by the revised Canadian cholesterol guidelines (age: >45 for men, >55 for women, family history of premature CHD in a first-degree relative, smoking, diabetes, hypertension :≥140 mmHg systolic or ≥90 mmHg diastolic or using antihypertension medication) were abstracted from the medical charts of all personnel that met the eligibility criteria identified at each of the eleven bases. The medical risk factors for CHD were operationalized as follows

during the data abstraction: 1) Premature CAD in a first degree relative (men<55, women<65) was only considered a risk factor if the age of onset was documented in medical chart 2) The patient had to be a current smoker for smoking to be considered a risk factor 3) Hypertension and diabetes were only considered as risk factors if there was a medical diagnosis in the chart. The use of a medical diagnosis for hypertension and diabetes was felt to be appropriate because the diagnostic criteria provided in the cholesterol guidelines parallel widely disseminated guidelines, like those in the Canadian Guide to Clinical Preventive Health Care.[35] Also, because military personnel receive care from multiple physicians over the course of their military career, the likelihood that one of these medical conditions would go undiagnosed is minimized. Left ventricular hypertrophy, the last risk factor for CHD, was conservatively assumed not to be a risk factor for any of the personnel in the present investigation because it is not routinely assessed during military medical exams. Evidence of a personal history of coronary heart disease, defined as documented angina, myocardial infarction (MI), cardiac arrest (CA) , coronary artery bypass grafting (CABG) or a positive treadmill stress test, was also abstracted from the charts of each patient, as was the use of antihyperlipidemic drugs and their dose. Lastly, height and weight were recorded for each patient. A complete list of all the data abstracted from the medical charts appears in Table 1, while a copy of the chart abstraction form appears in Appendix A. Appendix B is a copy of the military medical exam forms completed at each of the scheduled routine medical check-ups. Because of the complete and comprehensive nature of these forms, missing data were not expected to be a problem in the present investigation.

Table 1 - List of Abstracted Variables

Risk Factor	Unit
Sex	Male/Female
Age	Years
Diabetes	Yes/No
Hypertension	Yes/No
Personal history of CHD	Yes/No
Premature History of CHD in 1st Degree relative	Yes/No
Current Smoker	Yes/No
Low Density Lipoprotein cholesterol (LDL-c)	mmol/L
High Density Lipoprotein cholesterol (HDL-c)	mmol/L
Triglycerides (TG)	mmol/L
Total cholesterol (TC)	mmol/L
Antihyperlipidemic Medication Prescribed	Yes/No
Name of Antihyperlipidemic Medication	(see appendix C)
Dose of Antihyperlipidemic Medication	daily dose
Height	Cm
Weight	Kg

Also abstracted from the charts was the date of the most recent complete fasting lipid profile. This date was recorded to determine the number of patients who had outdated lipid profiles, being those over five years old, as defined by the cholesterol guidelines. [27] A complete lipid profile was considered to include four cholesterol and lipoprotein measurements: High density lipoprotein cholesterol (HDL-c), Low density lipoprotein cholesterol (LDL-c), Triglycerides (TG) and Total Cholesterol (TC). Since LDL-c can be estimated from the other lipoprotein values using the Friedewald formula[III], missing LDL-c values were calculated, when possible. To reduce variability in data collection, all data were abstracted by one person, who

[III] Friedewald formula (all values in mmol/L): $TC - HDL\text{-}c - \frac{TG}{2.2} = LDL\text{-}c$ (valid only if $TG < 4.45$ mmol/L)

received training and strict criteria prior to the abstraction process. Reliability of the data abstraction was determined based on a re-abstraction of 3-4% the charts by the same data abstractor. Using the military pharmacy databases, the dates that antihyperlipidemic drug prescriptions were filled was also determined and recorded for patients on lipid lowering medication.

The number of patients with cholesterol levels above the target values being managed using non-pharmacologic therapy was not available or important to the present investigation. Given the poor long-term compliance to lifestyle modifications (see discussion, section 1.3) it was assumed in this investigation that patients would remain at risk for CHD because of elevated cholesterol, despite attempts to reduce their risk using non-pharmacologic therapy. Based on cholesterol values abstracted from the medical charts, patients with cholesterol levels at least 1 mmol/L above the recommended target level for LDL-c or one unit above the TC:HDL-c ratio were therefore considered as candidates for drug therapy.

Biologic variability of cholesterol measurements was an important consideration in this investigation, given that drug therapy classification was based on the lipoprotein fractions of one cholesterol measurement. There is evidence that the measurement of cholesterol demonstrates some within-person variability. Depending on the literature reviewed, the coefficient of variation (sd/mean X 100%), a commonly used measure of variability, ranges between 2% and 12% for the different lipoprotein fractions.[45,46] Triglyceride values tend to demonstrate greater variability, with the coefficient of variation ranging from 20% to 25%.[46] It should be noted that the magnitude of the coefficient of variation is highly dependent on the duration of time between measurements. Some studies that have found high coefficients of variation used measurements

taken one or more years apart.[47] One study took cholesterol values measured one, three and five years apart as a demonstration of cholesterol variability.[47] On the other hand, studies of cholesterol measurement variability that considered the change in cholesterol measurements over short durations (1-18 days), such as that by Rotterdam and colleagues[45] have found smaller coefficients of variation. This research group found a coefficient of variation of 2-3% at 1-4 days and a coefficient of variation of only 5% at 4-18 days.[45] Adding further evidence to the stability of cholesterol measurements is the fact that the cholesterol values of the control (placebo) group in many of the recent statin trials have shown only small fluctuations.[20,13] Given these findings, medical management decisions based on single cholesterol measurements were considered appropriate in the present investigation. The higher variability of triglyceride measurements was not a factor influencing the results of this investigation because medical management and the decision to initiate drug therapy does not depend on triglyceride measurements according to the current cholesterol guidelines.

Using the stratification method identified in the revised Canadian cholesterol guidelines[27], the ten-year risk of developing CHD was determined for each person. Using this method, patients were stratified to one of four risk categories (low, moderate, high and very high) based on their number of non-lipid risk factors (see Table 2). In keeping with the guidelines, all patients with a personal history of coronary heart disease were automatically placed in the very high risk category.

2.3 Identifying Sub-optimal Cholesterol Management

Candidates for cholesterol lowering pharmacotherapy were identified based on CHD risk and cholesterol levels using the chart which appears in the revised Canadian cholesterol

guidelines[27], which has been reproduced in Table 2. It can be seen in the chart that for each level of risk a target or desirable cholesterol value is identified for three lipoprotein fractions (LDL-c, TC/HDL-c, TG). Also identified in the chart are the values of LDL-c and TC/HDL-c at which drug therapy should be initiated for each level of risk. The drug initiation values are 1 unit greater than the target values for both of these lipoprotein fractions.

Table 2- Lipid target levels and patient's risk profile

Patient's risk category			Criteria for treatment				
Risk factors	**Risk level**	**10 year CAD risk (%)**	**Initiate drug treatment if** LDL-c Mmol/L	TC/HDL-c	**Target levels** LDL-c mmol/L	TC/HDL-c	TG mmol/L
≥4 or CAD	Very high	>40	>3.5	>5.0	<2.5	<4.0	<2.0
3	High	20-39	>4.5	>6.0	<3.5	<5.0	<2.0
2	Moderate	10-19	>5.0	>7.0	<4.0	<6.0	<2.0
≤1	Low	<10	>6.0	>8.0	<5.0	<7.0	<3.0

Source: Frohlich J, Fodor G, McPherson R, Genest J, Langner for the Dyslipidemia Working Group of Health Canada. Rationale for and outline of the recommendations of the Working Group on Hypercholesterolemia and Other Dyslipidemias: Interim report. Can J Cardiol 1998; 14(Suppl A): 17A-21A. Reproduced with permission.

Sub-optimal management was defined as one of the following:

1) Patients who met the criteria for drug therapy but were not currently being prescribed any lipid lowering medication

2) Patients currently on lipid lowering medication but not achieving the target goals based on their risk level

The potential benefits of improved cholesterol management with lipid lowering pharmacotherapy are greater in patients with symptomatic CHD, due to the higher event rate in this population. For this reason, sub-optimal cholesterol management in patients with CHD was considered separately.

While the revised cholesterol guidelines do not recommend the initiation of drug therapy if only triglyceride levels are exceeded (in the absence of other lipid imbalances) they do suggest that triglyceride levels be considered in the overall risk assessment.[27] For this reason personnel exceeding triglyceride target values by at least 1 mmol/L were identified, although they were not considered as being managed sub-optimally if only this lipid parameter was exceeded, and the potential benefits of improved triglyceride management were not considered for these personnel.

Because of the population being studied it was not expected that missing data would be a problem in this investigation. However, missing non-lipid risk factor data were recorded as "missing" in the data abstraction process. Missing values were not imputed. Missing, incomplete or outdated lipid parameters were also noted, since this prevented accurate determination of appropriate cholesterol management. Missing profiles were defined as those that were missing altogether, outdated profiles as those that were over five years old, and incomplete lipid profiles as those missing one or more lipid parameters that could not be calculated from the other lipid values (i.e TC, TG, HDL-c). In the event that the lipid profile was both outdated and incomplete, the lipid profile was considered outdated.

Sub-optimal cholesterol management in this study was determined based only on data available in the medical chart, so as to represent the information available to the treating physician. Therefore, missing values for non-lipid risk factors were conservatively assumed to be absent from the overall risk factor profile. Similarly, the identification of drug therapy candidates was determined solely based on lipid parameter values appearing in the medical charts. Missing lipid values did not therefore contribute to risk factor profile of the study subjects. The ultimate effect of this decision was likely to underestimate the extent of

hyperlipidemia in the military.

A final caveat with respect to the identification of sub-optimal cholesterol management specifically in personnel on lipid therapy relates to the how long the medication had been prescribed. Since the full benefit of lipid lowering medication, in terms of cholesterol reduction, are only achieved after three months of therapy[14], personnel on lipid lowering pharmacotherapy for shorter duration were omitted from consideration in the present investigation.

2.4 Rationale and Components of the Systematic Review

In order to quantify the role for improved cholesterol management with pharmaceutical agents in the clinical setting it is necessary to consider the costs and therapeutic benefit of this risk reduction strategy. The degree to which lipid lowering pharmacotherapy reduces the risk of CHD, at a price which society finds acceptable, determines the importance of incorporating this therapy into clinical practice, as well as the consequences of not doing so. The results of full economic evaluations of lipid lowering medication, which measure the incremental cost per unit of health gained from alternative interventions, can help determine a new therapy's place among currently accepted medical interventions and can assist decisions regarding the acceptance or rejection of a new therapy. Several guidelines have been published to improve the completeness of reporting of economic evaluations.[48,49]

Many economic analyses of lipid lowering pharmacotherapy for CHD prevention have been published. [50-54] These analyses have yielded a wide range of results ranging from several thousand dollars per life year saved[50] to several hundred thousand dollars per life year saved.[51] Therefore, while some economic evaluations conclude that lipid lowering pharmacotherapy is a cost-effective CHD risk reduction strategy, others do not. To address objectives two and three of

the present investigation, namely to determine the potential health benefits and cost-effectiveness of this risk management strategy, three options were identified and evaluated.

The first option was to combine the results of all relevant economic evaluations using a weighted average of the results based on the size of the study to arrive at a point estimate. This statistical procedure could not be carried out, however, due to the heterogeneity of the economic evaluations of lipid lowering medication in terms of the costs included in the evaluations and the length of benefit considered. Furthermore, the generalizability of the results obtained using this methodology to the population of this investigation would have been uncertain.

The second option available to meet objectives two and three was to identify a range of cost-effectiveness ratios and potential health benefits of lipid lowering medication. The focus of this method would have been the final cost-effectiveness ratios and not the method by which they were derived. Ranking of the cost-effectiveness ratios from lowest to highest would have provided a range and a "ball-park" estimate. Unfortunately, the results obtained using this methodology would have been of little value due to the high variability of the estimates.

The third and final option to answer objectives two and three was to subject the methodology of the existing economic evaluations to a rigorous examination using an objective set of criteria, in the form of a systematic review. The purpose of this review would be to identify economic evaluations of superior quality, which could then be considered further as the source of the estimates for the present investigation, taking into account the applicability of the results to the target population. This third option was chosen. The systematic review was undertaken with the aim of determining the resources required from a military perspective and identifying the potential health benefits and cost-effectiveness of better cholesterol management.

Systematic reviews differ from standard narrative reviews in several respects. Cook et al[55] outlined six design features which distinguish systematic reviews from narrative reviews, the key distinguishing feature being the extent to which scientific methods are used in the review process to minimize bias and error. Unlike narrative reviews, which tend to be broad in scope, non-specific in terms of sources and selection of studies and qualitative, systematic reviews are focused, comprehensive, criterion-based and include a quantitative summary. [55] If the quantitative summary provided in the systematic review uses statistical techniques it is termed a "quantitative systematic review", also known as a meta-analysis.

Economic analyses of cholesterol reduction by pharmaceutical agents have been considered in published overviews [56-58], but these overviews have been primarily descriptive in nature and results oriented, often focussing on the cost-effectiveness ratios obtained in the different economic analyses. The present systematic review was designed to more critically evaluate the methodologic quality of the economic analyses, using tools designed for this purpose, and to go beyond a simple assessment of the quality of reporting and discussion of the results.

Coronary heart disease has a long disease process. As such, the benefits of any preventive intervention, in terms of clinical outcomes such as death, will likely not be realized for several years. For this reason, modelling of disease outcomes in CHD is required to quantify the ultimate benefits of preventive therapy. Since modelling forms an integral part of economic evaluations of preventive therapies in CHD, the relative merit of economic evaluations are highly dependent on the quality of the models used to forecast the outcomes. As compared with other methodologic issues in economic evaluations, modelling has received surprisingly little

attention.[59] Specifically, while the validity of the inclusion/exclusion of production losses (i.e. lost wages) and the choice of discount rate of future costs and benefits have been at the forefront of several controversies and debates in economic health research [60,61], little attention has been paid to the methodology of economic modelling. Recently however, assumptions made in modelling have been shown to be powerful determinants of the results of economic evaluations in areas such as breast cancer research.[62] Any meaningful systematic review of the methodologic quality of economic evaluations in CHD prevention must therefore include a critical assessment of the modelling techniques, assumptions and omissions of the models used to generate the results.

While the methodology used to generate cost and benefit estimates in economic evaluations is important, so too is the quality of the reporting of these evaluations. Incomplete and poorly reported economic evaluations have the potential to provide a distorted picture of the cost-effectiveness of preventive programs. The importance of comprehensive and complete reporting of economic analyses has recently received increased emphasis in health care research. This has been reflected in the recent publication of reporting guidelines for economic analyses.[48,49]

The systematic review of the economic evaluations of lipid lowering pharmacotherapy in this investigation comprised two parts: an assessment of the quality of reporting of the analyses and an assessment of the quality of the models used to generate the estimates. By considering both of these components of the economic evaluations it was felt that high quality economic analyses could be identified. The completeness of reporting of the economic evaluations of lipid lowering therapy was assessed using previously developed published criteria.[48] Because

modelling techniques have not been subjected to the same scrutiny as other aspects of economic evaluations, published criteria with which to assess the quality of the models do not currently exist. For this reason, the quality of the models used in the economic evaluations being considered was determined using a checklist specifically developed for this investigation, based on a review of the modelling literature. A complete description of this checklist appears in a later section (p. 33) as does the rationale for inclusion of the checklist items. By considering the modelling methodology using this checklist, the appropriateness of the various models used in estimating the benefits of CHD prevention with lipid lowering medication was determined. A background to outcome modelling in CHD is provided in a later section. Also presented is a discussion of the types of models used to forecast long-term outcomes and benefits of preventive strategies for CHD. This is provided as a framework with which to understand the rationale for inclusion of criteria in the modelling checklist. Unlike the modelling checklist, a comprehensive description of the rationale for items in the reporting quality checklist has been described elsewhere[48] and will not be explored here.

Statins are the drugs of choice for managing elevated cholesterol, due to their potency and few associated side effects. For this reason, only economic evaluations of statins in primary and secondary prevention were included in the systematic review. Only full economic evaluations (cost-benefit, cost-utility, cost-effectiveness) were considered, since alternative preventive strategies for CHD differ in both the costs they incur and the benefits they produce. Cost-minimization analyses were specifically excluded from consideration in this review since these analyses specifically ignore the beneficial effect of a therapy on health outcomes, focussing only on the intervention costs and the costs averted by the therapy.

Since the aim of the systematic review was to quantify the potential long-term benefits and cost-effectiveness of improved cholesterol management, the review was restricted to clinically meaningful economic evaluations. These were considered as economic evaluations that considered long-term primary outcome measures (e.g. years of life saved) and not intermediate biological surrogates, such as cholesterol reduction. As such, economic evaluations that considered the cost per percent cholesterol reduction were specifically excluded from this review. Analyses which compared the cost-effectiveness of statins to alternative lipid lowering medications or compared a statin to another form of preventive therapy were only included in this review if the cost-effectiveness of statin therapy compared to usual care could be determined. No differentiation was made in this review between studies that included diet therapy as part of "usual care" and those that did not. This was due to the negligible effect that diet therapy has on risk modification. Also included in this systematic review were analyses that compared statin therapy to placebo since the effect of the placebo in the clinical trials on which these analyses were based is often found to be negligible.[12] In the event of double reporting of an economic analysis, both analyses were included only if the quality of reporting differed between the analyses. Also, studies that assessed the cost-effectiveness of a risk management strategy, of which statin therapy was only one part, were not included in this review because the cost-effectiveness of the statin therapy alone could not be determined. This systematic review was thought to be timely, in light of the recent advances in our understanding of the effect of statin therapy on cerebrovascular disease risk reduction, specifically on the risk of stroke. In the following two sections the reporting quality checklist and the modelling checklist are each described in turn.

