‘Statin’ Therapy in Dyslipidemia
An Evidence-Based Review for Family Physicians

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Introduction

In 2001 information from Statistics Canada indicates that cardiovascular disease is the number one killer of Canadians accounting for 74,824 deaths in that year alone (Statistics Canada, 2001). Thirty-three percent of Canadian males and 35% of females died of cardiovascular disease in that year. In 1998 the economic burden of cardiovascular disease in Canada was estimated at $18 billion annually (Statistics Canada, 2001).

Risk factors associated with cardiovascular disease are increasing at an alarming rate. Obesity is at an all time high, affecting 31% of Canadians (Genest et al, 2003). Rates of type II diabetes are also on the rise. The prevalence rate of diabetes in Canada in 1998 was 1.5 million, this rate is projected to double to 3 million people by 2010 (Genest et al, 2003). Increases in these important risk factors coupled with an aging population means that the management of cardiovascular disease will be an important health issue for years to come.

Despite increases in risk factors, the rate of death from coronary artery disease has actually declined over the past 25 years (Fodor et al, 2000). Much of this decline has been attributed to advancements in pharmacological management of blood pressure, hypercholesterolemia and acute coronary events. Management of cholesterol has been an area of enormous research in the past 50 years. There is now considerable data published on the use of cholesterol lowering drugs in the primary setting, secondary setting and acute event setting. Most of this research has been conducted on the HMG-CoA Reductase Inhibitor (better know as “statin”) class of lipid lowering medications.

Because of the success of the statin drugs in lowering cardiovascular mortality in a broad range of patients, they have become a very commonly prescribed medication. In 2004, information from IMS Health indicates that atorvastatin was Canada’s top prescribed medication with over 9 million prescriptions filled (IMS Health Canada, 2004). The use of cholesterol lowering therapy has increased 300% between 1995 and 2003 and this class of therapy is now the 6th largest (in terms of prescriptions filled) therapeutic class in Canada (IMS Health Canada, 2004b; IMS Health Canada, 2003)

Cholesterol Reduction

Statins reduce cholesterol by inhibiting HMG-CoA reductase enzyme which catalyses the biosynthesis of cholesterol in the liver (Lipitor Product Monograph, 2004). They also increase the uptake and catabolism of LDL particles. The degree to which the statins lower cholesterol varies depending on the different agents and dosages. Statins lower LDL cholesterol by an average of 34% and the total cholesterol by an average of 27% (Helfand et al, 2004). At higher doses, the two most potent statins, atorvastatin and rosuvastatin, can reduce LDL by over 50% (Helfand et al, 2004).
Beyond Cholesterol Reduction

Reductions in surrogate endpoints like LDL cholesterol are important only if they reflect reductions in clinical endpoints. Important clinical endpoints to consider include major cardiac events (normally defined as non-fatal MI and death from coronary heart disease), stroke and overall mortality. A drug that reduces cholesterol but does not impact any of these hard endpoints would not really be worth taking. Large randomized trials have looked at the benefits of statins in preventing or reducing these hard endpoints in a variety of patient populations. In reading these trials, it appears that some patients benefit from treatment a great deal more than others. For example, trials that look at statin use in the secondary prevention setting (patients who already have active vascular disease like history of heart attack, stroke, or unstable angina) tend to show more benefit than studies on statins in the primary prevention setting (patients with a range of vascular risk factors that fall short of being defined as vascular disease). We will make use of meta-analysis of the major cardiac end-points (non-fatal MI and death, overall mortality) to examine the benefit of statins in various sub-populations.
Utilization

Underutilization
Recommendations for pharmacological management of hyperlipidemia are similar in the Canadian and American guidelines. If a patient has existing cardiovascular disease they are automatically considered “high risk” for a second cardiovascular event, and as such both treatment guidelines recommend the initiation of pharmacological cholesterol reduction to specific cholesterol goals along with modifications to diet and lifestyle (Genest et al, 2003; Grundy et al, 2004). The same management goals are applied to patients who do not have existing cardiovascular disease but do have coronary heart disease risk equivalents. These risk equivalents include patients with cerebral vascular disease, peripheral vascular disease, chronic kidney disease, adult diabetes, or a 10 year risk of death or non-fatal MI of ≥20% (based on Framingham Risk Calculation) (Genest et al, 2003). Despite these strong treatment recommendations, there is evidence from retrospective cohort studies and retrospective database reviews that patients at high risk of cardiovascular events are not receiving appropriate drug therapy which is most commonly considered to be statin therapy.

A retrospective record review was published by Lewis et al. in May of 2004 (Lewis et al, 2004). It looked at both the prescribing of statins and the degree to which patients were treated to guidelines for 40,179 patients within a Managed Care Organization in the United States. The reporting period under consideration was January 1, 2001 to December 31, 2001. New treatment guidelines for US patients were published by the National Cholesterol Expert Panel: Adult Treatment Panel III in June of 2001 (Expert Panel - NCEP, 2001). Of the total treatment population, 14,770 patients had documented CAD while 25,409 had the risk equivalent of CAD. Only 39.8% of the total population of the study received at minimum 1 prescription for a statin (Lewis et al, 2004). Twenty-five percent of the total study population had at least 1 cholesterol level checked. There were 5141 patients who both received a statin and had at least one cholesterol test. Of those patients, only 2286 reached their target goals. Some patients that were not on statin therapy reached LDL targets as well, between the 2 groups (patients on statins and not on statins), 9.2% of the total study population were at or below lipid goals. Patients were more likely to be on a statin if they were male, were on at least 2 other medications, or had seen a cardiologist (as compared with a general practitioner or other specialist), and patients were more likely to reach their target cholesterol levels if they were on statin pharmacotherapy (Lewis et al, 2004).

A much larger retrospective cohort study was undertaken in Ontario looking at statin use in patients over the age of 66 years who had a history of cardiovascular disease or diabetes (Ko et al, 2004). The study followed patient records for three years starting in April of 1998. The cohort included 396,077 patients of which 68.6% had cardiovascular disease alone, 17.8% had diabetes mellitus alone and 13.6% had both conditions. Of the entire cohort, 75,617
(19.1%) of the subjects were prescribed a statin. The factors that increased the likelihood of a patient being prescribed a statin include being younger, being male, having a history of angina, acute MI or cardiac invasive procedure. Also, patients being followed by a cardiologist were more likely to be on active treatment. Patients were less likely to be prescribed a statin if they were diabetic, if they had CHF or stroke and if they were of lower socioeconomic status or living in a rural area. Essentially the trial found that higher the patients risk of death due to cardiovascular disease, the less likely they would be on a statin (Ko et al, 2004).

Another Canadian study by Brown et al. followed 12,106 newly diagnosed diabetics (identified between 1991 and 1996) until 2000 (Brown et al, 2004). The study utilized administrative records from the Saskatchewan Health database. The authors stratified patients into two groups, diabetics with manifestations of atherosclerotic disease (CAD, cerebrovascular disease and peripheral vascular disease) or diabetics without, and they monitored for utilization of antiplatelet, statin and ACE inhibitor therapy. Statin use in the overall diabetic population was 20%; in the population with existing coronary artery disease, the rate was significantly higher at 29%. The authors suggest that underutilization of therapies like statins may be due to practitioners’ tendency to focus on the glucose management in their diabetic patients without considering the mitigation of diabetic complications like cardiovascular disease (Brown et al, 2004).

**Adherence and Concordance**

Another important factor of drug utilization is patient concordance or adherence. We often focus on properly identifying patients that would benefit from lipid lowering therapy and the prescribing of a given agent. However, insuring that the patient takes the therapy as prescribed for a duration long enough to have benefit is ultimately the most important part of appropriate drug utilization. Higher rates of adherence result in improved coronary outcomes whereas patients who discontinue therapy after 6 month to 1 year are unlikely to experience any value from their therapy (Ellis et al, 2004). As such, insuring
patient adherence should be a prominent goal for healthcare practitioners managing patients at high risk for cardiovascular events.

Clinical trials of lipid lowering therapy often show very low rates of discontinuation, even after as much as 5 years of follow-up (Andrade et al, 1995). However several confounding variables affect these high compliance rates including restrictive selection criteria, provision of free drug and increased patient monitoring and follow-up. Studies of “real world” drug utilization patterns paint a different story on adherence.

A study published in 1995 monitored the discontinuation rates of over 2000 HMO patients prescribed lipid lowering therapy during a 2 year period (Andrade et al, 1995). The authors found the discontinuation rate varied between 45% for niacin and 13% for lovastatin. Adverse effect (including laboratory abnormality) and drug ineffectiveness were the most common reasons for discontinuation of therapy. A more recent study by Ellis et al. investigated both adherence and discontinuation rates on statins (Ellis et al, 2004). The author’s collected data on whether the patients were using the drug for primary or secondary prevention and what the “out of pocket” co-payment was for each patient; assuming that these factors may impact rates of utilization. Over half of the patients met the pre-determined criteria for non-adherence. On average, patients missed about 2 doses out of every 10 they were supposed to take. Previous cardiac events had no impact on adherence rates, but higher co-payments ($\geq$20) tripled the chance the patient was non-adherent. Discontinuation rates varied whether the patient was using for primary prevention or secondary prevention as shown in Table #1.

Table #1: Rate of Statin Discontinuation (Ellis et al, 2004)
The high rates of discontinuation of statins interfere with the potential benefit for patients. The concept of concordance establishes the need for shared decision making between patients and their physicians. Concordance is an agreement reached after negotiation between a patient and a physician that respects the beliefs and wishes of the patients in determining when and how medication are to be taken. Selection of patients that have a commitment to therapy prior to statin initiation may help to increase adherence in those patients that are prescribed statins. Prescribing statins to patients who have not made this commitment may be a waste of resources.

**Key Messages**

- A high proportion of patients who are at high risk for cardiovascular events are not receiving appropriate statin therapy.
- A high proportion of patients who are at high risk for cardiovascular events who are receiving a statin are not achieving recommended lipid targets.
- Poor adherence and early discontinuation of statin therapy are a common occurrence that mitigate any potential value of statin therapy may have in reducing cardiovascular events.
- Ensuring patient commitment to statin therapy as part of shared decision making may help to improve adherence.