2.5 Quality of Reporting of the Economic Evaluations of Statins

Published criteria were used to assess the comprehensiveness of reporting in economic evaluations of statin therapy. The criteria outlined in the guidelines published by Drummond and colleagues [48] for the BMJ Economic Evaluation Working Group were the main criteria used in the review. A copy of these guidelines appears in appendix D. These guidelines were chosen because of their scope and because they have been shown previously to have high inter-rater reliability [63] . Guidelines published by the Canadian Coordinating Office of Health Technology Assessment (CCOHTA) for the economic evaluation of pharmaceuticals[64] were used to supplement the Drummond guidelines with pharmaceutical specific criteria. Lastly, all criteria of the Drummond checklist related to modelling were removed from the checklist in the present assessment since the modelling quality of the economic evaluations was considered separately. Including these criteria in the reporting checklist would thus have resulted in double-counting.

Since a rationale for each criterion in the initial Drummond checklist has been provided previously by the authors of the checklist[48], the following discussion is limited to an explanation of modifications made to the initial checklist in the present investigation. These modifications were made to make the checklist more applicable to the present review and to remove items that would not contribute to the overall assessment. The first modification made was to the wording of questions 8 and 9 which was changed to include either efficacy or effectiveness. This was done to take into consideration the fact that most economic analyses of pharmaceuticals are based on the results of clinical trials, and are thus only considering efficacy. Because of this change, a criterion was added to the Drummond checklist[48] to determine if any consideration had been made by the authors in their economic analysis to take into account the differences commonly

observed between clinical trials and routine clinical care, such as drug compliance. This criterion appears as question 30 in the modified reporting quality checklist (Table 3).

Two criteria were added to the checklist to assess the degree to which quality of life was considered in the analyses and to determine if all appropriate costs were considered in determining the cost-effectiveness ratio. These additions appear as criteria 15 and 19, respectively, in the modified checklist. Since there is a current lack of reliable utility estimates in CHD, question 12 and 13 were omitted from the original Drummond checklist in the present investigation. Lastly, four pharmaceutical specific criteria identified in the CCOHTA document[64] mentioned previously, were added to the checklist (criteria 31-34), for a total of thirty-four criteria. A complete list of the modified checklist used to assess the reporting quality of the economic analyses of the statin therapy appears in Table 3. Each economic evaluation was assessed using this modified checklist.

While there were minor changes made to the initial Drummond checklist in the present review, these changes were not felt to impact negatively on the reliability of the checklist. Of the 35 criteria considered in the initial Drummond checklist 33 were retained in the modified reporting checklist or were covered in the modelling checklist. Furthermore, the two omitted criteria did not have any relevance to the present review and would have not contributed anything to the assessment.

Table 3 - Modified Reporting Checklist

Study Design Criteria	Yes	No	Not clear	Not applicable
1. The research question is stated				
2. The economic importance of the research question is stated				
3. The viewpoint(s) of the analysis are clearly stated and justified				
4. The rationale for choosing the alternative programmes or interventions compared is stated				
5. The alternatives being compared are clearly described				
6. The form of the economic evaluation used is stated				
7. The choice of form of economic evaluation is justified in relation to the questions addressed				
Data Collection				
8. The source(s) of effectiveness/efficacy estimates used are stated				
9. Details of the design and results of effectiveness/efficacy study are given (if based on a single study)				
10. Details of the method of synthesis or meta-analysis of estimates are given (if based on an overview of a number of effectiveness studies)				
11. The primary outcome measure(s) for the economic evaluation are clearly stated				
12. Productivity changes (if included) are reported separately				
13. The relevance of productivity changes to the study question is discussed				
14. Quantities of resources are reported separately from their unit costs				
15. Main costs considered				
16. Methods for the estimation of quantities and unit costs are described				
17. Currency and price data are recorded				
18. Details of currency of price adjustments for inflation or currency conversion are given				
Analysis and Interpretation of Results				
19. Justification for omission of quality of life (if not included) is provided				
20. Time horizon of costs and benefits is stated				
21. The discount rate(s) is stated				
22. The choice of rate(s) is justified				
23. An explanation is given if costs or benefits are not discounted				
24. Relevant alternatives are compared				
25. Incremental analysis is reported				
26. Major outcomes are presented in disaggregated as well as aggregated form				
27. The answer to the study question is given				
28. Conclusions follow from the data				
29. Conclusions are accompanied by the appropriate caveats				
30. Differences between efficacy and effectiveness considered				
Pharmaceutical Specific Criteria				
31. Therapeutic classification, dose, brand and generic name specified				
32. Approved indication specified				
33. Funding relationship specified				
34. Target population for the analysis specified				

A previous application of the reporting guidelines, in the area of perioperative transfusion[63] , distilled seven essential or desirable criteria from the comprehensive checklist developed by Drummond and colleagues. These selected criteria were also considered independently in this study. A list of the selected criteria appears in table 4.

Table 4 - Essential and Desirable Criteria in Economic Evaluations[63]

Essential Criteria
1) The viewpoint of the analysis
2) The form of economic evaluation
3) The primary outcome measure
4) Incremental analysis
Desirable Criteria
1) Relevance of productivity changes
2) Currency and price data
3) Justification of discount rate

2.6 Modelling the Benefits of Cholesterol Reduction with Statin Therapy

Due to the need for clinically meaningful economic evaluations which are based on long-term outcomes and not on intermediate endpoints, it has been recognized that modelling in economic evaluations is an "unavoidable fact of life".[65] This is especially true for diseases, such as CHD, with a long disease process. Models used to forecast the long-term outcomes of CHD with cholesterol reduction are of two types. The models either extrapolate final clinical endpoint data (CHD events, death) from clinical trials or base their estimates on intermediate endpoints (cholesterol reduction) and what is known about the association between cholesterol reduction and final clinical endpoints from epidemiological data. The first type of model is called an extrapolation model while the latter is defined as an epidemiological model. Each of these types of models will briefly be discussed in turn.

Extrapolation models used to estimate the long-term benefit of preventive risk

management strategies for CHD are necessitated by the short duration of most clinical trials, which are typically only five years in length. Extrapolation models in CHD typically develop survival curves using final clinical endpoint data, such as CHD events or death, from randomized controlled trials. These curves are then usually extended to estimate the long-term benefit of therapy in terms of life-years saved. Assumptions made regarding the benefits to be achieved from the therapy and the length of time over which the benefits are received are critical to the results of such models. For example, models that assume that benefits from a preventive therapy are accrued over a lifetime, and are not limited to a specific timeframe, will yield much higher beneficial estimates and will yield lower cost-effectiveness ratios. Equally important in such models is the choice of distribution (e.g. Weibull, Gompertz, exponential) used to forecast the outcomes based on the trial data.

Intermediate endpoints are commonly used in clinical trials to assess the efficacy of risk reduction strategies in diseases, such as CHD, where the final clinical outcomes take many years to develop. In forecasting future benefits based on intermediate endpoints, epidemiological models, as the name implies, take advantage of available information from epidemiological studies. Specifically, coronary heart disease models commonly use CHD risk equations based on risk factor data and intermediate cholesterol measurements developed from the results of the Framingham Heart Study[66] to forecast CHD events over time. In estimating the long-term benefit of cholesterol reduction on CHD, these models use pre and post treatment cholesterol levels from the clinical trials and estimate the corresponding reduction in risk of coronary events based on the association between cholesterol and heart disease from epidemiological data.

Decision analytic techniques are commonly used in the modelling component of

economic evaluations of cholesterol reduction in the prevention of CHD. Decision analysis allows complex problems to be disaggregated into more manageable units. The techniques used in decision analysis are designed to simplify and make explicit the process taking place in making a decision and the assumptions made in the prediction process. A special type of decision analytic model, the Markov model, is particularly useful in forecasting long-term CHD outcomes because of the fact that this type of decision analytic model allows for disease recurrence. Briefly, Markov models comprise a certain number of disease states and associated transition probabilities between the states. For this reason, these models are also referred to as state-transition models. Logistic functions from epidemiological studies in conjunction with risk factor data are used to develop the transition probabilities in these models when the long-term outcomes are forecast based on intermediate endpoints. However, when the estimates are based on final clinical endpoints (such as death) from randomized controlled trials the transition probabilities in these models are based on the hazard rates derived from the in-trial data. In all cases, simulations using Markov models are based on a certain number of cycles, the length and number of which are determined by the user of the model, based on the time over which estimates need to be forecast and the frequency with which the events occur. In all simulations, only one transition is allowed per cycle. In modelling the benefits of cholesterol reduction on life-expectancy, Markov models typically use a cycle length of one year and extend the simulations into old age. Models, whether based on intermediate or final clinical endpoints, are useful to the extent that they forecast relevant outcomes and are faithful to the disease process that is being modelled. With respect to CHD and preventive pharmacotherapy, a model will accurately forecast the benefits of the therapy to the extent that it: 1) takes into account both

disease and drug characteristics, 2) is based on clinical data and 3) accurately models clinical events over time.

2.6.1 Model Evaluation Checklist

To assess the quality of the models used in the economic analyses being reviewed a checklist for good modelling was created based on what is known about CHD, statins and appropriate modelling techniques. This checklist was based on a critical review of the existing literature in each of these fields. As mentioned previously, the generation of this checklist was necessitated by the absence of existing evaluative tools or scales to assess modelling quality in economic evaluations. The checklist generated comprised both generic and disease specific criteria. The generic criteria included in the checklist were those that are considered part of good modelling practice, and included the use of sensitivity analysis and accurate model description and validation. Disease specific criteria were designed to determine the appropriateness of the model being used to forecast long-term clinical outcomes based on what is known about CHD and statins given the existing literature. Criteria falling under this subheading included the time-horizon of the forecasted benefits of the therapy, the positive effect of statins on the risk of stroke and the type of clinical endpoint used to generate the forecasted estimates. Finally, the checklist was reviewed by both economic modelling and cardiovascular disease experts for content. The complete model evaluation checklist appears in Table 5 (p. 39). The quality of each model being reviewed was assessed based on the responses to each item in the checklist, and graded accordingly. Lastly, if a reference was provided in an economic analysis for a more complete model description in a separate publication, this publication was included in the modelling evaluation. The rationale for inclusion of each item in the checklist appears in the following

section. References for more complete discussions are provided where possible.

2.6.2 Rationale for generic criteria

1) Model type described in detail (or described accurately in separate publication)

Models used to forecast costs and benefits of preventive strategies should be described in enough detail to enable the reader to decide on the appropriateness of a model and to understand the process by which the outcomes were forecast. The variable modelling techniques used to forecast outcomes in CHD prevention pre-empted the use of rigid criteria in this respect. This criterion focussed primarily on model transparency.

2) Choice of modelling strategy justified

Rationale and model justification were considered important because of the many ways in which the long-term clinical outcomes in CHD can be forecast. The choice of modelling techniques used to forecast the long-term outcomes can affect the results of the study and should thus be justified. The justification provides evidence that the person conducting the economic evaluation carefully considered the options available to them in carrying out the analysis.

3) Model assumptions explicit and justified

Models represent a simplification of reality. In their development, assumptions must be made. These assumptions should be explicit and justified to allow the reader to assess the reliability and validity of the results obtained using the model. In the past, models have typically been criticized as having a "black box" feel to them. For this reason, it is important that predictive models be described explicitly and furthermore it must be clear to the reader what the model is and is not doing. Lastly, transparency in terms of the decisions made in the course of developing the model is also important.

4) Model assumptions tested using sensitivity analysis

While assumptions must be made in developing a model, it is important to assess the impact of differing assumptions on the results of the model. The outcome of sensitivity analysis, which assesses the robustness of model results, is important in illustrating the effects of the assumptions on the results of the model.

5) Key parameters of the model tested using sensitivity analysis

The results of economic models are usually contingent on the values of a set of key parameters. In CHD and statin therapy these parameters include the cost of the medication and subsequent medical care, the expected efficacy of the medication in lowering the risk of CHD and the discount rate used to discount future cost and benefits. Assessing the robustness of study results by varying these parameters provides insight as to how the cost-effectiveness of the prevention strategy can be improved, while providing support for the reliability and robustness of the results.

6) Ranges used in the sensitivity analysis stated

Being explicit about the range used in the sensitivity analysis allows the reader to evaluate for himself conclusions drawn regarding the robustness of the study results.

7) Ranges used in the sensitivity analysis justified

The ranges used in the sensitivity analysis should not only be explicit, but justified. The rationale behind the choice of the minimum and maximum values used in the analysis should be clearly stated and founded on statistical or clinical evidence; for example 95% confidence intervals, or smallest and largest risk reductions for CHD found in the literature, respectively. Sensitivity analysis carried out over too small a range could potentially provide misleading

information with respect to the robustness of the study results.

8) Approach to sensitivity analysis stated

Several forms of sensitivity analysis exist, including one-way and multi-way sensitivity analysis, threshold analysis and Monte Carlo simulations. The results obtained using each of these forms of sensitivity analysis will differ depending on the model used to forecast the results and the interaction among the key parameters in the model. It should be clear which of these forms of analysis was undertaken to test the robustness of the results.

9) Model validated

Having evidence that a model has been successful in its attempt to accurately portray reality provides support for the use of the model to forecast the benefits of a preventive therapy. Model validation is an essential component of modelling in economic evaluations.[67] The results of models whose predictions have been validated against observed external data, are more credible than results from non-validated models, since the validity of the model's estimates in the latter case is not known.

2.6.3 Rationale for Disease Specific Criteria

1) Appropriate duration of benefits given current clinical practice and epidemiological data

Coronary heart disease has a long disease process and has been shown to be age related, with the risk increasing with age. [9] The benefits to be gained from statin therapy therefore accrue over a life-time. For this reason, models which consider lifetime costs and benefits of statin therapy are more informative for guiding public policy than models which consider benefits from statin therapy of short duration (i.e. 3-5 years), like those based on short-term clinical trials. Short-term cost-effectiveness estimates can yield different results than long-term estimates, often

underestimating the benefits of therapy.[68]

2) Appropriate time horizon used to forecast long-term outcomes

Independent from the duration of the benefits received by statin therapy, the time horizon used to forecast the long-term cost-effectiveness of statin therapy should ideally span a life time or to a sufficiently old age. Estimates of changes in life expectancy due to a preventive therapy should consider the potential life span of the population for which the estimates are being derived, and not a portion thereof.

3) Model includes the decrease in CHD risk after coronary events with the use of statins

Since the effectiveness of statin therapy in reducing the risk of CHD has been demonstrated in both primary and secondary prevention, patients prescribed statin therapy to lower their risk of having a coronary event would not subsequently be taken off the medication in clinical practice after such an event. Models that attempt to accurately forecast the benefits of statin therapy in terms of life expectancy should therefore also consider the benefits of statin therapy in risk reduction after a coronary event. This is also true in people who have a personal history of CHD and have a recurrent event (tertiary prevention).

4) Model includes positive effect of statins on stroke

Statin therapy in both primary [12] and secondary prevention[13] has been shown to reduce the risk of stroke by almost 30%. Any model that does not include this effect will underestimate the benefits of statin therapy.

5) Model incorporates a lag-period

Therapy with statins has repeatedly been shown to be subject to a "lag-period".[12,13] During this time, statins are being consumed, but the full benefit of the therapy in terms of a

reduction in clinical events is not being realized. Models that attempt to forecast the long-term benefits of statin therapy should therefore include the effect of this lag-period in the model so as not to overestimate the benefit of the therapy.

6) Appropriate risk equation used to model final clinical outcomes or appropriate techniques used to extrapolate final clinical endpoint data

Risk equations, such as those developed from the Framingham heart study, have undergone revisions and updates since their initial publication.[66,69] Risk equations based on more accurate and up to date information will lead to more accurate predictions. With respect to extending final clinical endpoints beyond the end of the trial, the statistical methods used must be explicitly described and justified in the analysis.

7) Extent to which the forecasted outcomes are based on clinical data

Models based on intermediate endpoints observed in clinical trials, such as total cholesterol or LDL-c reduction, need to forecast long-term benefits of statin therapy based on what is known about the association between CHD and cholesterol, using epidemiologic data. The use of epidemiologic data to predict long-term benefits of cholesterol reduction involves assumptions regarding the relationship that exists between cholesterol reduction and associated coronary event reduction. The use of final outcome data observed in clinical trials to forecast the long-term benefits of therapy has traditionally been preferred over intermediate endpoints in modelling.

8) If intermediate endpoints are used, what lipoprotein fraction(s) are used to model the outcomes?

The Framingham equations which are commonly used to estimate the long-term benefits from intermediate endpoints have used different lipoprotein fractions to estimate the clinical

benefits of cholesterol reduction. While initial risk estimations were based on reductions in total cholesterol, more recent estimations based on increases in HDL-c or the ratios of either TC to HDL-c or LDL-c to HDL-c have been shown to lead to more accurate predictions.[5]

Table 5 - Model Evaluation Checklist

Generic Criteria	**Response**	**Points**
1) Model type described in detail (or reference provided)	Y/N	no = 0, yes=1
2) Choice of model justified	Y/N	no = 0, yes=1
3) Model assumptions explicit and justified	Y/N	no = 0, yes=1
4) Model assumptions tested using sensitivity analysis	Y/N	no = 0, yes=1
5) Key parameters of the model tested using sensitivity analysis	Y/N	no = 0, yes=1
6) Ranges used in sensitivity analysis stated	Y/N	no = 0, yes=1
7) Ranges used in the sensitivity analysis justified	Y/N	no = 0, yes=1
8) Approach to sensitivity analysis stated	Y/N	no = 0, yes=1
9) Model validated	Y/N	no = 0, yes=1
Disease Specific Criteria		
1)Appropriate duration of benefits considering clinical practice	Y/N	no = 0, yes=1
2)Appropriate time horizon used to forecast long-term outcomes	Y/N	no = 0, yes=1
3)Model includes the decrease in CHD risk after coronary event	Y/N	no = 0, yes=1
4)Model includes positive effect of statins on stroke	Y/N	no = 0, yes=1
5)Model incorporates a "lag-period"	Y/N	no = 0, yes=1
6)Appropriate risk equation used to model final outcomes or appropriate techniques to extrapolate final clinical endpoints	Y/N	no = 0, yes=1
7)Extent to which forecasted outcomes are based on clinical data		
a) expert opinion	a	0
b) intermediate end-points (proceed to #8)	b	1
c) final clinical outcomes (CHD events, death)	c	2
8)If intermediate end-points are used to model long-term outcomes, what lipoprotein fraction(s) was used?		
a) total serum cholesterol	a	0
b) TC/HDL, HDL, or LDL/HDL	b	1

2.7 Choice of Economic Evaluation and Model

Two factors were considered in choosing an analysis on which to base the estimates of the potential benefits and cost-effectiveness of improved cholesterol management in the military. The first was how well the analysis fared in the systematic review and the second was the relevance of the estimates generated in the analysis to the present study population. With respect to the quality of the economic evaluations, the results obtained in the modelling component of the review carried more weight in the overall assessment of the analyses than did the reporting component. Complete reporting of results of an economic analysis based on a low quality model was considered to be inferior to an analysis based on a high quality model whose results were slightly less explicit. Inclusion of analyses in the final assessment was, however, limited to analyses that met the reporting criteria well. Analyses were only considered as a potential source for estimates if the reporting quality of the analysis scored in the top half of the reporting component of the review.