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**Targets, Guidelines and Risk**

Consideration of a given person’s risk for having a cardiac event is an important aspect in deciding appropriate medical management. Analysis of data from large population studies such as the Framingham Heart or UKPDS have led to the development of risk calculators. These calculators assign varying degrees of event risk to individuals based on the presence, absence or degree of key risk factors. In Canada and the United States, treatment guidelines are based on the Framingham risk calculations while in Europe, the UKPDS-based risk calculator is used. In the most recent update to the Canadian Guidelines on the management of dyslipidemia (Genest et al, 2003), an adapted Framingham risk calculation was adopted that is the same as the one used in the United States. The new risk calculation is designed to estimate a patient’s 10-year risk of “hard cardiac endpoints” (death from coronary artery disease or non-fatal myocardial infarction). The calculation is not designed to estimate the risk for diabetics or patients with existing cardiovascular disease as they are automatically considered to be in the High Risk category.

The Framingham Risk Calculator is based solely on 6 patient characteristics: sex, age, total cholesterol, HDL cholesterol, smoking status and systolic blood pressure. The INTER-HEART study, a large, case-control study (15 152 cases, 14 820 controls) was published in September of 2004 (Yusuf et al, 2004). This study suggests that the presence of absence of 9 risk factors account for 90% of patient’s risk of myocardial infarction. The risk factors were ranked as follows:

1) Ratio of ApoB/Apol. These measures of cholesterol are thought to be more specific than HDL and LDL levels. An elevated ratio was associated with higher risk of MI. Testing for these values are not currently available to practitioners in Manitoba.
2) Smoking. Current smokers were considered as anyone who smoked any tobacco in the past 12 months. Current smokers were found to be at a higher risk of MI.
3) Abdominal Obesity. Measured by the waist/hip ratio, men with a ratio >0.95 and women with a ratio >0.90 were found to be at higher risk.
4) Hypertension. Presence of the condition, treated or untreated was associated with a higher risk of MI.
5) Diabetes. Presence of the condition, treated or untreated was associated with a higher risk of MI.
6) Stress. Patients with several episodes of or permanent stress at work, at home or both were considered to have high general stress. These patients were at higher risk of MI.
7) Regular Exercise. Moderate or strenuous exercise for ≥4 hours/week was found to be protective against MI.
8) Vegetable and Fruit Intake. Daily intake of vegetables and fruit was found to be protective against MI.
9) Alcohol Intake. Consumption of ≥3 units of alcohol/week was found to be protective against MI.
Although risk calculators like the Framingham are useful in benchmarking risk levels and guiding therapeutic decision making, they obviously do not take into account all factors that affect a patient’s cardiovascular risk. Thus, practitioners must be aware of the presence of all of a patient’s aggressive and protective factors in deciding what, if any, pharmacotherapy is warranted.

The most recent updates to the Canadian Guidelines on the management of dyslipidemia were published in October of 2003 (Genest et al, 2003). This publication updated the previous Working Group recommendations published in 2000 and incorporates information from a number of trials published since then. Besides the adoption of the modified Framingham Risk score, their were also alterations to treatment cut-offs and targets. Table #2 outlines the Risk categories and their associated treatment goals.

Table #2: Canadian Lipid Guideline Targets

<table>
<thead>
<tr>
<th>Risk Category</th>
<th>10 year risk of CAD</th>
<th>LDL-C (mmol/L)</th>
<th>HDL-C ratio (mmol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>High Risk</td>
<td>≥20%</td>
<td>&lt;2.5</td>
<td>&lt;4</td>
</tr>
<tr>
<td></td>
<td>diabetes, atherosclerosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderate Risk</td>
<td>11-19%</td>
<td>&lt;3.5</td>
<td>&lt;5</td>
</tr>
<tr>
<td>Low Risk</td>
<td>&lt;10%</td>
<td>&lt;4.5</td>
<td>&lt;6</td>
</tr>
</tbody>
</table>

The guidelines recommend immediate initiation of pharmacological management of hyperlipidemia in all patients at High Risk to achieve LDL-c and cholesterol ratio goals. It is noted that a majority of patients can reach their target LDL-C goals with statin monotherapy, and that patients at High Risk should be treated with statin doses equivalent to simvastatin 40mg/day. Depending on individual patient lipid profiles, combination of statin with niacin, bile acid binding resins, fibrates or cholesterol absorption inhibitors may be required.

The United States published a similar updates to their guidelines in 2004 (Grundy et al, 2004). Key differences between the U.S. and Canadian guidelines include:
  - A fourth Risk Category (Moderately High) in the US
  - LDL-C levels are the only target levels applied
  - Optional target of LDL-C of <1.8 in the High Risk Category

Both the American and Canadian guidelines are helpful in grouping patients based on risk and providing management guidance. However, it should be recognized that assumptions and generalizations have to be made in order to simplify the guidelines enough to make them practical. These assumptions and generalizations may not be entirely founded in primary literature and often reflect expert opinion. Unfortunately, neither of the guidelines grade the evidence behind their recommendations, making it difficult for practitioners to know what guidance is supported by unambiguous randomized controlled trials and what has been extrapolated from expert opinion or less rigorous research.
### Key Messages

- 90% of the risk of myocardial infarction is related to modifiable risk factors (cholesterol - Apo /Apol, smoking, abdominal obesity, hypertension, stress, exercise, fruit and vegetable intake, alcohol intake).
- All individuals with previous vascular disease or diabetes are considered high risk and should be treated to a LDL target of <2.5.
- Non-diabetics without previous vascular disease should be assessed using a risk calculator (Framingham Risk Calculator) to determine risk level and LDL targets.
- There is emerging evidence suggesting treating to lower targets LDL <1.8 may be desirable in some patients.

ADD Framingham risk calculator as a separate sheet.
Statins in Men
Over the years, the majority of patients in statin trials have been men. Because of this abundance of research data, we can make very definitive statements about the benefits of statin therapy in males

Secondary Prevention
Four large randomised controlled trials have documented the effects of statins used in secondary prevention in men (LIPID Study Group, 1998; Sacks et al, 1996; Scandinavian Simvastatin Survival Study Group, 1994; Heart Protection Study Collaborative Group, 2002). All of these studies have shown significant reduction in the end-point of cardiac death and non-fatal MI producing a pooled relative risk of 0.74 (95% CI 0.70 to 0.79). In terms of overall mortality 3 of the 4 trials showed significant reduction and the pooled estimate of relative risk 0.86 (0.81 to 0.91) clearly shows a mortality benefit. There is no debate on the importance of statin therapy for men with pre-existing disease. The challenge here is to ensure that these patients receive treatment.

Primary Prevention
In the primary prevention setting, four trials have found that treating men with risk factors for cardiovascular disease can reduce the incidence of major cardiac events (the combination of non-fatal MI or fatal coronary heart disease) as shown in Figure #1 (Shepherd et al, 1995; Downs et al, 1998; Sever et al, 2003; Colhoun et al, 2004). None of these trials was able to produce a significant reduction in all-cause mortality but the pooled estimate suggests a marginally significant reduction in overall mortality (Figure #2). This result applies to men since they made up 85% of the population in the included trials. We excluded the PROSPER trial from this analysis because it contained a high percentage of females (52%) and patients with previous vascular disease (42%) (Shepherd et al. 2002). The ALLHAT trial was also excluded because of the high percentage of females (49%), patients with previous vascular disease (14%) and design problems (non-blinded, statin use in control group) (ALLHAT Collaborative Research Group, 2002). Others have included these trials and found a marginally insignificant result for overall mortality (Therapeutics Initiative Newsletter, 2003). We would suggest that there is evidence showing a reduction in overall mortality in high-risk men without a history of vascular disease. It is worth noting that almost ¼ of the people in these studies had diabetes.
**Key Messages**

- Statin therapy reduces cardiac death, non-fatal MI and overall mortality in men with a history of vascular disease.
- For men with risk factors but no history of vascular disease there is strong evidence that statins reduce cardiac death and non-fatal MI. There is also marginally statistically significant evidence that statin reduce overall mortality in this patient population.
Statins in Women
Cardiovascular disease is the #1 cause of death in women in Canada (Grace 2003). Women with equivalent risk are less likely to receive lipid lowering therapy than men (Miller 2000, Shaw 1994). Women have also been less studied in RCTs evaluating statin therapy.

Secondary Prevention
While only 2 of the 4 major trials have shown a significant reduction in CHD death or non-fatal MI, this may be related to the smaller number of women in these trials. Meta-analysis can be used to combine these trials and gives a clear estimate of a significant benefit in women with previous atherosclerotic disease (Figure #3.). These results are consistent with the other meta-analysis (LaRosa et al, 1999; Walsh et al, 2004). Statins have not been shown to significantly reduce all-cause mortality in women with a history of vascular disease (RR 1.00 95%CI 0.77 to 1.29) (Walsh et al, 2004).

Figure #3. Meta-analysis of secondary prevention of CHD death or non-fatal MI

<table>
<thead>
<tr>
<th>Study</th>
<th>Risk ratio (95% CI)</th>
<th>% Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>4S (1997)</td>
<td>0.74 (0.55, 0.98)</td>
<td>22.1</td>
</tr>
<tr>
<td>CARE (1998)</td>
<td>0.63 (0.38, 1.03)</td>
<td>8.8</td>
</tr>
<tr>
<td>LIPID (2003)</td>
<td>0.88 (0.68, 1.15)</td>
<td>23.9</td>
</tr>
<tr>
<td>HPS (2002)</td>
<td>0.68 (0.55, 0.84)</td>
<td>45.2</td>
</tr>
<tr>
<td>Overall</td>
<td>0.74 (0.64, 0.85)</td>
<td>100.0</td>
</tr>
</tbody>
</table>
Primary Prevention
There are very limited data to evaluate the efficacy of statin in primary prevention in women. Only the AFCAPS/TEXCAPS and ASCOT LLA provide fully usable data (Downs et al, 1998; Sever et al, 2003). A pooled estimate (CHD death and non-fatal MI) from these two studies produces a RR of 0.85 (95% CI 0.51 to 1.45) giving us no indication of benefit. Several other studies could be considered in an assessment of primary prevention in women.