The relevance of the estimates to the current study population was graded as high, medium or low depending on whether the estimates were based on Canadian, American or European data, respectively. In choosing an appropriate model on which to base the estimates it was decided that if the model used in the chosen economic evaluation was not applicable to both primary and secondary prevention then the results of two separate models would be used, using the next best model that included the missing clinical population (primary/secondary). This was necessary because the study population included in this investigation comprised military personnel with and without pre-existing CHD.

2.8 Application of Model to Target Population

Objectives two and three of the present investigation were met by applying the results of the identified analysis(es) to the study population. This application enabled estimation of the potential benefits of improved cholesterol management and the cost-effectiveness of this CHD risk reduction strategy in the study population. To determine the additional financial resources required to improve cholesterol management (from a military perspective), the intervention cost estimates of the chosen economic analysis were applied to the identified drug therapy candidates. Calculations in the present investigation were based on the annual cost of the intervention and the number of years left of service for each military member identified as a drug therapy candidate, assuming that all personnel retired at the mandatory age of retirement (age 55). To determine the additional cost for improved cholesterol management in personnel already on lipid lowering medication, the intervention costs were assumed to be limited to the cost of the higher dose medication in the calculations. Monitoring tests and physician visits were thus considered identical under both current and optimal care. As with drug therapy candidates, the costs were similarly calculated for the remaining years left of service. In these calculations, if personnel were being prescribed fibrates only, statin therapy (simvastatin 20mg) was added to the drug therapy. If personnel were already receiving the highest dose of a statin, these patients were switched to a moderate dose of a more potent statin, such as atorvastatin. Drug therapy unit prices used to estimate the cost of improved cholesterol management in this population were obtained directly from the military pharmacy at the National Defence Medical Centre.

Given the young age of the study cohort, costs avoided by the military by averting coronary events while the personnel were still in the military would be negligible and were thus

not considered in any of the above calculations. Lastly, if parameters not covered in the initial sensitivity analysis of the chosen economic evaluation were identified as being important to the results of the investigation, it was decided these parameters would be tested with further sensitivity analysis. Included in any additional sensitivity analysis would be the testing of any parameters that might be used to invalidate the results of this investigation.

3.0 RESULTS

3.1 Sub-optimal cholesterol management

A total of 1424 charts were reviewed for the present investigation. This represented approximately one quarter of all personnel over the age of forty-five in the Canadian military. Data re-abstraction of 50 charts resulted in identical results for 98% of the recorded values. Eighty-four percent of the study sample had a complete and recent fasting lipid profile. As expected, based on the occupational setting, there were many more men than women (1348 vs 76) in the study sample. The mean age was 48.25 years (s.d. 2.54 years), the difference in age between the genders being negligible. The prevalence of non-lipid CHD risk factors in the study sample (other than age) is presented for both genders in Table 6.

Table 6 - CHD Risk Factors by Gender

Risk Factor	Men N= 1348		Women N= 76	
	#	%	#	%
Smoking	398	29.5	19	25.0
Diabetes	34	2.5	0	0.00
Hypertension	143	10.6	5	6.6
Premature CHD in first degree relative	153	11.4*	8	10.5*
Personal history of CAD	26	1.9	0	0.00

*information not available for (n=29 male, n=1 female) adopted military personnel

All personnel in the study sample were stratified by risk level based on the presence of non-lipid risk factors. Missing non-lipid risk factor information was limited to the family history of premature CHD in a first-degree relative, which was not known in adopted military personnel (n=30). All other non-lipid risk factor data were available for all military personnel. Twenty-six personnel were identified as having a personal history of coronary heart disease. These personnel

were automatically considered to be at very high risk, as recommended by the revised cholesterol guidelines. The distribution of the study sample across risk levels is presented in Table 7 for both genders. While most personnel in the study sample were at low risk of developing CHD, there were a large number of men at moderate to very high levels of risk. Specifically, 45.8 % (617 of 1348) men in this study, had two or more non-lipid risk factors for CHD.

Table 7 - Risk Level Distribution by Gender

Men (n=1348)			**Women (n=76)**		
Risk level	n	%	Risk level	n	%
low	731	54.2	low	70	92.1
moderate	501	37.2	moderate	6	7.9
high	82	6.1	high	0	0.0
very high	34	2.5	very high	0	0.0

To address the first objective of this investigation, specifically the extent of sub-optimal cholesterol management with lipid lowering medication in the military, the number of personnel on lipid lowering medication was determined. Since sub-optimal cholesterol management was considered under two definitions, namely personnel meeting criteria for drug therapy but not receiving it and patients on drug therapy but not being treated to target, the cholesterol levels of personnel on lipid lowering therapy were considered separately from those not receiving pharmacotherapy for CHD prevention. Of the 1424 military personnel included in this sample, 1313 were not receiving lipid lowering pharmacotherapy. The mean lipid values of this group are presented in Table 8. The "n" in this table identifies the number of values on which these calculations were based.

Table 8 - Mean Lipid Values for Personnel not on Lipid Lowering Medication (n=1313)

	Men (n=1239)				Women (n=74)			
	n	mean	95% CI	Range	n	Mean	95% CI	Range
TC	1222	5.55	±0.05	1.98-10.06	72	5.07	±0.21	3.39-7.47
TG	1218	1.80	±0.06	0.26-12.22	72	1.20	±0.15	0.31-3.41
HDL-c	1203	1.11	±0.02	0.30-2.95	71	1.41	±0.09	0.83-2.83
LDL-c	1172	3.65	±0.05	0.16-7.42	72	3.16	±0.19	1.66-5.33
TG/HDL-c	1204	5.32	±0.09	1.46-13.15	71	3.75	±0.30	0.96-8.30

Personnel not on lipid lowering medication exceeding any target lipid levels by greater than 1 unit for lipid parameters identified by the revised Canadian cholesterol guidelines were identified. The distribution of personnel not receiving lipid lowering medication by risk category is presented in Table 9 as are the number of personnel in each CHD risk category exceeding the lipid parameter target values by greater than 1 unit. The total number of personnel exceeding one or more target values in each risk category is also presented in Table 9. The number of lipid values on which each calculation was based is identified in the denominator of the "proportion over target" column (POT). While the denominators in each POT column are consistently lower than the total "n", the percentage of missing values is never greater than 6% in any one group (27/470=0.058). The number of outdated lipid profiles among personnel not on lipid lowering medication was similarly low (8%). The possible effect that these missing values had on the results of the investigation is reserved for the discussion section.

Table 9 - Personnel not on lipid lowering medication exceeding one or more lipid parameters by at least 1 unit

Risk Level	n	LDL			TC/HDL			TG			LDL or TC/HDL or TG over target by 1 unit	%
		Target value (mmol/L)	POT*	%	target value	POT*	%	target value (mmol/L)	POT*	%		
Low	763	5.0	5/725	0.6	7.0	28/736	3.8	3	22/749	2.9	51	6.7
Moderate	470	4.0	29/443	6.5	6.0	85/460	18.5	2	67/462	14.5	129	27.4
High	70	3.5	14/65	21.5	5.0	36/70	51.4	2	17/70	24.3	39	55.7
Very high	10	2.5	3/9	33.3	4.0	5/9	55.6	2	1/9	11.1	7	70.0
Total	1313	-	51/1242	4.1	-	154/1275	12.1	-	107/1290	8.3	226	17.2

* POT= Proportion Over Target by at least 1 unit, denominator varies based on available data

Among personnel not currently on lipid lowering medication, 550 of the 1313 personnel in the study had a moderate to very high risk of CHD based on non-lipid risk factors. A total of 226 personnel exceeded one or more of the lipid parameter target values by a minimum of 1 unit.

Since only personnel exceeding either the target LDL-c or TC/HDL-c parameters by 1 unit are considered as candidates for drug therapy these personnel were considered separately. The number of military personnel by risk category exceeding either of these two lipid parameters, and thus identified as a drug therapy candidate, is presented in Table 10.

Table 10 - Percentage of Personnel Not on Lipid Lowering Medication Who Were Drug Candidates

Risk Level	n	# Drug therapy candidates	%
Low	763	33	4.3
Moderate	470	95	20.2
High	70	37	52.9
Very High	10	7	70.0
TOTAL	1313	172	13.1

A total of 172 military personnel in the study sample not on lipid lowering pharmacotherapy were exceeding either LDL-c or TC/HDL-c lipid parameters by enough to qualify them for drug therapy. These personnel were not being managed appropriately according to the revised cholesterol guidelines, under the assumption of no effect of lifestyle modifications on CHD risk reduction. While this represents just over thirteen percent of all study personnel not on lipid lowering pharmacotherapy, a greater proportion of personnel were found to meet the criteria for drug therapy among those already at an elevated risk of CHD based on non-lipid risk factors. Specifically, drug therapy was warranted in 70.0%, 52.9%, and 20.2% of the study personnel at very high, high and moderate levels of risk, respectively.

While only personnel exceeding target values for either LDL-c or TC/HDL-c by at least 1 unit are candidates for drug therapy, any degree of elevated cholesterol is of general concern, based on the relationship which exist between cholesterol and heart disease. By focussing only on personnel whose lipid profiles qualify them for drug therapy, the extent of hyperlipidemia and other dyslipidemias in the military is masked. This is evidenced by comparing the number of individuals over their target lipid levels (by any amount) in each risk category to the number of individuals qualifying for drug therapy. Considered in Table 11 as the "multiplication factor", the number of personnel over one or more target lipid values was 1.29-3.91 times greater than the number of drug therapy candidates identified, depending on the risk category. For example, only 33 drug therapy candidates were identified among personnel at low risk of CHD even though 129 personnel were exceeding one or more target lipid values in this risk group. Among all personnel not on lipid therapy, over 35% (460 of 1313) were exceeding the target value of one or more of the lipid parameters.

Table 11- Elevated cholesterol by risk category for personnel not on lipid lowering medication

Risk level	Total	Number over one or more target values (N.O.T)	Drug therapy candidates (D.T.C)	Multiplication factor (N.O.T/D.T.C)
Low	763	129	33	3.91
Moderate	470	262	95	2.76
High	70	60	37	1.62
Very high	10	9	7	1.29
TOTAL	1313	460	172	2.67

Determining the number of personnel receiving lipid lowering pharmacotherapy in whom the maximum benefit of the therapy is not being achieved is as important as identifying those personnel who would benefit from this therapy but are currently not receiving any. To determine the number of personnel in the study on lipid lowering medication not being treated to target cholesterol levels, the cholesterol values of personnel on lipid lowering pharmacotherapy were considered and the number not meeting the target values for each lipid parameter were identified.

Among the 111 personnel in the study sample on lipid lowering therapy, statins were the drug most commonly prescribed (77%), followed by fibrates (18%), with other lipid lowering agents being prescribed with much less frequency. The mean lipid values for male personnel on lipid lowering therapy are presented in Table 12. The value of all lipid parameters for the female personnel on lipid therapy are presented on an individual basis in Table 12 since only two women in the study were on lipid lowering pharmacotherapy for cholesterol reduction.

Unlike personnel not on lipid lowering pharmacotherapy values were available for almost all lipid parameters for personnel on lipid lowering drugs, with the exception of seven missing LDL-c values. These seven values could not be calculated because of excessively high triglyceride levels. Only one military personnel on lipid therapy had an outdated lipid profile.

The effect of these missing or outdated values on the results of the study will again be reserved for the discussion section.

Table 12 - Mean lipid values for personnel on lipid lowering pharmacotherapy

	Men (n=109)			Women (n=2)	
	n	mean	95% CI	n	Lipid values
TC	109	5.50	±0.10	2	5.72,6.29
TG	109	2.20	±0.13	2	2.13,2.46
HDL-c	109	1.08	±0.03	2	1.52,1.88
LDL-c	102	3.47	±0.09	2	3.08,3.41
TG/HDL-c	109	5.42	±0.16	2	3.35,3.76

The number of personnel on lipid lowering therapy exceeding target values by risk level are presented in Table 13. It can be seen that over half the personnel in the study on lipid lowering pharmacotherapy (64 of 111) were above at least one target value. As with personnel not on lipid lowering pharmacotherapy, more personnel on lipid therapy among those already at a high risk of CHD were found to not be meeting target endpoints. When the above analysis was limited to personnel who had been on lipid lowering medication for more than three months, 11 of the identified personnel were omitted from consideration, leaving a total of 53 personnel whose cholesterol was being managed sub-optimally.

Table 13 - Personnel on drug therapy not meeting target endpoints

Risk Level	n	LDL			TC/HDL			TG			LDL or TC/HDL Or TG Exceeding treatment Endpoint	%
		Endpoint (mmol/L)	POT*	%	Endpoint	POT*	%	Endpoint (mmol/L)	POT*	%		
Low	38	5.0	2/37	5.4	7.0	3/38	7.9	3	4/38	10.5	9	23.7
Moderate	37	4.0	10/34	29.4	6.0	15/37	40.5	2	20/37	54.0	26	70.3
High	12	3.5	5/11	45.5	5.0	7/12	58.3	2	5/12	41.7	10	83.3
Very high	24	2.5	11/22	50.0	4.0	16/24	66.7	2	12/24	50.0	19	79.2
Total	111	-	28/104	26.9	-	41/111	36.9	-	41/111	36.9	64	57.7

* POT= Proportion Over Target endpoint, denominator varies based on available data

In summary, of the 1424 personnel included in the study, the cholesterol levels of a total of 225 (15.8%) were found to be managed sub-optimally based on the revised Canadian cholesterol guidelines, under the assumption of no beneficial effect of lifestyle modification on CHD risk reduction. One hundred and seventy-two of the study personnel that were not on lipid lowering medication were drug therapy candidates, while fifty-three personnel on lipid lowering medication were not meeting target endpoints, despite having been on lipid lowering pharmacotherapy for over three months. The degree of sub-optimal cholesterol management with pharmacotherapy was found to be greatest among personnel at higher levels of risk for CHD based on non-lipid risk factors in both of the these clinical populations. A discussion of possible explanations for this finding is reserved for the discussion section.

When the above analysis was limited to personnel with symptomatic CHD, the proportion of personnel whose cholesterol was not being managed appropriately increased, as indicated in Tables 14a) and 14b). Twenty-three of the twenty-six personnel with a personal history of CHD in this study were on lipid lowering medication. Of these personnel, seventeen (73.9%) were not being treated to target and were thus not gaining the maximum benefit from lipid lowering pharmacotherapy (Table 14a). Furthermore, more than half (12 of 23) were not meeting the target endpoints of two or more of the lipid parameters identified in the revised cholesterol guidelines. Of the three personnel with a history of CHD but not on lipid lowering medication, two were drug therapy candidates and thus were also being managed sub-optimally with respect to their cholesterol levels.

Considered together, the cholesterol management of patients in secondary prevention

(patients with CHD) is poor. Almost three quarters (17/23) of the patients with CHD on lipid lowering medication were not achieving the maximum benefit from the medication and still others were not on the medication even though they met the criteria for drug therapy. These results are considerably worse than those in primary prevention (patients without CHD) as evidenced by the results presented in Table 14b). In primary prevention only 13% (170/1310) of the personnel not on lipid lowering therapy were candidates for drug therapy. Of those on drug therapy, 40.9% (36/88) were not meeting the target endpoints for treatment. Considered together, of the 1398 personnel in this study who have no previous history of CHD, 14.7 % (206/1398) were not being managed appropriately with respect to their cholesterol levels. The percentages inadequately treated might eventually be higher, however, since some persons treated for less than 3 months might never reach target levels. It should also be noted that the number of lipid parameters being exceeded in primary prevention could not be determined for some personnel because of missing lipid values.

Table 14a) - Sub-optimal Cholesterol Management in Secondary Prevention

Personnel on lipid lowering medication			**Personnel not on lipid lowering medication**		
# of lipid parameters exceeded	# of personnel exceeding target endpoints	%	# of drug initiation parameters exceeded	# of personnel exceeding lipid parameters	%
3	4	17.4			
2	8	34.8	2	0	0
1	3	13.1	1	2	66.6
0	5	21.7	0	1	33.3
Missing	2*	8.7	Missing	0	0
Omitted (<3m)	1	4.3			
Total	23	100	Total	3	100

* Both personnel were exceeding target endpoints but were missing values for some lipid parameters

Table 14b) Sub-optimal Cholesterol Management in Primary Prevention

Personnel on lipid lowering medication			Personnel not on lipid lowering medication		
# of lipid parameters exceeded	# of personnel exceeding target endpoints	%	# of drug initiation parameters exceeded	# of personnel exceeding lipid parameters	%
3	5	5.7			
2	9	10.2	2	33	2.5
1	20	22.7	1	119	9.1
0	42	47.7	0	1140	87.0
Missing	2*	2.3	Missing	18**	1.4
Omitted (<3m)	10	11.4			
Total	88	100	Total	1310	100

* Both personnel were exceeding target endpoints but were missing values for some lipid parameters
** All personnel met criteria for drug therapy initiation but were missing values for some lipid parameters

3.2 Systematic Review of Economic Evaluations of Statin Therapy for CHD Prevention

A MEDLINE search using the keywords cost-effective, cost-benefit, cost and co-st analysis in combination with statin, HMG-CoA or hydroxymethylglutaryl CoA reductase inhibitors yielded one hundred and thirty-two hits. From this list a total of twenty full economic evaluations were identified.[50-54,70-84] The references of these evaluations were searched for additional economic evaluations. This search yielded another four analyses [85-88] for a total of twenty-four. All of the economic evaluations were cost-effectiveness analyses and had as their primary outcome years of life saved (YOLS). Just under half (9 of 24) of the analyses were assessing cost-effectiveness in secondary prevention, three of which were also assessing cost-effectiveness in primary prevention. In all analyses the comparator was either a placebo or routine care, either with or without diet therapy. In two analyses the cost-effectiveness of two or more statins against placebo were directly compared while seven analyses compared the cost-effectiveness of statin therapy and other lipid lowering medications to routine care or placebo. The remaining analyses (15) only assessed the cost-effectiveness of one statin compared to

routine care or placebo.