- ALLHAT study showed no benefit of statins but was a non-blinded study with considerable statin use in the control group (ALLHAT Collaborative Research Group, 2002)
- PROSPER included older women with and without previous vascular disease (i.e. mixed primary and secondary) (Shepherd et al. 2002).
- HPS has been used in another meta-analysis of primary prevention in women (Walsh et al, 2004). Unfortunately the data available is only for women with diabetes a portion of whom also have vascular disease (secondary).

A sensitivity analysis of the effect of these other studies on the meta-analysis shows that only by excluding ALLHAT and including the mixed data from PROSPER and HPS can we produce a marginally significant pooled estimate 0.85 CI (0.73 to 0.99). We can not rule out that this end point is largely driven by secondary patients in the PROSPER and HPS studies. We have insufficient evidence to conclude that statin therapy reduces major coronary events and over-all mortality in women without a previous history of vascular disease.

Key Messages
- Cardiovascular disease is the #1 cause of death in women.
- Women may be under-treated with lipid lowering therapy.
- There is good evidence that statin therapy can reduce the incidence of major cardiovascular events in women with a history of vascular disease.
- Statin therapy has not been conclusively proven to reduce incidence of important cardiovascular endpoints in women at high risk for their first vascular event.
Statins in Elderly
Approximately 80% of all coronary heart disease deaths occur in people over the age of 65 (Dalal et al, 2002). Unfortunately dyslipidemia in the elderly is often under-treated. Ontario data suggests that paradoxically higher risks elderly patients are less likely to be treated than lower risk patients (Ko et al, 2004). The higher event rates found in elderly patients produce larger absolute impacts from cholesterol treatment than in younger individuals (Denke et al. 1990).

Secondary Prevention
Five major RCTs have included and reported on CHD death or non-fatal MI for patients 65 years of age or older (up to 80 yrs). Each trial has shown benefit and the overall meta-analysis suggests a clear benefit of statin therapy in elderly patients with previous vascular disease (Figure #4). All-cause mortality has only rarely been reported for the elderly subpopulations (Miettinen et al, 1997; Lewis et al, 1998), but available data suggest there may be an absolute mortality benefit to statin therapy in secondary prevention in the elderly (Figure #5). The PROSPER trial did not show an overall survival advantage but included patients with and without previous vascular disease (Shepherd et al, 2002). We have sufficient evidence to conclude that patients ≥ 65 with previous vascular disease show benefit in major cardiac events and overall mortality.

Figure #4. Meta-analysis of secondary prevention of CHD death and non-fatal MI

<table>
<thead>
<tr>
<th>Study</th>
<th>Risk ratio (95% CI)</th>
<th>% Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>4S (1997)</td>
<td>0.73 (0.60, 0.89)</td>
<td>11.8</td>
</tr>
<tr>
<td>CARE (1998)</td>
<td>0.66 (0.50, 0.88)</td>
<td>6.7</td>
</tr>
<tr>
<td>LIPID (1998)</td>
<td>0.82 (0.70, 0.95)</td>
<td>21.3</td>
</tr>
<tr>
<td>HPS (2002)</td>
<td>0.80 (0.72, 0.88)</td>
<td>47.0</td>
</tr>
<tr>
<td>Prosper (2002)</td>
<td>0.79 (0.65, 0.95)</td>
<td>13.2</td>
</tr>
<tr>
<td>Overall</td>
<td>0.78 (0.73, 0.84)</td>
<td>100.0</td>
</tr>
</tbody>
</table>
Primary Prevention
Study of primary prevention in the elderly (≥ 65) has been limited. Several primary prevention trials have included patient ≥ 65 but most have not reported the data for this age group separately. The PROSPER trial was the only trial to report primary prevention results for those ≥ 65 (Shepherd et al, 2002). PROSPER did not show significant reductions in coronary death, MI or stroke in the primary prevention elderly population. Primary prevention in elderly patients would benefit from further study, but at present we have insufficient evidence to demonstrate a significant benefit of statins in this patient population.

Key Messages
- The majority of cardiovascular events occur in patients ≥ 65.
- High risks elderly patients are less likely to receive treatment than low risk elderly patients.
- Treatment of high risk (history of vascular disease) elderly patients is strongly supported with evidence for reduction of important cardiovascular endpoints and over-all mortality.
- Treatment of lower risk elderly patients (no history of vascular disease) has not been conclusively proven to reduce incidence of important cardiovascular endpoints.
Statins and Diabetes
It is generally accepted that individuals with diabetes mellitus (DM) are at increased risk of cardiovascular events. Diabetic patients who also have a history of vascular events are at an extremely high risk of having subsequent events. Secondary prevention trials that include diabetic patients have demonstrated substantial reductions in major cardiovascular events (Scandinavian Simvastatin Survival Study Group, 1994; LIPID Study Group, 1998). Reductions in all-cause mortality have not been found with secondary prevention in diabetics.

Diabetics have been included in 4 primary prevention clinical trials. Two of the trials did not show significant reductions in any of the cardiovascular endpoints for the diabetic subpopulation. The other trials, CARDS and HPS-Diabetic Subgroup, provide more insight into the potential benefits of therapy in these patients (Colhoun et al, 2004; Heart Protection Study Collaborative Group, 2003). A majority of what we know on this topic comes from the CARDS trial as it only included diabetic patients without known vascular disease but at least one other risk factor (n=2,838). They found a significant reduction in the combined rate of CHD mortality, non-fatal MI, unstable angina, stroke and need for revascularization. The HPS also had a very small subgroup of diabetic patients that did not have documented vessel disease. These patients had a significant reduction in the rate of first major vascular event (coronary event, stroke or need for revascularization).