Two analyses that were not included in this review deserve special mention. The first of these analyses assessed the cost-effectiveness of forty-seven strategies for cholesterol reduction, including both dietary and pharmacologic therapy.[89] In this analysis, the cost-effectiveness of statin therapy over usual care (with and without diet therapy) was only presented in graphical form. This allowed only for a rough estimation of the cost-effectiveness of statin therapy over usual care. Since the aim of the present review was to identify an economic analysis that allowed for a more precise estimation of expected costs and benefits of improved pharmacotherapy for cholesterol reduction, the results of this analysis were not considered appropriate for the present investigation, and therefore this analysis was excluded from consideration. The second analysis which was excluded from the present systematic review considered the cost-effectiveness of a statin with intensive diet therapy over usual care.[90] The results of this analysis were not thought to be relevant to the clinical setting of the present investigation since the cholesterol management strategy in the military would not likely include intensive diet therapy.

3.3 Quality of Reporting of Economic Evaluations of Statin Therapy

The quality of reporting in cost-effectiveness research on statins was assessed by how well the analyses met the modified Drummond checklist, the aggregate results of which are presented in Table 15. In keeping with the structure of the initial checklist, these results are presented according to the possible answers:yes, no, not sure and not applicable. Five criteria, namely criteria 10, 12, 18, 23 and 33 of the modified checklist were not applicable in the majority of cases. Specifically, only five analyses used multiple sources of efficacy estimates and only one study reported on productivity costs. Further, over half of the studies did not require

any price conversion, and future costs and benefits were discounted in all analyses. Lastly, only half of the analyses stated that they had any pharmaceutical company sponsorship.

Table 15- Quality of Reporting of Economic Evaluations of Statin Therapy - Aggregate Results

Study Design Criteria	Yes	No	Not Clear	Not Applicable
1. The research question is stated	23	1	-	-
2. The economic importance of the research question is stated	19	4	1	-
3. The viewpoint(s) of the analysis are clearly stated and justified	14	10	-	-
4. The rationale for choosing the alternative programmes or interventions compared is stated	22	2	-	-
5. The alternatives being compared are clearly described	23	1	-	-
6. The form of the economic evaluation used is stated	23	1	-	-
7. The choice of form of economic evaluation is justified in relation to the questions addressed	24	0	-	-
Data Collection				
8. The source(s) of effectiveness estimates used are stated	22	2	-	-
9. Details of the design and results of effectiveness study are given (if based on a single study)	12	7	-	5
10. Details of the method of synthesis or meta-analysis of estimates are given (if based on an overview of a number of effectiveness studies)	2	3	-	19
11. The primary outcome measure(s) for the economic evaluation are clearly stated	24	0	-	-
12. Productivity changes (if included) are reported separately	1	0	-	23
13. The relevance of productivity changes to the study question is discussed	5	18	-	1
14. Quantities of resources are reported separately from their unit costs	9	15	-	-
15. Main costs considered	21	2	1	-
16. Methods for the estimation of quantities and unit costs are described	22	1	1	-
17. Currency and price data are recorded	10	13	1	-
18. Details of currency of price adjustments for inflation or currency conversion are given	8	2	-	14
Analysis and Interpretation of Results				
19. Justification of omission of quality of life (if not included)	3	19	-	2
20. Time horizon of costs and benefits is stated	24	0	-	-
21. The discount rate(s) is stated	24	0	-	-
22. The choice of rate(s) is justified	3	21	-	-
23. An explanation is given if costs or benefits are not discounted	-	-	-	24
24. Relevant alternatives are compared	23	0	1	-
25. Incremental analysis is reported	24	0	-	-
26. Major outcomes are presented in disaggregated as well as aggregated form	13	11	-	-
27. The answer to the study question is given	24	0	-	-
28. Conclusions follow from the data	24	0	-	-
29. Conclusions are accompanied by the appropriate caveats	20	4	-	-
30. Difference between efficacy and effectiveness considered?	3	21	-	-
Pharmaceutical Specific Criteria				
31. Therapeutic classification, dose, brand and generic name specified	24	0	-	-
32. Approved indication specified	24	0	-	-
33. Funding relationship specified	12	0	-	12
34. Target population for the analysis specified	24	0	-	-

At the aggregate level, the quality of reporting of economic analyses of statin therapy is generally poor. Specifically, with respect to the essential criteria identified by Fergusson and colleagues[63] (Table 4), while all the of analyses were explicit about the form of economic evaluation and the primary outcome measure, the viewpoint of the analysis was clearly stated in only fourteen studies. Incremental analysis, another of the "essential" criteria, considers the extra cost required for one extra unit of health in one programme over a second programme.[91] Based on this definition of incremental analysis, the analyses considered in this review fared well. All evaluations compared the additional benefits of statin therapy over usual care, which usually included diet therapy. Only marginal costs of the treatment intervention were considered and only additional benefits in terms of cerebrovascular or coronary events averted with the use of statin therapy over routine care were included in the analysis.

With respect to the desirable criteria identified by Fergusson and colleagues[63], while all the studies discounted all future costs and benefits to take into consideration time preference, a justification for the choice of discount rate was only provided in three analyses. Furthermore, only five of the twenty-three studies which did not report on productivity (indirect) costs made any attempt to discuss how inclusion of these costs would have affected their results. An equally troubling finding in many of the analyses is the lack of transparency with respect to cost data, the last of the desirable criteria. Costs considered in economic evaluations of statin therapy are often limited to direct costs and usually fall into two broad categories: intervention and treatment costs. The types of costs considered within each of these categories can vary across analyses, depending on assumptions made regarding their importance. Regardless of the costs considered, the appropriate inclusion of which can be assessed independently by the reader, the price

estimates for these costs must be explicitly stated. As important as knowing how costs were estimated, is knowing the value of the estimates. It is in this respect that transparency in the economic evaluations being reviewed is lacking. Specifically, while ten analyses presented data for both intervention and treatment costs, a large number of analyses reported only on the intervention costs (ten analyses) or did not present any cost estimates and chose only to present the final cost-effectiveness ratios (four analyses). The reporting of resource utilization in the analyses is equally poor, with only nine analyses providing an adequate description of the estimated quantity of intervention and treatment resources. This last criterion, while not considered by Fergusson and colleagues[63] as an essential reporting criteria, can have a large impact on the resulting cost-effectiveness ratios. The number of events averted under competing strategies should thus be clearly specified in the analysis, but in many cases was not.

The lack of transparency in both reporting of resource utilization and cost estimates severely restricts comparisons among analyses and assessment of the relevance of the results obtained in these analyses to one's own clinical setting. Because health care delivery varies between countries, the resource utilization and costs of managing and treating coronary disease and stroke will likely not be the same. In order for readers to be able to determine the relevance of study results to their setting, resource utilization and cost estimates for various procedures should be presented.

The results obtained on a number of other important criteria in the revised Drummond checklist, not identified as essential or desirable by Fergusson and colleagues[63], also deserve special mention. Specifically, the results of the two criteria added to the initial Drummond checklist to assess the degree to which issues of quality of life and efficacy versus effectiveness

had been considered in the economic evaluations were of particular concern. Not one of the economic evaluations considered quality of life issues in their primary outcome measure and only two considered this parameter in the sensitivity analysis. This observation is surprising given that quality adjusted life years (QALY) is the commonly preferred unit in economic analyses. This type of analysis has the advantage over simple cost-effectiveness analyses using years of life saved (YOLS) in that it allows for the effect that a disease can have on the quality of life. Unfortunately, only three of the 22 analyses which did not consider quality of life in the sensitivity analysis provided any rationale for not doing so. A possible explanation for the lack of inclusion of quality of life issues in the reviewed economic analyses is the relatively recent attention that this issue has received in economic evaluations.

With respect to the clinical effectiveness of statin pharmacotherapy, only three of the studies reviewed considered the possibility that the forecasted benefit of statin therapy found in clinical trials might not be attained in all clinical settings, thus differentiating between the efficacy and effectiveness of this intervention strategy. While still other analyses considered the possibility that less than 100% of the forecasted benefits of the therapy based on intermediate endpoints and epidemiological data would be achieved, the majority of the analyses were based directly on the results of clinical trials and assumed the maximum benefit suggested by epidemiologic data. Maximum benefit in this context assumes that people who have their cholesterol levels artificially lowered to a given level will have the same risk of coronary heart disease as people who have the same naturally occurring levels of cholesterol.

The last criterion that was inconsistently met by the analyses is again related to issues of transparency. Specifically, only just over half of the analyses provided their results in both

disaggregate and aggregate form. The final aggregate results obtained by the different analyses (presented as $/YOLS) is ultimately the result of interest in economic evaluations. The presentation of disaggregate data however, with the numerator and denominator data presented separately, can provide valuable information as to why economic analyses conducted on similar populations yield different results. Results of the analyses considered in this review were often only presented as cost per year of life saved (11 studies), the number of expected life years saved or the cost by risk category never explicitly being defined. Again, this lack of transparency precludes any comparison among analyses since it can often not be determined whether differing cost-effectiveness ratios are a reflection of different life expectancy estimates, cost estimates or a combination of both.

Since the aim of the systematic review was to identify high quality economic evaluations of statin therapy, the quality of reporting of each analysis was considered independently. The results of this assessment have been grouped into the three headings initially suggested by Drummond[48] (design, data collection, analysis and interpretation) and a fourth, pharmaceutical specific heading added to the assessment. These results are presented in Table 16, as are the summed totals. The denominators vary depending on the number of applicable criteria under each heading. In this assessment, "not clear" responses obtained on the revised Drummond checklist were considered as "no" responses. In table 16, the analyses are presented in decreasing order based on the sum totals.

Table 16 - Quality of Reporting in Economic Evaluations of Statin Therapy - Individual results

First Author and Year of Publication	Study Design* criteria	Data Collection* criteria	Analysis and Interpretation criteria*	Pharmaceutical specific criteria*	Total	%
Caro/97[54]	6/7	7/8	10/11	4/4	27/30	90.0
Huse/98[74]	7/7	6/7	8/10	3/3	24/27	88.9
Johannesson/97[75]	6/7	9/10	8/10	4/4	27/31	87.1
Jonsson/96[76]	6/7	9/9	8/11	4/4	27/31	87.1
Pharoah/96[83]	7/7	6/8	9/11	4/4	26/30	86.7
Muls/98[80]	6/7	8/9	8/11	4/4	26/31	83.9
Grover/99[72]	7/7	6/8	8/11	3/3	24/29	82.7
Caro/99[53]	7/7	6/9	8/11	4/4	25/31	80.6
Ashraf/96[52]	5/7	8/9	8/11	4/4	25/31	80.6
Hamilton/95[70]	7/7	5/8	8/11	4/4	24/30	80.0
Riviere/97[50]	6/7	7/8	7/11	4/4	24/30	80.0
Goldman/91[64]	6/7	7/9	7/11	3/3	23/30	76.7
Perreault/96[82]	7/7	5/8	7/11	3/3	22/29	75.9
Perreault/98[81]	7/7	5/8	7/11	3/3	22/29	75.9
Martens/90[78]	6/7	5/9	8/11	4/4	23/31	74.2
Martens/94[79]	5/7	6/9	8/11	4/4	23/31	74.2
Guibert/93[66]	6/7	6/9	7/11	3/3	22/30	73.3
Troche/98[51]	7/7	4/8	7/11	3/3	21/29	72.4
Goldman/93[71]	6/7	5/9	7/11	3/3	21/30	70.0
Martens/89[77]	6/7	4/8	7/11	3/3	20/29	69.0
Hay/91[73]	6/7	2/8	9/11	3/3	20/29	69.0
Taylor/90[65]	6/7	4/8	7/11	3/3	20/29	67.0
Glick/92[88]	5/7	3/8	8/11	3/4	19/30	63.3
Hjalte/92[47]	5/7	4/9	6/11	4/4	19/31	61.3

*Denominator varies depending on the number of applicable criteria within each category

The completeness of reporting in the economic evaluations is variable. This variability is not limited to differences observed between the quality of different economic analyses. There was also internal variability across different types of criteria within individual analyses. Examples of this internal variability is demonstrated by the economic analyses of Glick/92[88],

Hay/91[73] and Troche/98[51] that are presented in Table 16. All three of these analyses have similar reporting profiles, scoring very well on study design criteria, poorly in the data collection criteria and moderately on the data analysis and interpretation criteria.

While the reporting results show a high degree of variability, some trends were noted. Almost all analyses performed consistently higher on some types of criteria and poorly on others. In general, reporting of the design in the analyses was of good quality: Specifically, eight analyses obtained a perfect score and twelve studies missed only one criterion in this category. The data collection criteria were less well met for reasons discussed previously. Only seven analyses were missing one or less of the criteria defined under this heading. The analysis and interpretation criteria were also generally well met by most of the analyses.

Pharmaceutical specific criteria in the review were met well by all analyses and contributed little to differentiating good from poor analyses in the present review. The therapeutic classification and dose of the statin being considered in each analysis was always explicitly stated or referenced. Funding relationships, where applicable, were specified, as was the target population for the analysis. The target population was occasionally found to be restricted to males, but most often considered both males and females, at varying cholesterol levels with different numbers of risk factors. Cost-effectiveness ratios for different target populations within the same analysis were usually presented separately.

At the aggregate level, and based on the results of a few specific criteria, there is substantial room for improvement in the reporting of economic evaluations of statin therapy. The assessment of individual analyses in the present investigation, however, yielded a slightly more optimistic impression of the reporting quality of these analyses. While there is notable

variation in the quality of reporting across the analyses considered in this review, the top half of the analyses achieved a score of 76% or better on the reporting criteria, based on the summed totals as presented in Table 16. The differences in the transparency of reporting of cost data and resource utilization differentiated the well from very well reported analyses of these top analyses.

The quality of the economic analyses considered in the review also appears to be improving over time. This is likely a reflection of the increased emphasis that has been placed on the reporting of economic evaluations in recent years. Studies that did not fare as well in the present assessment were generally older studies: the five analyses with the worst reporting were all published between 1989 and 1992. It should however be mentioned that the economic analysis which had the second lowest score on the reporting criteria was not a full economic assessment and was only presented as an illustration for the use of a CHD life-expectancy model.[88]

3.4 Methodologic Quality of CHD Models Used in Economic Evaluations of Statin Therapy

The results of the second component of the systematic review, which assessed the methodologic quality of the models used in the economic evaluation of statin therapy, are outlined in Table 17 and 18. In Table 17, the results are presented in aggregate form for each of the modelling criteria. As with the revised reporting checklist, possible answers include: yes, no, not sure and not applicable. In Table 18, scores have been determined for each individual analysis and a score has been calculated for both generic and disease specific criteria with the aim of identifying superior economic evaluations. These scores have also been combined into a total score to allow for an overall assessment of the modelling quality of the each analysis. In

Table 18, all responses that were considered "not clear" in Table 17 were coded as "no".

Analyses are presented in Table 18 in decreasing order according to their sum totals.

Table 17 - Methodologic Quality of Economic Evaluations of Statin Therapy - Aggregate results

Generic Criteria	Yes	No	Not clear	Not applicable
1) Model type described in detail (or reference provided)	23	1	-	-
2) Choice of model justified	3	21	-	-
3) Model assumptions explicit and justified	16	8	-	-
4) Model assumptions tested using sensitivity analysis	5	19	-	-
5) Key parameters of the model tested using sensitivity analysis	13	11	-	-
6) Ranges used in sensitivity analysis stated	18	6	-	-
7) Ranges used in the sensitivity analysis justified	4	20	-	-
8) Approach to sensitivity analysis stated	2	22	-	-
9) Model validated	6	18	-	-
Disease Specific Criteria				
1)Appropriate duration of benefits considering clinical practice	18	6	-	-
2)Appropriate time horizon used to forecast long-term outcomes	23	1	-	-
3) Model includes the decrease in CHD risk after coronary event	7	6	11	-
4) Model includes positive effect of statins on stroke	7	17	-	-
5) Model incorporates a "lag-period"	19	5	-	-
6) Appropriate risk equation used to model final outcomes or appropriate techniques to extrapolate final clinical endpoints	23	0	1	-
7) Extent to which forecasted outcomes are based on clinical data				
a) expert opinion	0	-	-	-
b) intermediate end-points (answer #8)	15	-	-	-
c) final clinical outcomes (CHD events, death)	9	-	-	-
8) If intermediate end-points used to model long-term outcomes, what lipoprotein fraction(s) was used to model long-term outcomes?				
a) total serum cholesterol	10	-	-	-
b) LDL/HDL, HDL, or TC/HDL	5	-	-	-

Table 18 - Methodologic Quality of Economic Evaluations of Statin Therapy – Individual results

First Author and year of publication	Generic Criteria		Specific Criteria		Total	
Grover/99[72]	6/9	66.7	7/9	77.8	13/18	72.2
Goldman/91[64]	7/9	77.8	6/9	66.7	13/18	72.2
Goldman/93[71]	6/9	66.7	6/9	66.7	12/18	66.7
Troche/98[81]	4/9	44.4	7/8	62.5	11/17	64.7
Riviere/97[80]	5/9	55.6	6/8	75.0	11/17	64.7
Jonsson/96[76]	5/9	55.6	6/8	75.0	11/17	64.7
Huse/98[74]	5/9	55.6	6/9	66.7	11/18	61.1
Hamilton/95[70]	4/9	44.4	7/9	77.8	11/18	61.1
Ashraf/96[62]	4/9	44.4	6/8	75.0	10/17	58.8
Caro/97[54]	4/9	44.4	6/8	75.0	10/17	58.8
Pharoah/96[63]	7/9	77.8	3/8	37.5	10/17	58.8
Muls/98[60]	4/9	44.4	6/8	75.0	10/17	58.8
Caro/99[51]	3/9	33.3	6/8	75.0	9/17	52.9
Johannesson/97[75]	4/9	44.4	5/8	62.5	9/17	52.9
Perreault/96[82]	2/9	22.2	7/9	77.8	9/18	50.0
Perreault/98[61]	2/9	22.2	7/9	77.8	9/18	50.0
Hay/91[73]	4/9	44.4	5/9	55.6	9/18	50.0
Martens/89[77]	4/9	44.4	4/9	44.4	8/18	44.4
Martens/94[79]	3/9	33.3	5/9	55.6	8/18	44.4
Taylor/90[85]	2/9	22.2	5/9	66.7	7/18	44.4
Martens/90[78]	2/9	22.2	5/9	55.6	7/18	38.9
Guibert/93[66]	1/9	11.1	5/9	55.6	6/18	33.3
Glick/92[58]	1/9	11.1	5/9	55.6	6/18	33.3
Hjalte/92[57]	0/9	0.00	5/9	55.6	5/18	27.8

*denominator varies depending on the number of applicable criteria

There is a high degree of variability across analyses with respect to both generic and disease specific model criteria. Specifically, generic criteria were met between zero and almost seventy-eight percent of the time as presented in Table 18. Within this category of criteria, the quality of the models was most often determined based on how explicitly the sensitivity analysis

was described and if the model on which the estimates were based was validated. The sensitivity analysis carried out in the economic analyses was generally of poor quality, with only two analyses providing any information regarding the approach taken (Table 17). Also shown in Table 17, only four of the eighteen analyses that provided ranges in the sensitivity analysis provided any rationale for the range of values used. With respect to model validation, only two CHD models used to estimate the cost and benefits in the economic evaluations being reviewed were validated. Results of four analyses included in this review [70,72,81,82] were based on the first validated model while two others analyses[84,71] were based on the second validated model. With respect to the remaining generic criteria presented in Table 17, most of the studies were described in enough detail, although the choice of model was rarely justified. Likewise, while the assumptions made in deriving cost and benefit estimates were often stated, justification for the assumptions was rarely provided.

In general, disease specific criteria were met with greater frequency than the generic criteria, as demonstrated in Table 18. Responses to the first disease specific criterion were determined entirely by the extent to which the estimates of clinical efficacy were based on intermediate endpoints or final clinical outcomes, in all but four analyses. Specifically, analyses which were based on the final clinical outcome data of recent clinical trials such as the WOSCOPS[12] or the 4S[13] typically limited the benefit of statin therapy to the duration of the trial, which was usually a maximum of five years. Notable exceptions in this respect are the analyses by Riviere/97[50], Troche/98[51], Ashraf/98[52] and Muls/98[80]. The first of these analyses, although based on the results of the 4S, forecasted the benefits of statin therapy according to three premises, namely of continued benefit over fifteen years, benefit to a maximum of ten years and

lastly benefit limited to the duration of the study from which the results were taken.[50] The second analysis, although similarly based on final clinical outcomes, extended the benefits of therapy under the assumption that the linear distribution of effects observed in the trial would continue for five years past the termination of the study.[51] The last two analyses, both based on the results of the PLACI/II studies of three years duration, considered the possibility of an additional seven year benefit from the therapy, thus bringing the patient population in this study to a mean age of seventy.[52,80] Because of the extended length of the benefits[50] or the age at the end of the benefit extension[52,80] , three of these four analyses were considered to have an appropriate duration of benefit. Unlike economic analyses based on final outcome data, however, analyses which were based on intermediate endpoints such as reduction in LDL-c or total serum cholesterol, assumed that benefits from the therapy would be life-long or extend into old age. Independent of the duration of benefit assumed, all but one of the analyses used an appropriate time horizon that extended into old age to forecast the changes in life-expectancy.

With respect to the third disease specific criterion, it was unclear in many of the models whether the benefits of statin therapy after an event were considered in forecasting the long-term outcomes. While most of the models that were based on intermediate endpoints stated that the statin therapy would be life-long, and thus that statins would be taken until death, it was often not explicitly stated what affect, if any, the therapy was assumed to have in terms of risk reduction after a coronary event. This was true in both primary and secondary prevention economic evaluations, including both first and subsequent coronary events. One quarter of the studies in this review did, however, state that benefits of statin therapy were limited to the time prior to the event, while seven others stated that reduction in risk after a coronary event was considered in

the analysis, leaving half of the analyses with this question unanswered.

As expected, only recently published analyses included the positive effect of statin therapy on the risk of stroke in forecasting the benefits of statin therapy, the fourth of the disease specific criteria considered in this review. By considering the difference in overall mortality observed in recent statin trials, analyses which were based on final clinical outcome data using results of studies such as that of WOSCOPS[12] and the 4S[13] trials indirectly included the benefit of statin therapy on the risk of stroke in their estimates since the risk of death from stroke was reduced in these studies. Other analyses, such as that of Grover and colleagues[72] , which was based on intermediate endpoints, explicitly included the 30% risk reduction in stroke observed in these studies in their model to forecast the life-time benefits of statin therapy. Most earlier economic evaluations did not include this effect in their analyses since only the more recent studies were adequately powered to detect this effect.

The majority of analyses (19 of 24) included a "lag-time" for statin therapy, and all of the analyses were based on appropriate risk equations or used appropriate statistical models to forecast long-term outcomes. The majority of analyses based on intermediate endpoints used the Framingham equations to forecast the long-term outcomes, although the most recent analysis included in this review (Grover/99[72]) was based on logistic equations developed based on data from a 15% random sample in Lipid Research Clinics trial.[22] The models used to forecast changes in life expectancy based on final outcome data varied according to assumptions made regarding the duration of the benefit and the subsequent risk of events in the intervention and control or usual care group.

Nine analyses were based on final clinical endpoints from randomized controlled trials.

The remaining fifteen analyses were based on intermediate clinical endpoints, such as cholesterol reduction. Among the latter analyses, one third (5 of 15) used risk equations based on reductions of LDL-c or of the ratio of HDL-c/LDL-c or TC/HDL-c to forecast the long-term benefits of statin therapy. The remaining analyses used less accurate risk equations based on the reductions in total serum cholesterol.

Based on both disease specific and generic criteria, a number of CHD models emerged as methodologically superior in quality in forecasting the cost-effectiveness of statin therapy. The results of the top two analyses in the modelling component of the review, namely the models by Grover/99[72] and Goldman/91[84], performed similarly well against both types of modelling criteria. Also faring well was the model used by Perreault and colleagues.[81,82] Unfortunately, criteria of good modelling practice, such as sensitivity analysis and model validation, were poorly met by these latter analyses, thus placing the methodologic quality of these economic analyses behind those of Grover/99[72] and Goldman/91[84] . For similar reasons other models which also scored well in the disease specific criteria scored low overall.

3.5 Identifying High Quality Economic Evaluations

To identify high quality economic evaluations for the purpose of quantifying the cost-effectiveness and potential benefits of improved cholesterol management in the military, both the reporting and modelling criteria were considered together. Only analyses scoring in the top half in the reporting portion of the review were considered in this final assessment. Based on this exclusion criterion, twelve analyses were omitted from consideration. Two analyses[71,51] with higher quality models were omitted because of poor reporting. The omission of these two analyses however did not have any effect on the conclusions of the study. The results of the

analyses considered in the final assessment are presented in Table 19. The analyses are presented in decreasing order of the quality of the model, according to scores achieved in the modelling component of the review.

Table 19 – Systematic Review Combined Results - High Quality Economic Evaluations of Statin Therapy

First Author and Year of Publication	Modelling Component of systematic Review (%)	Reporting Component of Systematic Review (%)
Grover/99[77]	72.2	82.7
Goldman/91[44]	72.2	76.7
Jonsson/96[78]	64.7	87.1
Riviere/97[50]	64.7	80.0
Huse/98[74]	61.1	88.9
Hamilton/95[70]	61.1	80.0
Caro/97[54]	58.8	90.0
Pharoah/96[61]	58.8	86.7
Muls/98[80]	58.8	83.9
Caro/99[51]	58.8	80.6
Ashraf/96[52]	58.8	80.6
Johannesson/97[75]	52.9	87.1

The top half (6) economic analyses appearing in Table 19 were considered further as potential sources for the estimates needed to quantify the potential benefits of improved cholesterol management in the military with pharmacotherapy for cholesterol reduction. In this subgroup, the reporting quality was 76.7% or higher for all analyses, while the modelling quality ranged from 61-72%. The results of these six analyses were considered together with the relevance of the data used to generate the cost-effectiveness estimates of each analysis to the current clinical population. The relevance of the estimates to the present investigation, in addition to target population considered in each analysis, is presented in Table 20 for each of the six economic analyses identified as superior, based on the results of the systematic review.

Table 20 - Relevance of High Quality Economic Evaluations Estimates to Clinical Setting

First Author and Year	Modelling Criteria (%)	Reporting Criteria (%)	Relevance of Estimates*	Target Population (sex, age, level of risk/cholesterol level, CHD)
Grover/99[72]	72.2	82.7	High	m+f, 40-70, chol >5.46, CHD+
Goldman/91[44]	72.2	76.7	Moderate	m+f,35-84, ?,CHD+/-
Jonsson/96[76]	64.7	84.4	Low	m+f, mean=60, chol 5.5-8.0, CHD+
Riviere/97[50]	64.7	80.0	High	m+f, mean=60, chol 5.5-8.0, CHD+
Huse/98[74]	61.1	88.9	Moderate	m+f, 45-65, chol>3.36, CHD+/-
Hamilton/95[70]	61.1	80.0	High	m+f, 30-70, chol 10th percentile,CHD-

*high=Canadian data, moderate=American data, Low=European data

Based on the quality of the model and the relevance of the estimates generated in the economic analysis to the current clinical setting, taking into account the quality of reporting of the analysis, the results of the Grover/99[72] analysis was identified as the most appropriate model on which to base the estimates of the potential benefit of improved cholesterol management. A brief description of this model is provided in Appendix E.

3.6 Potential Cost-effectiveness of Improved Cholesterol Management

Using their most recent CHD model[72], the Grover research team forecasted the potential health benefits and cost-effectiveness of statin therapy for the drug therapy candidates identified in this study using the risk factor profiles and cholesterol values. Gaining direct access to the model allowed for greater precision in forecasting, since the use of the previously published cost-effectiveness estimates would have necessitated grouping people into a more limited number of pre-existing risk categories, and resulted in a subsequent loss of information. The results generated from the study sample using the Grover model (Tables 21-23) are considered from a

societal perspective and are based on lifetime therapy. Since hypertension was coded as a dichotomous variable in the present investigation, the missing systolic and diastolic blood pressures were imputed for all subjects using simple linear regression developed from the Canadian Heart Health Databases. Predictor variables used in the regression analysis in this imputation included age, sex, hypertension, body-mass index, smoking and a previous history of CVD. Life-time cost-effectiveness estimates and corresponding estimates of the years of life saved are presented in both undiscounted and discounted form, using a 3% discounted rate as recommended by the Panel on Cost-effectiveness in Health and Medicine. [92]

Estimates for both years of life saved and the incremental cost were generated for the 172 personnel in the study sample not currently on lipid lowering therapy who were drug therapy candidates. These results are presented in Table 21 and 22, respectively. The incremental cost-effectiveness ratios for each risk level are presented in Table 23. In all tables, the ranges represent the lowest and highest values obtained for patients within each category. Estimates of the potential health benefits and cost effectiveness of statin therapy could not be generated for sub-optimally treated personnel on drug therapy (i.e. those personnel on lipid lowering therapy not meeting target endpoints) because pre-treatment cholesterol levels were not collected in the present investigation.

Table 21 - Forecasted Benefits in Years of life Saved (YOLS) with Lifetime Statin Therapy

Risk Level	n	Total YOLS* (undiscounted)	Average YOLS* per person (undiscounted)	Range of YOLS* (undiscounted)	Total YOLS* (discounted**)	Average YOLS* per person (discounted**)	Range of YOLS* (discounted**)
Low	33	90.18	2.73	1.46-3.84	42.99	1.30	0.69-2.08
Moderate	95	273.76	2.88	1.28-4.52	139.46	1.47	0.58-2.43
High	37	111.86	3.02	1.36-4.57	59.56	1.61	0.67-2.52
Very high	7	21.15	3.02	1.86-4.61	12.09	1.73	0.99-2.47
Total	172	496.95	2.89	1.28-4.61	254.09	1.48	0.58-2.52

* YOLS = Years of Life Saved
** discount rate of 3%

Table 22 - The Forecasted Incremental Cost of Lifetime Statin Therapy

Risk level	n	Mean Incremental cost (undiscounted)	Range Incremental cost (undiscounted)	Mean Incremental cost (discounted)*	Range Incremental cost (discounted)*
Low	33	$26 012.76	$20 500.91-$30 289.60	$15 345.96	$11 600.29-$18 605.23
Moderate	95	$22 237.83	$16 321.48-$33 037.09	$13 437.88	$10 184.76-$19 624.65
High	37	$22 405.33	$16 421.81-$28 835.13	$13 479.51	$10 792.30-$17 031.97
Very high	7	$22 304.13	$20 464.35-$28 147.28	$13 293.24	$12 924.70-$14 443.91
Total	172	$23 000.82	$16 321.48-$33 037.09	$13 807.03	$10 184.76-$19 624.65

*Discount rate of 3%

Table 23- Cost-effectiveness of Treating Elevated Cholesterol in the Military Based on Lifetime Statin Therapy

Risk Level	n	Mean Incremental C/E* ratio (undiscounted)	Range C/E* ratios (undiscounted)	Mean Incremental C/E*Ratio (discounted)**	Range C/E* ratios (discounted)**
Low	33	$9519.08	$5450.34-$20 740.62	$11780.14	$5566.89-$26 766.27
Moderate	95	$7716.93	$5567.42-$25 240.15	$9153.68	$5597.42-$33 958.19
High	37	$7410.96	$5717.56-$19 085.87	$8373.49	$5833.76-$25 052.19
Very high	7	$7382.68	$6140.76-$11 421.15	$7699.85	$5728.00-$13 370.96
Total	172	$7960.89	$5450.34-$25 240.15	$9345.97	$5566.89-$33 958.19

* C/E is the cost in 1996 dollars (Cdn.) per years of life saved (YOLS)
** Discount rate 3%

Regardless of the risk category, the potential health benefits in personnel identified as being managed sub-optimally in the study population range between two and three undiscounted years of life saved (or one and two discounted years of life saved). Based on the forecasted

benefits of improved prophylactic cholesterol management with statin therapy, a substantial number of years of life could be saved in the identified population in the present investigation. Specifically, lifetime statin therapy could potentially add almost 497 undiscounted years of life among the study personnel whose cholesterol levels made them candidates for drug therapy. The mean incremental cost of lifetime statin therapy in drug therapy candidates was approximately $23 000 (undiscounted) and $14 000 (discounted), showing only a small variation across the risk levels, as suggested by the results of Table 22.

The cost-effectiveness ratios of cholesterol reduction using statins in the drug therapy candidates are presented in Table 23. The undiscounted ratios all fall under $10,000 per year of life saved, and the discounted cost-effectiveness ratios are only slightly higher. There is variation with respect to both the years of life saved and the cost-effectiveness of this risk management strategy at the individual level. However, even the least favourable individual cost-effectiveness estimate ($33,958/YOLS) falls within the range of currently accepted medical interventions, such as coronary angiography (recently estimated to cost between $17,000-$44,000).[93]

3.7 Cost of Improved Cholesterol Management from a Military Perspective

3.7.1 Personnel Not Currently on Lipid Lowering Pharmacotherapy

The cost of intervention in drug therapy candidates from a military perspective are presented in Table 24. These estimates are based on the intervention schedule and associated costs described by Grover and colleagues in their 1995 publication[70], with the substitution of simvastatin for lovastatin. This substitution was made because the efficacy estimates used to estimate the benefits of pharmacotherapy for cholesterol reduction were based on results from the 4S study (which used simvastatin). A detailed description of the estimated resource utilization

and associated costs for the intervention schedule described by Grover and colleagues [70] is presented in Appendix F. Results are presented in Table 24 for both initial and subsequent years of intervention since the treatment schedule suggested by Grover and colleagues in the first and subsequent years differ. In this investigation, the drug therapy candidates (n=172) had a combined total of 1160 years of service remaining. Given that each drug therapy candidate had one year of initial treatment, there were 988 years of subsequent intervention prior to retirement for this subsample. The treatment costs that would have been incurred as part of routine medical care (539 physician visits, 165 lipid profile measurements, 165 blood collections) were subtracted from the total cost of treatment for the remaining years of service for the 172 personnel identified. Treatment intervention costs identified in Table 24 thus only represent the additional costs resulting from the initiation and maintenance of drug therapy in drug therapy candidates in the study not currently on lipid lowering pharmacotherapy for their remaining years left of service. Based on the results presented in Table 24, it would cost the military just over one million dollars to initiate and maintain statin therapy in drug therapy candidates found in this investigation until they retire. If the results of the present investigation are representative of the entire military population over the age of 45, the Canadian military could expect to pay approximately 4 million dollars for statin therapy for this cohort since the study sample represents approximately one quarter of all Canadian military personnel over the age of 45.