Despite the treatment guidelines published by the Canadian Diabetes Association that recommends pharmacological lipid lowering therapy in all diabetics to achieve specific goals, very little evidence supports the treatment of patients with diabetes as a sole risk factor (Canadian Diabetes Association Clinical Practice Guideline Expert Committee, 2003). However, it should be noted that patients with diabetes tend to possess multiple risk factors for vascular disease thus careful screening of diabetics for elevate cholesterol, hypertension, smoking, renal insufficiency and other important risk factors is crucial when deciding whether to initiate statin therapy.

Key Messages
- Statin therapy can reduce the incidence of major cardiovascular events in people with a history of diabetes and vascular disease.
- Statin therapy can reduce the incidence of first major cardiovascular events in people with diabetes in conjunction with other vascular risk factors.

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Statins in ACS

Three trials have investigated the potential benefits of using high-dose statin administration (atorvastatin 80mg and simvastatin 80mg) directly after an acute cardiac event. Results from these trials have been mixed. The A to Z trial compared high dose simvastatin to moderate dosing of the same drug but did not find any reductions in cardiovascular death, nonfatal MI, repeat acute coronary syndrome or stroke after 2 years (Lemos et al, 2004). The MIRACL trial compared high dose atorvastatin to placebo and found a barely significant ($p=0.048$) reduction in the composite endpoint of death, non-fatal MI, cardiac arrest and recurrent, symptomatic MI requiring hospitalization (Schwartz et al, 2001). Most of the reduction was driven by a reduction in recurrent, symptomatic MI. The PROVE-IT trial provides a comparison between high dose atorvastatin and moderate dose pravastatin (Cannon et al, 2004). At 2 years there was a significant reduction in the composite endpoint of all-cause mortality, MI, unstable angina, need for revascularization and stroke. The positive result was largely driven by a reduction in need for revascularization and unstable angina. Although statins are generally considered to be a safe therapy, some increases in adverse events have been noted with the use of high dose therapy that warrants consideration. In the A to Z trial there were 9 incidents of severe myopathic events (defined as CK > 10x ULN plus symptoms) in the high dose group and one incident in the low dose group (Lemos et al, 2004). In the MIRACL trial there was a 4 fold increase in the incidence of transaminase levels rising 3x ULN (Schwartz et al, 2001).

**Key Messages**

- Statin therapy in high doses directly after an acute event may reduce incidents of subsequent cardiac events.
- Careful monitoring of patients taking high dose statin therapy is required in light of increased risk in severe adverse effects noted in clinical studies.

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Lifestyle Issues

The Canadian Recommendations for the management and treatment of dyslipidemia suggest lifestyle changes for all patients with elevated cholesterol (Fodor et al, 2000). Patient specific healthy life style changes along with drug therapy are recommended for those at highest risk. For patients at moderate risk a 3-month lifestyle intervention is suggested with drug therapy initiated only if target is not achieved. For lower risk patients 6 months of healthy lifestyle change is suggested before considering drug therapy. It is important to recognise that lifestyle modifications play an important and complementary role even once drug therapy is initiated. In one report lifestyle modifications combined with drug therapy produced a 5% reduction over drug therapy alone. This complementary reduction is equivalent to doubling the statin dose (Hunningshake et al, 1993). Adherence to the Mediterranean Diet has even been shown to reduce all-cause mortality with benefits highest in older, heavier, sedentary non-smokers (Trichopoulou et al, 2003). The recommendations for a healthy lifestyle are summarised in the guidelines in Table 4. They focus on diet (balance, reduced fat and cholesterol, increased fibre), exercise, weight control, moderate alcohol consumption, and smoking cessation (Fodor et al, 2000).

Table 4: Recommendations for healthy lifestyle

<table>
<thead>
<tr>
<th>Eat a healthy diet</th>
<th>Canada Food Guide</th>
</tr>
</thead>
<tbody>
<tr>
<td>5–10 servings of grain products per day (emphasize whole grain)</td>
<td></td>
</tr>
<tr>
<td>5–10 servings of fruits and vegetables per day</td>
<td></td>
</tr>
<tr>
<td>2–4 servings of low-fat milk products per day</td>
<td></td>
</tr>
<tr>
<td>2–3 servings of low-fat meat and alternatives per day</td>
<td></td>
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</tbody>
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<table>
<thead>
<tr>
<th>Low fat diet</th>
<th>&lt; 30% of total calories from fat</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt; 10% of total calories from saturated fat and trans fatty acids</td>
</tr>
<tr>
<td></td>
<td>&lt; 300 mg cholesterol per day</td>
</tr>
</tbody>
</table>

| High-fiber diet | > 25–35 g of fiber per day |

| Get regular physical activity | 30–60 min of endurance (cardiovascular) activities (e.g., brisk walking, jogging) 4–7 days a week. |