Table 24 - Cost of Improved Prophylactic Cholesterol Management From a Military Perspective in Drug Therapy Candidates Not on Lipid Lowering Pharmacotherapy

	Total Number of Years Left of Service (n=172 personnel)	Yearly Costs	Costs
Treatment			
Initial Year	172	1008.76	$173 506.72
Subsequent Years	988	898.58	$887 797.04 **$1 061 303.76**
Routine Care			
	539 visits @ $25.20/visit 165 lipid profiles @ $19.26/analysis 165 blood collections @ $4.81/sample		$13609.75 $793.65 $3177.90 **$17581.30**
Incremental cost	**Treatment costs – Routine Care**		**$1 043 722.46**

3.7.2 Personnel on Lipid Lowering Pharmacotherapy

The cost estimates presented in the previous section are based on improved prophylactic cholesterol management in military personnel not currently on lipid lowering pharmacotherapy. Also identified in the present investigation were those personnel on lipid lowering medication not being treated to target lipid values. A total of fifty-three personnel were identified. Presented in Table 25 are the cost estimates of improved cholesterol management in this population.

Table 25 - Cost of Improved Prophylactic Cholesterol Management from a Military Perspective in Patients on Lipid Lowering Pharmacotherapy not Being Treated to Target

Drug class	Total Current Cost of lipid lowering pharmacotherapy*	Total Cost of lipid lowering pharmacotherapy at next higher dose*	Difference (next highest dose - current)
Statins	$120 858.85	$179 244.20	-
Fibrates	$20 757.55	$0.00	-
Bile acid sequestrants	$3 328.80	$4161.00	-
Nicotinic acid	$438.00	$2628.00	-
Nicotinic acid and fibrates (combination therapy)	$4270.50	$5584.50	-
Statin and Fibrate (combination therapy)	$28 101.35	$94 629.90	-
Statin and Nicotinic acid (combination therapy)	$2784.95	$5467.70	-
Total	$180 540.00	$291 715.30	$111 175.30

* for remaining years left of service

Based on the above calculations, it would cost the military an additional $111,175.30 to successfully lower and maintain the cholesterol levels of the fifty-three personnel on lipid lowering therapy not obtaining the maximum benefit of drug therapy for their remaining years left of service, under the assumption that the next higher dose would lower cholesterol to target values. If the population in this study is representative of the entire military cohort over the age of 45, the extra costs for improved management of personnel on lipid lowering medication for their remaining years of service would be just under a half a million dollars.

3.8 Sensitivity Analysis

While the results of the Grover model have been shown to be robust (see Appendix E), and relatively insensitive to changes in key parameters, a sensitivity analysis in the present investigation was undertaken to examine the effect of non-compliance on the cost-effectiveness estimates obtained for drug therapy candidates in this study. This additional sensitivity analysis

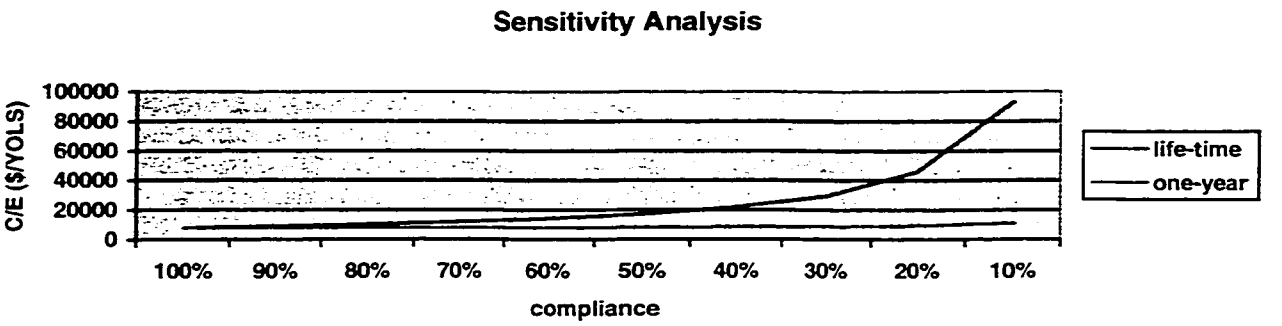
was also considered important because of the fact that only half of the military personnel were found to have been successfully lowered to target cholesterol levels. Also, the cost-effectiveness and health benefit estimates obtained in this investigation were generated by a model that used results from a clinical trial (where there is often a high degree of compliance). These high levels of compliance might not exist in the current clinical setting. This fact alone could be used to threaten the validity of the results of this investigation. The results of the sensitivity analysis undertaken here would therefore provide valuable information as to the effect of poor compliance on the overall cost-effectiveness of this preventive strategy. In this analysis, $50,000/YOLS, a commonly cited threshold [93], was identified as the threshold over which statin therapy in this population may not be cost-effective.

Cost-effectiveness estimates were calculated for decreasing levels of compliance. Compliance in this context was considered at the group level and not at the level of the individual. All calculations were determined under two scenarios. In the first scenario, it was assumed that people who did not comply with drug therapy would be discontinued from the therapy one year after initiation. This scenario was designed to reflect current medical practice. In the second scenario, it was assumed that once initiated, drug therapy would continue up to age seventy-five. This second scenario was designed to explore the sensitivity of the cost-effectiveness estimates to lifetime non-compliance.

In calculating the cost-effective estimates, the intervention costs of statin therapy calculated by Grover and colleagues[70], were applied to the patients who were assumed to be non-compliant. These were the same intervention costs that were used to calculate the cost of statin therapy from a military perspective. One hundred percent compliance was assumed to yield the

results obtained in the 4S study.[13] While this rate of compliance is slightly higher than that obtained in the 4S study[13] this was not felt to have greatly affected the estimates. To determine the cost and benefits of intervention in personnel that comply with the therapy the average number of undiscounted years of life saved per person (2.89) and the mean incremental undiscounted cost-effectiveness ratio ($7960.89) determined in this investigation were used. Therefore, for each level of compliance tested in this sensitivity analysis the non-compliers contributed only costs to the analysis while the compliers accrued both costs and health benefits. Lower levels of compliance yielded more costs (because of extra morbidity) and fewer benefits, resulting in a less cost-effective preventive strategy. For example, at a 70% rate of compliance, 7 out of 10 people complying with the therapy would accrue both health benefits and incremental costs. The remaining 3 non-compliers would get no benefit from the therapy but would incur intervention costs of treatment. The cost-effectiveness of the prevention strategy for all 10 people would be determined by considering the benefits gained by the 7 compliers and incremental costs of the compliers (intervention costs minus costs averted due to reduction in CHD) together with the intervention costs of the non-compliers. The outcome of these calculations are presented graphically in figure 1 in undiscounted form.

Figure 1



Based on the results displayed in Figure 1, the cost-effectiveness of statin therapy in the military population identified by the revised cholesterol guidelines are highly insensitive to the rate of compliance with drug therapy. As expected, the cost-effectiveness of this therapy decreases with increasing levels of non-compliance, but only at very high levels of non-compliance does statin therapy become cost excessive. Specifically, compliance of only 20% to lifetime statin therapy still yielded a cost-effectiveness ratio of just under $50,000 per year of life saved based on the above calculations. Also, for all levels of non-compliance up to 90%, the cost-effectiveness estimates all remained less than $16,000 per year of life saved if only the first year of intervention costs are considered in non-compliers.

4.0 DISCUSSION

4.1 Implications

Despite recent advances in life saving medical procedures for CHD and stroke and an almost 40% decrease in the death rate from CHD in the last two decades, cardiovascular disease continues to be Canada's number one killer. Any strategy that can prevent or delay the onset of this disease has the potential to greatly improve the health of Canadians. Cholesterol reduction through the use of statin drug therapy is a proven means by which to reduce the risk of developing both fatal and non-fatal coronary events and consequently, overall mortality. More recent evidence suggests that the risk of stroke is also reduced in patients on statin therapy. Given its limited number of negative side effects, following recommendations for the appropriate use of this therapy outlined in current evidence-based cholesterol guidelines is therefore a clinical imperative.

Preliminary evidence suggesting that cholesterol guideline recommendations are not always followed in clinical practice was supported by the results of this investigation. Sub-optimal cholesterol management in the military does not, however, appear to be the result of poor cholesterol screening since complete and recent lipid profiles were available for eighty-four percent of personnel included in the study. These are unlike the results obtained by Fodor[41], who found that only twenty-three percent of all patients included in his survey of primary care practice had ever had a complete lipid profile. It should be noted however that the survey by Fodor was not limited to patients over the age of forty-five for whom such measurements are recommended on a routine basis.

Unlike results obtained in other studies[42], the majority of personnel with symptomatic

coronary disease included in the present investigation were receiving lipid lowering medication (23 of 26). This proportion is substantially higher than the results obtained by McCormick and colleagues[42] who found that only one third of patients in secondary prevention with elevated cholesterol were receiving appropriate pharmacotherapy for cholesterol reduction.

It is, however, important to consider the number of personnel with coronary disease on lipid lowering medication not being treated to target cholesterol levels. Only five of the twenty-three personnel with CHD receiving prophylactic pharmacotherapy for cholesterol reduction were meeting the target level for all three lipid parameters identified by revised cholesterol guidelines. These results are comparable to those obtained by Marcelino and Feingold[43] who found that only 33% of the subjects on statin therapy, the majority of whom were receiving therapy in secondary prevention, were meeting the target LDL-c level. Since a greater proportion of personnel free of heart disease on lipid lowering medication were reaching target endpoints (42/88), the overall results in this study were slightly better. Lastly, one eighth of the personnel not on lipid lowering medication should have been on drug therapy, under the assumption of no effect of diet therapy. The majority of these personnel were free of coronary disease.

In this study it was found that personnel most at risk of CHD, based on non-lipid risk factors, were those most likely to qualify for drug therapy. Specifically, drug therapy was indicated in 70.0%, 52.9% and 20.2% of the study personnel at very high, high and moderate levels of risk, respectively, in patients not on drug therapy in the present investigation. These results are likely due to three factors. Firstly, because the cholesterol guideline recommendations are based on a global risk assessment, lower cholesterol levels are promoted in

high risk personnel with multiple non-lipid risk factors. As a result, high risk personnel only have to have moderate levels of cholesterol to qualify for drug therapy. Secondly, the results obtained in this investigation imply that high risk personnel are not being specifically targeted by the military, another factor contributing to the greater proportion of personnel at high risk qualifying for drug therapy. Thirdly, patients at higher levels of risk are more likely to have elevated cholesterol levels, due to the clustering of risk factors commonly observed.[94]

The results of this study suggest that a number of patients who are not currently on lipid lowering pharmacotherapy would benefit in terms of CHD risk reduction from this risk management strategy. In choosing to medicate a population, however, it is important to weigh the benefits to be derived from the therapy against any potentially negative effects. The diagnosis of elevated cholesterol itself could be a negative effect of improved cholesterol management, since there may be a negative response from the patient to being "labeled". But identifying medical conditions that could potentially shorten the life of a patient is the first step in addressing the problem, especially for medical conditions for which the negative social stigma is minimal. Given the ease of administration of cholesterol lowering medication and the limited number of negative side effects resulting from it, the chance of a diagnosis of elevated cholesterol limiting the deployability of military personnel is negligible.

With respect to the economic evaluations of statin therapy, the quality of the analyses is variable but improving over time. Based on the results of the systematic review undertaken in this investigation, recently published guidelines designed to improve the reporting of economic evaluations are having the desired effect, with more recently published analyses performing better on the reporting component of the systematic review. Areas of needed improvement

include the need for increased explicitness in the reporting of cost and resource utilization. The quality of economic evaluations would also benefit from a greater exploration of the rationale behind the choice of model used to forecast benefits and the intervention and treatment costs of lipid lowering therapy.

While models based on final endpoints, such as coronary events and death, have typically been considered as superior to those based on intermediate endpoints[76], estimates of the cost and clinical benefit of statin therapy in the present analysis were based on results from the latter type of model. Modelling in economic evaluations requires assumptions to be made regarding the benefits to be gained and costs that will be incurred from a given therapy. These assumptions will ultimately affect the results of the analysis. In economic evaluations of statin therapy in CHD there is an apparent relationship between the assumed duration of the benefit from statin therapy and the clinical outcome data used. Most models considered in the present review that were based on final clinical outcome data assumed that the benefit of the therapy was limited to the duration of the trial on which the analysis was based, although in some cases the therapeutic benefit extended a few years. Models based on intermediate clinical outcomes, however, assumed that the benefits of therapy would extend over a lifetime, or at least until old age. As has been suggested by Hlatsky[68], in a recent paper on the role of economic models in randomized clinical trials, short-term and long-term estimates of the cost-effectiveness of statin therapy are likely to differ, the latter estimates more accurately reflecting the true costs and benefits.[68] While clinically more appealing, the superiority of cost-effectiveness results based on clinical outcome data from clinical trials of short duration might not therefore be justified on two counts. Firstly, it is unlikely that once prescribed, statin therapy would subsequently be discontinued by

a treating physician. Secondly, based on the results obtained by Rivière and colleagues[50] who determined the cost-effectiveness of statin therapy assuming different durations of benefit, statin therapy is more cost-effective if extended benefits are considered.

Based on the estimates of a validated Canadian CHD life-expectancy model used in this investigation, there could be large health benefits of improved cholesterol management with lipid lowering pharmacotherapy in the military population. Estimates derived from the drug therapy candidates not on lipid lowering medication suggest on average that lifetime lipid lowering pharmacotherapy could extend the life of these personnel by two to three years. While the exact representativeness of the study sample to all regular force Canadian military personnel over the age of forty-five is not known, the fact that almost one quarter of the eligible cohort was included in this study makes these results meaningful for management of cholesterol in the Canadian military. Similarly, the results of this investigation should be relevant to other closely monitored clinical populations and other military populations.

The benefits that could potentially be attained through improved cholesterol management in military personnel come at a price, however. From a military perspective, the cost to improve cholesterol management with pharmacotherapy would be substantial. The additional cost to manage drug therapy candidates identified in the present investigation for their remaining years left of service was estimated at over one million dollars, based on published estimates of annual intervention costs (assuming that all personnel identified continue with the Canadian military until they retire at age fifty-five). The cost to improve cholesterol management in personnel currently on lipid lowering pharmacotherapy was also notable. From a military perspective, lipid lowering pharmacotherapy might not be considered cost-effective if limited to the timeframe

prior to retirement, since the vast majority of the benefits of cholesterol reduction will occur after personnel have left the military.

The lifetime cost-effectiveness of lipid lowering pharmacotherapy, which considers the lifetime cost and benefits of this risk management strategy, is acceptable given the cost-effectiveness of currently accepted medical interventions. The average incremental cost-effectiveness ratios for drug therapy candidates were found to be under $12,000 per year of life saved for all risk levels in both discounted and undiscounted form.

In estimating the cost-effectiveness of statin therapy among personnel identified by the revised cholesterol guidelines it was assumed in model simulations that the effectiveness of the therapy would be similar to that obtained in the 4S study.[13] Patient compliance can affect the efficacy of a preventive therapy in reducing the risk of disease. In the 4S study[13], patient compliance over the duration of the study (5.4 years) to the therapy was found to be almost 90%.[13] The high compliance undoubtedly contributed to the large benefits observed in that trial.

In estimating the extra cost to get personnel on lipid lowering pharmacotherapy to target levels, it was assumed that the next higher dose would be successful in lowering cholesterol, thus suggesting a titration problem as the reason that personnel were not reaching target values. In fact, however, personnel might not have been meeting target lipid levels due to non-compliance to drug therapy. If the proportion of personnel on drug therapy not meeting target endpoints in the present investigation is representative of the rate of non-compliance to drug therapy in the military (and not the result of sub-therapeutic doses of lipid lowering medication being prescribed) the benefits achieved in the 4S study[13] would not be realized. The results generated by the Grover model would therefore be optimistic in forecasting the health benefits and cost-

effectiveness of this preventive therapy. However, based on the results obtained in the sensitivity analysis, the cost-effectiveness of statin therapy in the identified military population is relatively insensitive to patient compliance. Specifically, the potential benefits in this population are so great that even with only 20% compliance and assuming lifetime costs of drug therapy, the cost-effectiveness of this therapy is just under $50,000 per life year saved. These results imply that not all of the study personnel identified as drug therapy candidates would need to achieve target cholesterol levels for statin therapy to be considered cost-effective. Even if sub-optimal benefit in terms of cholesterol reduction among the identified personnel was achieved, because of either the prescription of sub-therapeutic doses or patient non-compliance, statin therapy as a risk management strategy for CHD would remain cost-effective.

Based on the study results and the forecasted benefits of lipid lowering pharmacotherapy, the revised Canadian cholesterol guidelines are able to successfully identify patients for whom lipid lowering pharmacotherapy could be a cost-effectiveness management strategy for CHD risk reduction. Furthermore, the forecasted benefits of statin therapy among personnel not on lipid lowering pharmacotherapy identified by the guidelines were substantial in the present investigation.

4.2 Limitations and Future Research

In this investigation, complete data were available on almost all non-lipid risk factors and the majority of lipid values. The effect of any missing data on the results of the present investigation likely is to underestimate the true degree of sub-optimal cholesterol management. The fact that the determination of sub-optimal cholesterol management in the present investigation was based solely on available data assumes that the lipid measurements that were

not taken or recorded were all below target levels. If this was not the case, greater numbers of personnel might have met the criteria for drug therapy. The number of outdated lipid measurements (8%) although not terribly elevated also prevented precise determination of inappropriate cholesterol management. It should however be noted that the date of the most recent fasting lipid profile in many of the outdated profiles only exceeded the five year threshold by a small amount (<1yr).

While the reliability of the data abstraction process in the present investigation was found to be high (98%), the potential bias which exists because the data was abstracted by only one abstractor cannot be ignored. To make the data abstraction process as objective as possible the military data abstractor was provided with strict training and criteria prior to data abstraction. Also, the highly structured format of the military charts and forms that are completed during the routine medical exams reduce the likelihood of multiple interpretations, and increase the likelihood that multiple abstractions will yield identical results. Lastly, the highly objective nature of the data required for the present investigation also limited the potential for bias and subjectivity in the data abstraction process. Considered together, these factors help to support the reliability of the data abstraction process and the results of this study.

In this investigation drug therapy candidates were identified based on the lipid profile values from one cholesterol measurement. While cholesterol measurements have been shown to demonstrate stability over short time intervals, any treatment decisions based on threshold values being exceeded might be subject to change upon re-measurement due to the effect of regression towards the mean. The potential effect of this trend on the results of the present investigation would likely be to reduce the number of patients meeting the criteria for drug therapy. However,

given that the drug initiation values are 1 unit greater than the ideal target values for each risk level, re-measurement values that demonstrated a regression towards the mean would still likely exceed the ideal target values outlined by the guidelines. Most patients would thus likely continue to be at risk based on their elevated cholesterol levels and would still benefit from cholesterol reducing drug therapy, although perhaps not to the same extent as forecasted in this investigation.

The systematic review of the present investigation had two components, a modelling component and a reporting component. While the checklist used to address the latter of these two components has been published previously and has been shown to have good inter-rater reliability, the modelling checklist was developed specifically for the present investigation. This was necessitated by the current lack of existing modelling checklists. The modelling checklist was checked for content by experts in the field on economic evaluations and cardiovascular research. Although based on a review of existing literature in the areas of modelling, CHD and statins it will require validation by other external sources in future studies.

The present investigation did not consider the indirect (productivity) costs associated with CHD. Unfortunately, these costs were not available because of the costing system currently used at the Department of National Defence. While inclusion of these costs might have improved the cost-effectiveness of this risk management strategy from the military perspective, these costs would likely be minimal given that most coronary events occur after personnel have retired from the military.

Also not considered in the present investigation were issues relating to quality of life. All cost-effectiveness analyses included in the systematic review had as their primary outcome

measure years of life saved. This is likely a reflection of a lack of reliable utility estimates in CHD. Further research in the area of quality of life in CHD could yield cost-effectiveness estimates that more accurately reflect the reality of this intervention strategy.

In forecasting the benefits and cost-effectiveness of statin therapy in the military several assumptions were made. It was assumed that diet therapy and other lifestyle modifications would have no effect on risk reduction for CHD in personnel meeting the criteria for drug therapy. This assumption was based on what is currently known about the long-term effectiveness of lifestyle modification strategies in cardiovascular disease risk reduction. If, however, compliance with such strategies is improved, the cost-effectiveness of statin therapy would likely be reduced.

In estimating the additional costs required to treat personnel on lipid lowering medication to target it was assumed that the next higher dose would successfully lower cholesterol levels. If, however, military personnel on lipid lowering therapy were not meeting target values because of non-compliance with the drug therapy, the additional funds invested in pharmacotherapy for cholesterol reduction would yield no additional benefits and would have large negative financial consequences for the military.

Another underlying assumption in the present investigation was that the benefits of statin therapy obtained in the military setting would be similar to those obtained in clinical trials. The aim of the present investigation was not only to determine the discrepancy between current practice and optimal cholesterol management, but also to forecast the *potential* benefits of "optimal" cholesterol management. The sensitivity analysis undertaken in this study, however, implies that except for extreme cases of non-compliance with this preventive risk management

strategy, statin therapy is cost-effective in populations identified by current cholesterol guidelines.

With respect to the generalizability of the results generated in the present investigation to other clinic settings several issues deserve mention. Firstly, the fact that there is full financial coverage for all prescription and non-prescription medicine for military members makes it unlikely that any non-compliance to drug therapy would be the result of financial barriers. Such is not the case in the civilian sector where the price of statin therapy might be prohibitive for some patients. Therefore, any attempts to improve the clinical management of patients with high cholesterol in the civilian sector might be hampered by other factors not affecting military personnel. Based on the sensitivity analysis carried out in this investigation not all drug therapy candidates identified in the clinical setting would need to comply with the therapy for it still to be a cost-effective CHD risk management strategy. Any future decreases in the cost of statin therapy will undoubtedly help ensure that this therapy is available to the greatest number of people who stand to benefit from the therapy.

A final caveat to the results of the present investigation is the fact that the health benefits and associated cost-effectiveness of statin therapy in the military were estimated based on a life-expectancy model, and not measured directly. This was necessary because of the absence of any long-term clinical outcome data. If, in the future, such information becomes available, the estimates in the present investigation might be found to over or underestimate the true cost-effectiveness of statin therapy in populations with elevated cholesterol. Estimates in the present investigation were derived from a validated CHD model developed on the best currently available data.

4.3 Conclusion

Coronary heart disease is the leading killer in most industrialized countries. Statin therapy is an efficacious method to reduce the risk of coronary events, stroke and death in people with elevated cholesterol. The degree to which this form of preventive therapy will translate into improved health of the population will be determined by how well it is integrated into current medical practice. The results of this study would indicate that there is room for improvement in this respect in the military. According to a recent statement from health care professionals[95], non-compliance to preventive recommendations is multi-level in the clinical setting. Non-compliance among patients in addition to professional health care providers may contribute to the maximum beneficial effects of statin therapy not being realized. Just as we need to improve compliance of patients with diet therapy if this risk management strategy is to be considered as an effective strategy for CHD prevention, so too do we need to improve patient compliance to drug therapy. Several studies have shown this to be a problem in the primary care setting.[96,97] While multi-level, a hierarchy of non-compliance in preventive pharmacotherapy for CHD prevention does exist, with primary care health providers at the top. Non-compliance among health care providers preempts issues of non-compliance in the patient population. A comprehensive discussion of issues related to improving physician compliance to guideline recommendations is beyond the scope of the present endeavour given the complex nature of this topic.[IV]

[IV] Issues related to improving professional practice through guidelines are discussed in "How to ensure that guidelines are effective", BMJ 1995; 311: 237-242 and "No magic bullets: a systematic review of 102 trials to interventions to improve professional practice" CMAJ 1995; 153(10): 1423-1431.

The aim of the present investigation was to determine the extent of the gap between current and optimal cholesterol management and to identify the potential benefits and the cost-effectiveness of improved pharmacotherapeutic management of patients with elevated cholesterol in the military. A gap was shown to exist, and to increase with level of risk. Cholesterol reduction with statin therapy was shown to be highly cost-effective, even at moderate levels of non-compliance to drug therapy. Furthermore, there is the potential for substantial health benefits to military personnel in terms of reduced CHD events and stroke and increased longevity. It is now up to the military and other similar health care providers to improve physician and patient compliance to this preventive strategy for CHD. It is hoped that the small size of the medical community within the military, combined with the more vigorous implementation of policies, will facilitate the required improvements with respect to adherence to cholesterol guideline recommendations in the military setting. Such improvements have the potential to greatly improve the health of a population devoted to public service.

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APPENDIX A

Data Abstraction Form

PT	Sex (M/F)	Age (yr)	HT (cm)	WT (kg)	Smoker Y/N	Htn Y/N	Diab Y/N	CAD Y/N	Fam Hx Y/N	LLD* Y/N	Dose (mg)	TC	TG	HDL	LDL	Ratio TC/ HDL	Date of profile D/m/y

* LLD: lipid lowering drugs

APPENDIX B

MEDICAL EXAMINATION RECORD
(PERIODICAL HEALTH EXAMINATION)

FICHE D'EXAMEN MÉDICAL
(EXAMEN DE SANTÉ PÉRIODIQUE)

REASON FOR EXAMINATION – MOTIF DE L'EXAMEN		EXAMINATION UNIT – ÉTABLISSEMENT MÉDICAL CFSU (O) HCC MIR CFSU(O) SEM	
SURNAME – NOM	GIVEN NAMES – PRÉNOMS	SN – NM	SEX – SEXE M / F
HOME UNIT – UNITÉ D'APPARTENANCE		DOB – DDN	MOC – GPM
ENROLMENT DATE – DATE D'ENRÔLEMENT	TOTAL FLYING TIME – TEMPS TOTAL DE VOL	TOTAL PAST YEAR – TOTAL DE L'ANNÉE DERNIÈRE	

1. HISTORY AND/OR FINDINGS PERTINENT TO EXAMINATION – ANTÉCÉDENTS MÉDICAUX ET/OU OBSERVATIONS PERTINENTES À L'EXAMEN MÉDICAL

2. DIAGNOSIS – DIAGNOSTIC

3. MEDICAL OFFICER'S RECOMMENDATIONS (STATE SPECIFIC LIMITATIONS ON EMPLOYMENT)
RECOMMANDATIONS DU MÉDECIN MILITAIRE (BIEN PRÉCISER LES RESTRICTIONS À L'EMPLOI)

DATE FOR NEXT EXAMINING BOARD
DATE DE LA PROCHAINE ÉVALUATION MÉDICALE ➧

4. PROFILE – PROFIL	YOS	V	CV	H	G	O	A	EXAMINING MEDICAL OFFICER SIGNATURE – SIGNATURE DU MÉDECIN MILITAIRE EXAMINATEUR
PRESENT ACTUEL ➧								
RECOMMENDED RECOMMANDÉ ➧								DATE

5. REMARKS – APPROVING MEDICAL OFFICER – OBSERVATIONS DU MÉDECIN MILITAIRE APPROBATEUR

DATE	APPROVING MEDICAL OFFICER SIGNATURE – SIGNATURE DU MÉDECIN MILITAIRE APPROBATEUR

6. CMB RECOMMENDATIONS – RECOMMANDATIONS DU CMC		7. SURGEON GENERAL APPROVAL – APPROBATION DU CHEF DU SERVICE DE SANTÉ	
DATE	SIGNATURE CMB – SIGNATURE DU CMC	DATE	SIGNATURE DGHS – SIGNATURE DU DSSS

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7530-21-924-3532

PROTECTED B PROTÉGÉ

Design: Forms Management 994-0162
Dessin: Gestion des formules 997-6814

APPENDIX B

PROTECTED B PROTÉGÉ

EXAMINATION – EXAMEN

1 TESTS – PROCEDURE	YES OUI	NO NON
UR ALYSIS ANALYSE D'URINE		
BIOCHEMISTRY BIOCHIMIE		
HEMATOLOGY HÉMATOLOGIE		
ECG		
CHEST X-RAY RADIOGRAPHIE PULMONAIRE		
OCCULT BLOOD SANG OCCULTE		
SIGMOIDOSCOPY SIGMOÏDOSCOPIE		

5 FINDINGS (NO TO SUMMARIZE) – RÉSULTATS (SOMMAIRE PAR NON)

*9 OTHER TESTS YES/NO SPECIFY
AUTRES TESTS OUI/NON PRÉCISER

11. AUDIOGRAM RESULT (Loss in dB) – AUDIOGRAMME – RÉSULTATS (Perte de dB)
(FREQUENCY X 1000 CPS) (FRÉQUENCE X 1000 CPS)

HEIGHT TAILLE (CM)	WEIGHT POIDS (KG)	WEIGHT GAIN/LOSS (KG) PAST YEAR POIDS GAIN/PERTE DERNIERS 12 MOIS	BMI (BODY MASS INDEX) MASSE CORPORELLE (INDEX)

EAR OREILLE	.5	1	2	3	4	6	8
RIGHT DROITE							
LEFT GAUCHE							

*12 PULSE RATE AND RHYTHM
POULS FRÉQUENCE ET RYTHME ___ /Min

BLOOD PRESSURE
PRESSION ARTÉRIELLE ___ S ___ D

*13 ITEMS – DETAILS		R – D	L – G
VISION – ACUITÉ VISUELLE			
UNCORRECTED – SANS LUNETTES		6/	6/
CORRECTED – AVEC LUNETTES		6/	6/
EYES – FUNDI FOND D'ŒIL			
INTRA-OCULAR PRESSURE R/D PRESSION INTRA-OCULAIRE L/G			
EARS (INCLUDING AUDIOGRAM) OREILLES (AUDIOGRAMME COMPRIS)			
NOSE NEZ			
MOUTH AND TEETH BOUCHE ET DENTS			
HEAD AND NECK TÊTE ET COU			
BREASTS SEINS			
LUNGS POUMONS			
HEART CŒUR			
ABDOMEN			
SPINE COLONNE VERTÉBRALE			
EXTREMITIES MEMBRES	UPPER SUPÉRIEURS		
	LOWER INFÉRIEURS		
SKIN PEAU			
NEUROLOGIC EXAM EXAMEN NEUROLOGIQUE			
PSYCHIATRIC EXAM EXAMEN PSYCHIATRIQUE			
GENITALIA (INCLUDING HERNIA) ORGANES GÉNITAUX (AUSSI HERNIE)			
RECTAL EXAM EXAMEN RECTAL			
PELVIC EXAMINATION EXAMEN PELVIEN			
SCARS – BIRTHMARKS – TATTOOS – VISIBLE CICATRICE – TACHE DE NAISSANCE – TATOUAGE (VISIBLE)			

14. POSITIVE FINDINGS AND REMARKS – SIGNES CLINIQUES ET OBSERVATIONS

OPHTHALMOLOGY CONSULTATION – REQUIRED YES ☐ NO ☐
CONSULTATION EN OPHTALMOLOGIE – REQUISE OUI ☐ NON ☐

*15 MEDICAL OFFICER'S COMMENTS – REMARQUES DU MÉDECIN MILITAIRE

PROTECTED B PROTÉGÉ

APPENDIX B

National Defence / Défense nationale

PROTECTED B (when completed) – PROTÉGÉ B (une fois rempli)

MEDICAL QUESTIONNAIRE - QUESTIONNAIRE MÉDICAL

Surname – Nom de famille	Given name(s) – Prénom(s)	SN – NM	Unit phone no. – Nº téléphone de l'unité

Rank – Grade	Sex – Sexe: M / F	DOB – Date de naissance	MOC – GPM	Parent Unit – Unité d'appartenance

PART 1 – PARTIE 1 : PAST MEDICAL HISTORY – ANTÉCÉDENTS MÉDICAUX

Have you had / Éprouvez-vous parfois l'un des phénomènes suivants :

	No / Non	Occasional / De temps à autre	Frequent / Fréquemment
Chest pain / pressure Douleur ou pression à la poitrine			
Shortness of breath – Essoufflement			
Irregular / rapid heart beat Rythme cardiaque irrégulier ou rapide			
Weakness, dizziness Faiblesse ou étourdissement			
Wheezing – Sifflement asthmatique			
Chronic cough – Toux chronique			
Hoarseness – Enrouement			
Sore throat – Mal de gorge			
Difficulty swallowing – Difficulté à avaler			
Nausea and / or vomiting Nausées ou vomissements			
Indigestion			
Abdominal cramps / pain Crampe ou douleur abdominale			
Change in appetite / thirst Changement d'appétit ou de soif			
Diarrhea / constipation Diarrhée ou constipation			
Change in appearance of stool Changement dans l'aspect de vos selles			
Transient loss of coordination / control of fine movement of hands Perte passagère de coordination ou de contrôle de votre dextérité manuelle			
Transient confusion – Confusion passagère			
Frequent / painful urination Miction fréquente ou douloureuse			
Urinary discharge – Écoulement urinaire			

	No / Non	Occasional / De temps à autre	Frequent / Fréquemment
Back pain – Mal de dos			
Painful / swollen / stiff joints Jointures douloureuses, enflées, ou raides			
Leg cramp / pain Crampe ou douleur aux jambes			
Vaginal discharge – Pertes vaginales			
Irregular menstruation Menstruations irrégulières			
Weight loss / gain – Perte ou gain de poids			
Weakness / numbness / tingling in extremities Faiblesse, engourdissement ou picotement dans les membres			
Difficulty sleeping – Difficulté à dormir			
Changes in mood – Changement d'humeur			
Allergies			
Bleeding associated with – Saignement :			
a. spitting or coughing en crachant ou en toussant			
b. a bowel movement en évacuant les intestins			
c. urination – en urinant			
Heat / cold intolerance Intolérance à la chaleur ou au froid			
Loss of memory – Perte de mémoire			
Easily fatigued Faible résistance, fatigue rapide			

PART 2 – PARTIE 2 : RECENT MEDICAL HISTORY / PROBLÈMES DE SANTÉ RÉCENTS

Have you had recently (in the past year): Avez-vous éprouvé, récemment (au cours de la dernière année), l'un des phénomènes suivants :	No / Non	Yes / Oui
Fever / chills / night sweats Fièvre, frissons, sueurs nocturnes		
Persistent headaches – Maux de tête persistants		
Persistent swollen glands Gonflement persistant des ganglions		
Change in vision – Changement de la vue		
Change in hearing – Changement de l'ouïe		
New skin growths Nouvelles excroissances sur la peau		
Change in colour / shape of skin moles / warts Changement de couleur ou de forme de grains de beauté ou de verrues		
Tendency to bruise or bleed easily Tendance à vous faire des bleus ou à saigner facilement		

PART 3 – PARTIE 3 : FAMILY HISTORY / ANTÉCÉDENTS FAMILIAUX

Does a blood relative have a history of: Est-ce que l'un de vos parents consanguins a souffert de l'une des maladies suivantes :	No / Non	Yes / Oui	Who / Qui
Diabetes – Diabète			
Gout – Goutte			
High Blood Pressure – Hypertension artérielle			
Heart Problems – Problèmes cardiaques			
Cancer			
Stroke – Attaque de paralysie			
Depression or other psychiatric problems Dépression ou autre maladie psychiatrique			
Any other significant diseases Toute autre maladie importante			

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Design: Forms Management 993-4050 3-95
Conception: Gestion des formules 993-2778

APPENDIX B

PART 4 – PARTIE 4 : RISK PROFILE CHECK – VERIFICATION DU PROFIL DE RISQUE

A. Marital Status *(Please specify)* **– Situation de famille** *(Veuillez preciser)*

☐ Single – Célibataire ☐ Married – Marié(e) ☐ Widowed – Veuf(ve) ☐ Separated – Séparé(e) ☐ Divorced – Divorcé(e)

B. Stress
Etat de tension

At the present time, are you concerned, pre-occupied or worried about any of the following:
En ce moment-ci, êtes-vous préoccupé ou inquiet au sujet de l'une des choses suivantes :

	No Non	Yes Oui	If yes, specify briefly – Si oui, expliquer brièvement ▶
Personal / family relationships Vos relations interpersonnelles ou familiales			
Work / professional relationships Votre travail ou vos relations professionnelles			
Financial problems – Des problèmes financiers			
Other issues – D'autres problèmes			

C. Personal Habits – Habitudes personnelles

1. Smoking status
Consommation de tabac

☐ Never smoked / N'a jamais fumé ☐ Ex-smoker / Ancien fumeur ☐ Current smoker / Fume actuellement ☐ Pipe ☐ Cigar / Cigare ☐ Cigarette

If EX-SMOKER, how long has it been since you last smoked? _____ *How much did you smoke per day?* _____ *For how many years?* _____
Si ANCIEN FUMEUR, quand avez-vous fumé la dernière fois? _____ *Combien fumiez-vous par jour?* _____ *Pendant combien d'années?* _____

If CURRENT SMOKER, how much do you smoke per day? _____ For how many years? _____ Are you trying to quit? ☐ No Non ☐ Yes Oui
Si FUME ACTUELLEMENT, combien fumez-vous par jour? _____ Depuis combien d'années? _____ Essayez-vous d'arrêter?