| Maintain ideal body weight | Patients with dyslipidemia who are overweight (body mass index [BMI] > 25) or have a waist circumference > 90 cm (women) or > 100 cm (men) should be advised to reduce their weight. Patients should be encouraged to attain and maintain a healthy body weight (BMI of 20–25). |

| Consume alcohol in moderation | Patients who choose to drink should limit alcohol consumption to ≤2 standard drinks per day. Patients with elevated triglyceride levels should be advised to decrease or eliminate alcohol consumption. |

| Stop smoking | Patients who smoke should be advised to quit, young people should be encouraged not to. Patients who are unable to quit on their own should be provided with information on smoking-cessation programs, nicotine replacement therapy and drug therapy where indicated. |
Saturated Fat
The Canadian Guidelines suggest <10% of calories from saturated or trans fat (Fodor et al, 2000), while the US NCEP suggest <7% saturated fat (National Cholesterol Education Program, 2002). It appears for every 1% decrease in saturated fat intake there is a reduction of serum cholesterol of about 2% (Kris-Etherton et al, 1997). A Cochrane Review analysed dietary interventions targeting reductions in overall and saturated fats (Hooper et al, 2001). They found a small reduction in cardiovascular events in patients who maintained lifestyle changes for at least 2 years. The major sources of saturated fatty acids include high fat dairy products (whole milk, cheese, butter, ice cream), high fat meats, tropical oils (palm coconut) and baked products containing high fat ingredients. The NECP guidelines suggest a population mean intake of saturated fatty acids of 11% (National Cholesterol Education Program, 2002).

Trans Fatty Acids
Trans fatty acids are produced by the hydrogenation of vegetable oils (stick margarine). Trans fatty acids raise LDL cholesterol levels and when substituted for saturated fatty acids they actually reduce HDL levels. The average US intake of trans fatty acids represents 2.6% of total energy intake (National Cholesterol Education Program, 2002). The Canadian guidelines combine trans and saturated fatty acids and recommend an intake of less than 10% (combined population mean intake 11% (sat)+ 2.8% (trans) = 13.8%) (National Cholesterol Education Program, 2002; Ascherio et al, 1999; Fodor et al, 2000).

Dietary Cholesterol
Dietary cholesterol intake can increase LDL levels (Clarke et al, 1997). The Canadian Guidelines recommend <300mg per day (Fodor et al, 2000), while the NCEP guidelines are more aggressive with a target of <200mg/day (National Cholesterol Education Program, 2002). US population numbers suggest an overall mean daily intake of 256mg (331mg men and 213mg women) (National Cholesterol Education Program, 2002). The main source of cholesterol is eggs, high fat meat and high-fat dairy products.

Total Fat
The Canadian Guidelines suggest limiting the total calories from fat to 30% of total calories (Fodor et al, 2000). The NCEP guidelines have moved away from this recommendation (National Cholesterol Education Program, 2002). Only saturated and trans fatty acids have been shown to increase LDL cholesterol levels (National Research Council, 1989). Isocaloric exchanges of fat for carbohydrate do not produce weight gain (Hirsch et al, 1998). The concern is that reduction in total fat intake will lead to over-consumption of carbohydrates resulting in increasing obesity and aggravation of metabolic syndrome (National Cholesterol Education Program, 2002). The NCEP guidelines therefore focus on saturated and trans fatty acid reduction and warn against extremes of total fat intake (too high or low) with carbohydrate intake limited to 60% of calories (50% with metabolic syndrome) (National Cholesterol Education Program, 2002).
Fibre
The Canadian Guidelines recommend a high fibre diet with 25-30g of fibre per day. While there are many important reasons for maintaining a high fibre diet, it appears that it is soluble fibre that reduces LDL levels while insoluble fibre does not have a significant effect (Anderson et al, 1999). Soluble fibre of 5–10g per day can produce a 5% reduction in LDL cholesterol (Anderson et al, 1999). Oats, pectin, guar and psyllium are sources of soluble fibre.

Moderate Alcohol Intake
Observational studies suggest that moderate alcohol intake, (no more than 1 drink per day for women or 2 drinks per day for men) is associated with lower mortality (Dufour, 2001; Thun et al, 1997). Higher consumption is associated with higher mortality. Given the problems with misuse of alcohol, the advantages and disadvantages of its use need to be weighed carefully. The NCEP guidelines suggest that persons who do not drink should not be encouraged to initiate regular alcohol consumption (National Cholesterol Education Program, 2002).

Maintain Ideal Body Weight
Patients should be encouraged to maintain a healthy body weight with a BMI of 20-25. Waist circumference may be a better predictor of cardiac risk (Yusuf et al, 2004). Women with waist circumference >90cm (35.5 inches) or men with a waist circumference >100cm (39.5 inches) are at increased risk (Fodor et al, 2000) The approach in the US guidelines is to emphasise other dietary measures (saturated fat and cholesterol reduction and increased fibre intake) prior to focussing on weight reduction to avoid overloading patients (National Cholesterol Education Program, 2002). A weight loss of 10 pounds can produce an LDL cholesterol reduction of 5 to 8% (National Cholesterol Education Program, 2002; Jenkins et al, 2000).