2. Do you drink alcohol?
Buvez-vous de l'alcool? ☐ No Non ☐ Yes Oui

Daily intake / Quantité par jour _____ or / ou Weekly intake / Quantité par semaine _____

(a) Have you ever felt you should cut down on your drinking? – Avez-vous déjà ressenti que vous deviez diminuer votre consommation d'alcool? ☐ No Non ☐ Yes Oui
(b) Have people annoyed you by criticizing your drinking? – Cela vous a-t-il déjà irrité de vous faire critiquer sur votre façon de consommer de l'alcool? ☐ No Non ☐ Yes Oui
(c) Have you ever felt badly or guilty about your drinking? – Vous êtes-vous déjà senti mal ou coupable au sujet de votre consommation d'alcool? ☐ No Non ☐ Yes Oui
(d) Have you ever had a drink first thing in the morning (eye opener) to steady your nerves or to get rid of a hangover?
En vous levant le matin, avez-vous déjà consommé de l'alcool pour stabiliser vos nerfs ou pour vous débarrasser de votre queule de bois? ☐ No Non ☐ Yes Oui

3. Do you exercise regularly?
Faites-vous régulièrement de l'exercice? ☐ No Non ☐ Yes Oui

Hours per day / Nombre d'heures par jour _____ Hours per week / Nombre d'heures par semaine _____

4. If you participate in sports, specify:
Si vous pratiquer des sports, dites lesquels :

5. What medications do you currently take?
Quels médicaments prenez-vous actuellement?

6. Have you been treated in the past year for what you consider a significant condition?
Au cours de la dernière année, avez-vous été traité pour des problèmes de santé que vous jugez sérieux?

☐ No Non ☐ Yes *(If yes, please give details):* Oui *(Si oui, dites de quoi il s'agissait)* : ▶

7. Are you allergic to any medication?
Êtes-vous allergique à certains médicaments? ☐ No Non ☐ Yes *(If yes, specify):* Oui *(Si oui, precisez)* : ▶

D. Do you have concerns you want to bring to the attention or discuss with a medical officer?
Avez-vous des inquiétudes dont vous voudriez faire part à un médecin ou dont vous souhaiteriez discuter avec lui? ☐ No Non ☐ Yes *(If yes, specify)* Oui *(Si oui, precisez)*

_____ _____
(Signature of Member – Signature du militaire) (Date)

PART 5 – PARTIE 5 : SUMMARY OF ANCILLARY INVESTIGATIONS TESTS
SOMMAIRE DES RÉSULTATS DES EXAMENS COMPLÉMENTAIRES

Height / Taille ▶ _____ (cm) Weight / Poids ▶ _____ (Kg) BP / Tension artérielle ▶ _____ / _____ Total Cholesterol / Cholestérol total _____

VISUAL ACUITY / ACUITÉ VISUELLE :

	Without glasses – Sans verres		With glasses – Avec verres	
	R / D _____ / _____	L / G _____ / _____	R / D _____ / _____	L / G _____ / _____

URINALYSIS – ANALYSE D'URINE
A dipstick – par bandelette réactive _____
B microscopic – au microscope _____

PART 6 – PARTIE 6 : MEDICAL OFFICER'S REVIEW – RÉVISION PAR LE MÉDECIN

1. Is the medical category and/or limitations still valid? – Le profil médical et/ou les restrictions valent-ils toujours? ☐ No Non ☐ Yes Oui
2. Is an interview required? – Une entrevue est-elle requise? ☐ No Non ☐ Yes Oui

Remarks – Remarques :

_____ _____
(Signature of Medical Officer – Signature du médecin) (Date)

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APPENDIX C

Lipid Lowering Pharmaceutical Agents

Drug Class	Drug Name
Bile acid sequestrants	Cholestyramine resin
	Colestipol hydrochloride
Fibrates	Bezafibrate
	Clofibrate
	Fenofibrate (micronized)
	Gemfibrozil
HMG-CoA reductase inhibitors	Atorvastatin calcium
	Fluvastatin sodium
	Lovastatin
	Pravastatin sodium
	Simvastatin
Niacin Derivatives	Niacin
	Xanthinol niacinate

APPENDIX D

Guidelines For Submission of Economic Evaluations - Referees' Checklist

Referees' checklist (also to be used, implicitly, by authors)

Item	Yes	No	Not clear	Not appropriate
Study design				
(1) The research question is stated	☐	☐	☐	
(2) The economic importance of the research question is stated	☐	☐	☐	
(3) The viewpoint(s) of the analysis are clearly stated and justified	☐	☐	☐	
(4) The rationale for choosing the alternative programmes or interventions compared is stated	☐	☐	☐	
(5) The alternatives being compared are clearly described	☐	☐	☐	
(6) The form of economic evaluation used is stated	☐	☐	☐	
(7) The choice of form of economic evaluation is justified in relation to the questions addressed	☐	☐	☐	
Data collection				
(8) The source(s) of effectiveness estimates used are stated	☐	☐	☐	
(9) Details of the design and results of effectiveness study are given (if based on a single study)	☐	☐	☐	☐
(10) Details of the method of synthesis or meta-analysis of estimates are given (if based on an overview of a number of effectiveness studies)	☐	☐	☐	☐
(11) The primary outcome measure(s) for the economic evaluation are clearly stated	☐	☐	☐	
(12) Methods to value health states and other benefits are stated	☐	☐	☐	☐
(13) Details of the subjects from whom valuations were obtained are given	☐	☐	☐	☐
(14) Productivity changes (if included) are reported separately	☐	☐	☐	☐
(15) The relevance of productivity changes to the study question is discussed	☐	☐	☐	☐
(16) Quantities of resources are reported separately from their unit costs	☐	☐	☐	
(17) Methods for the estimation of quantities and unit costs are described	☐	☐	☐	
(18) Currency and price data are recorded	☐	☐	☐	
(19) Details of currency of price adjustments for inflation or currency conversion are given	☐	☐	☐	
(20) Details of any model used are given	☐	☐	☐	☐
(21) The choice of model used and the key parameters on which it is based are justified	☐	☐	☐	☐
Analysis and interpretation of results				
(22) Time horizon of costs and benefits is stated	☐	☐	☐	
(23) The discount rate(s) is stated	☐	☐	☐	☐
(24) The choice of rate(s) is justified	☐	☐	☐	☐
(25) An explanation is given if costs or benefits are not discounted	☐	☐	☐	☐
(26) Details of statistical tests and confidence intervals are given for stochastic data	☐	☐	☐	☐
(27) The approach to sensitivity analysis is given	☐	☐	☐	☐
(28) The choice of variables for sensitivity analysis is justified	☐	☐	☐	☐
(29) The ranges over which the variables are varied are stated	☐	☐	☐	☐
(30) Relevant alternatives are compared	☐	☐	☐	
(31) Incremental analysis is reported	☐	☐	☐	☐
(32) Major outcomes are presented in a disaggregated as well as aggregated form	☐	☐	☐	
(33) The answer to the study question is given	☐	☐	☐	
(34) Conclusions follow from the data reported	☐	☐	☐	
(35) Conclusions are accompanied by the appropriate caveats	☐	☐	☐	

Source: Drummond MF, Jefferson TO on behalf of the BMJ Economic Evaluation Working Party. Guidelines for authors and peer reviewers of economic submissions to the BMJ. BMJ 1996; 313:275-283.

APPENDIX E

Grover Model Description

The newest life-expectancy model developed by Grover and colleagues[72] to forecast the costs and benefits of preventive strategies in CHD is a Markov model. In this model three death states and four non-death states are identified, for a total of seven disease states. The transition probabilities to the three death states in this model (death from coronary disease, stroke or other causes) are based on the regression coefficients of three multivariate models derived from a 15% random sample from the Lipid Research Clinics (LRC) follow-up study [22] and risk factor data from the study population of interest. A list of the variables included in each of these models appears in the table on p110. Simulations derived from these models are based on a cycle length of one year. To determine the annual transition probabilities of death in the simulations the 10-year risk estimates developed using the multivariate models and risk factor data are divided by ten. Transition probabilities to non fatal cardiovascular disease states in the Markov model are based on the ratio of non-fatal to fatal events observed in three studies, namely the Lipid Research Clinics[22], the Framingham study[66] and the 4S study.[13] The four non-fatal events considered in this model include coronary insufficiency, non-fatal MI, transient ischemic attack and non-fatal stroke. By associating cost values to certain disease states, simulations using this model can not only forecast life expectancies but can also forecast the expected management and treatment costs of the disease. Of greater interest, results of simulations of competing preventive strategies using the model can be valuable in determining the cost-effectiveness of the strategies. How the model generates these three parameters (life-expectancy, cost and cost-effectiveness) will be briefly discussed in turn.

Independent Risk Factors Included in the Multivariate Grover Models*

Risk factor	CHD Death	Stroke Death	Other Death
Cigarette Smoking	✓	✓	✓
Sex	✓		✓
Mean BP	✓	✓	
Cardiovascular Disease	✓	✓	
Age	✓	✓	
Age^2			✓
Glucose Intolerance	✓	✓	
Natural Log LDL/HDL	✓	✓	

*Source: Grover SA, Paquet S, Levington C, Coupal L, Zowall H. Estimating the benefits of modifying risk factors of cardiovascular disease: a comparison of primary and secondary prevention. Arch Int Med 1998; 158: 655-662.

To estimate the life-expectancy, a cohort of 1000 people (with or without CVD) is entered into the model, the risk profile of which is identified a priori. Transition probabilities to each of the disease states in the model is determined based on the regression coefficients and the risk profile of the cohort. In the simulations, survivors can either remain healthy, develop non-fatal CVD, or die from CVD or non-CVD causes at the end of every cycle. Surviving subjects are aged one year and are then re-entered into the model. Model simulations continue up until the age of 102 (the oldest age of survival assumed by the model). All the remaining survivors are assumed to die after the age of 102. Due to the lack of evidence of the benefit of cholesterol reduction on CHD in old age, this model conservatively assumes that the benefits of cholesterol reduction end at age 75. The intervention costs, however, accrue over a lifetime since all members of the cohort are assumed to continue receiving treatment intervention until death. Finally, the mean life-expectancy of the cohort is estimated by dividing the total number of

person-years for the cohort by the cohort size.

In model simulations, the beneficial effect that a preventive CHD risk management strategy has on life-expectancy is determined solely by the degree to which the strategy eliminates or reduces risk factors from the overall risk profile, such as by lowering cholesterol with statin therapy. Changes in the risk profile result in changes to the transition probabilities to disease states and death in the Markov model and ultimately affects the estimated life-expectancy. To estimate the long-term health benefit of one treatment over an alternative treatment using this model the forecasted life-expectancies are compared. The years of life saved by one intervention over its alternative is defined as the difference in life-expectancy estimates generated by the model.

In estimating the health care costs associated with CHD, the Grover model considers both treatment and surgical costs, in addition to the intervention costs. Treatment costs considered in the model include both hospital costs and physician fees, as well as outpatient and emergency services. A complete description of the methods used to estimate all costs is provided by the authors in the economic analysis cited in the present review. [72] Briefly, all hospital costs are based on Canadian Institute Health Information (CIHI) data, for case-mix groups which have been categorized based on resource utilization. Surgical costs are similarly estimated using probability-weighted costs and are estimated for all coronary surgical procedures, including angioplasty, artery bypass grafting, coronary artery catheterization, and pacemaker insertion and replacement. The probability of surgical procedures by type in this model is determined based on hospital separation data. Specifically, the ratio of the hospital separations by surgical procedure to the total number of hospital admissions for acute MI is considered. The costing of physician

services is based on reimbursement fees from Ontario and Quebec. Lastly, outpatient costs are developed separately for the first and subsequent years after a CVD event.

To determine the incremental cost of a risk reduction strategy for CHD, such as cholesterol reduction with statin therapy, the lifetime medical costs both with and without the intervention are considered. As with life-expectancy estimates, the lifetime medical costs under alternative interventions will differ to the extent that these strategies affect the overall CHD risk profile of the patients and thus the transition probabilities to disease states and death. With fewer people entering disease states there will be lower overall treatment costs for the cohort. Lastly, the cost-effectiveness of preventive strategies for CHD using this model is determined by combining the life-expectancy estimates and the cost information generated in the simulations. To the extent that risk factors are removed from the overall profile, life-expectancy will increase and CHD related costs will decrease, therefore increasing the cost-effectiveness of the risk reduction strategy.

Unlike most other CHD models, this model, as well as others previously developed by Grover and colleagues, has been validated against external data. Estimates of the most recent model have been shown to have a high degree of correlation with the results observed in nine randomized controlled trials, in both primary and secondary prevention.[98] In the published validation study, estimates derived using this model were shown to fall well within the confidence intervals of the trial results.[98] The advantage of the most recent model developed by Grover and colleagues[72] over those previously developed by this research group, is that the new model takes into consideration the positive effect that statin therapy has been shown to have on the risk of stroke.

Not only have the results of the current Grover model been validated by external data, but they have also been shown to be robust. In sensitivity analysis carried out in the economic analysis in secondary prevention considered in the present review the results of the analysis were subjected to varying discount rates (3%, 5%), cost data (Canadian, United States, Sweden) and varying strength of benefits of therapy on CHD (constant versus diminishing with age). The benefits of statin therapy were also considered both with and without the effect on the risk of stroke. In all cases in the sensitivity analysis, the resulting cost-effectiveness estimates always fell well under the $50,000/YOLS, a commonly used threshold, and the therapy was therefore still considered cost-effective in spite of these varying parameters.

In summary, while based on intermediate and not final clinical endpoints, the Grover model has proven its worth by validation and is more comprehensive and up-to-date than other existing CHD models. Furthermore, the reporting quality of the economic evaluation based on this model has proven to be of high quality, based on the systematic review undertaken in the present investigation. Perhaps most importantly, estimates of this model are generated based on Canadian data: Canadian resource utilization and costs were used and the population used to develop the risk equations, namely the 15% random sample from the LRC trial[22], also included Canadians. Other models that are based on intermediate clinical endpoints have typically used the Framingham equations, which are based on a middle-class American population.

While the most recent economic evaluation published by Grover and colleagues[72] is a cost-effectiveness analysis of statin therapy in secondary prevention, the newest CHD life-expectancy model can generate cost-effectiveness estimates for both primary and secondary prevention, since the random sample from the LRC trial[22] included patients both with and

without CHD. The validation study, mentioned previously, validated the primary prevention estimates generated by the model against the results of three primary prevention lipid lowering studies, in addition to three secondary prevention lipid lowering trials and three hypertension trials.[98] The results predicted by the model and those actually observed in all nine of these trials, including those in primary prevention, were found to correlate strongly (R^2=0.96).[98] Furthermore, of the 26 outcomes considered in this validation study, estimates of 25 (96%) fell within the 95% confidence interval of the observed outcomes.[98]

Estimates of the benefit of treatment using the most recent Grover model are based on results obtained in the 4S study, described previously.[13] A reduction in total cholesterol and low-density lipoprotein of 25% and 35% respectively is assumed, as well as an increase in high density lipoprotein of 8%.[13] Although health benefit estimates in terms of cholesterol reduction are taken from the results of a secondary prevention drug trial, these estimates are equally applicable in primary prevention since recent primary prevention drug trials, such as the West of Scotland study[12], have yielded similar results. All cost and cost-effectiveness estimates generated by the model are in 1996 Canadian dollars and compare treatment with the status quo (no treatment).[72]

Life-expectancy estimates generated using this model in both primary and secondary prevention (for both high and low risk patients) have been published previously.[98] The benefits of lipid lowering pharmacotherapy have been shown to be both age and gender related. In patients without CVD, there is greater benefit in terms of life-expectancy for men over women and for younger people. Life-expectancy estimates in patients with CVD are comparable between men and women, although the trend of decreasing benefit with increasing age is still

apparent. The rough estimates of life-expectancy generated by the model using only two risk categories (high and low risk) were presented in the validation publication.[98] Forecasted life-expectancy estimates in primary prevention in low risk 40 year old men (YOLS=2.5) were found to be approximately half of the increase in life-expectancy in the high-risk patients (YOLS=4.74).

APPENDIX F

Lifetime Cost of Drug Therapy with Statins*

Initial Year of therapy	Item	Unit cost	Yearly Resource Utilization	Intervention cost
	Statin	$2.16/daily dose	365	$788.40
	Physician visit	$25.20/visit	4	$100.80
	Blood collection	$4.81/collection	4	$19.24
	Lipid profile	$19.26/profile	4	$77.04
	Biochemical profile	$5.82/profile	4	$23.28
TOTAL COST				**$1008.76**
Subsequent years of therapy	Statin	$2.16/daily dose	365	$788.40
	Physician visit	$25.20/visit	2	$50.40
	Blood collection	$4.81/collection	2	$9.62
	Lipid profile	$19.26/profile	2	$38.52
	Biochemical profile	$5.82/profile	2	$11.64
TOTAL COST				**$898.58**

*Source: Hamilton VH, Racicot FE, Zowall H, Coupal L, Grover SA. The cost-effectiveness of HMG-CoA reductase Inhibitors to prevent coronary heart disease: estimating the benefits of increasing HDL-c. JAMA 1995; 273(13): 1032-1038.