Regular Physical Activity
The Canadian Guidelines recommend 30-60 minutes of cardiovascular activity (brisk walking, jogging, cycling) 4 to 7 days per week (Fodor et al, 2000). Exercise can reduce VLDL levels and raise HDL cholesterol levels (Taylor et al, 2004). A meta-analysis of the effects of exercise in women showed statistically significant improvements in all lipid levels (Kelley et al, 2004). Exercise also plays a role in maintaining a healthy weight, alleviating metabolic syndrome and is an independent factor in reducing the risk for CHD (Yusuf et al, 2004).

Smoking Cessation
The Canadian Guidelines advise quitting and using smoking cessation programs, nicotine replacement products and drug therapy as required (Fodor et al, 2000)
**Overall Effect of Lifestyle Measures**

The combination of several dietary and lifestyle modifications can produce a reduction in LDL levels equivalent to reductions produced by standard doses of statins (National Cholesterol Education Program, 2002). The Cochrane Review of multiple risk factor interventions (dietary, smoking and physical activity) for primary prevention of coronary heart disease, produced modest reductions in cholesterol and smoking but not in all cause mortality Ebrahim et al, 2000). While some patients may achieve a 20-30% reduction in cholesterol with dietary changes (National Cholesterol Education Program, 2002; Jenkins et al, 2000), on average dietary advise seems to lead to a 3-6% reduction in total cholesterol (Tang et al, 1998).

**Key Messages**

- suggest reduction of saturated or trans fats to <10% of calories – every 1% decrease produces a 2% reduction in cholesterol
- suggest a dietary cholesterol below <300mg per day
- suggest a total fat intake <30% of calories but total calories intake equally important
- suggest a fibre intake 25-30g per day – soluble fibre (oats, pectin, psyllium) reduces LDL
- suggest maintenance of an ideal body weight BMI 20-25 or waist circumference < 90cm (35.5inches) in women and < 100cm (39.5inches) in men
- suggest regular physical activity 30-60 min 4 to 7 days per week
- discuss and encourage smoking cessation with each contact
- combined lifestyle measure may reduce cholesterol by 20-30% - however the average is a more modest 3-6%
Dosing Issues

The use of cholesterol lowering therapy has increased 300% between 1995 and 2003 and this class of therapy is now the 6th largest (in terms of prescriptions filled) therapeutic class in Canada (IMS Health Canada, 2004b; IMS Health Canada, 2003). Statins are by far the most commonly employed agents in this multi-million dollar therapeutic industry. With the amount of healthcare dollars being spent on reducing cholesterol it is not surprising that that market is rife with agents that practitioners can choose from. The 6 statins on the Canadian market are atorvastatin (Lipitor®), fluvastatin (Lescol®), lovastatin (generic), simvastatin (generic), pravastatin (generic), rosuvastatin (Crestor®). These agents vary in price, potency and the amount of literature published on their efficacy. Table #3 outlines the potency of the various agents in their ability to reduce the surrogate endpoint of LDL cholesterol. In general statins increase HDL cholesterol by about 7% irregardless of dose or agent (Law et al, 2003). The dollar figures in the table represent the cost/day of therapy with each drug. Cost savings can be achieved by splitting of the higher-dosed tablets when a lower dose is prescribed. None of the statins are scored for easy splitting; however, since statins don’t have a narrow therapeutic index, the use of a tablet splitter make the ½ doses is a reasonable option for those wishing to reduce the daily cost of their lipid lowering therapy.

Table #3: LDL Reduction and Cost/day† for all Statin Doses Available in Canada

<table>
<thead>
<tr>
<th>%LDL ↓*</th>
<th>Fluvastatin 20mg $0.92 &amp; 10mg-20mg $0.93-1.12</th>
<th>Pravastatin 20mg $1.09 &amp; 40mg $1.35</th>
<th>Lovastatin 5mg $0.62 &amp; 10mg $1.23</th>
<th>Simvastatin 80mg $1.52</th>
<th>Atorvastatin 80mg $1.52 &amp; 40mg $1.96</th>
<th>Rosuvastatin 80mg $2.57 &amp; 40mg $2.28</th>
</tr>
</thead>
<tbody>
<tr>
<td>20-25%</td>
<td>20mg</td>
<td>10mg-20mg</td>
<td>5mg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>26-30%</td>
<td>40mg</td>
<td>40mg</td>
<td>20mg</td>
<td>10mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>31-35%</td>
<td>80mg</td>
<td>80mg</td>
<td>20mg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>36-40%</td>
<td></td>
<td>40mg</td>
<td>20mg</td>
<td>10mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>41-45%</td>
<td></td>
<td>80mg</td>
<td>20mg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>46-50%</td>
<td></td>
<td></td>
<td>10mg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>51-55%</td>
<td></td>
<td></td>
<td></td>
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</tbody>
</table>

† All Costs based on Manitoba Pharmacare Reimbursement Price current to March 2005.

It is important to recognize that reducing levels of a cholesterol is not itself a clinically relevant endpoint. Reducing cardiovascular events, all-cause mortality and post-revascularization re-occlusion are all important endpoints. Placebo-controlled studies have demonstrated that fluvastatin, pravastatin, lovastatin, simvastatin and atorvastatin have value in reducing at least one of these important endpoints (Hefland et al, 2004). Research has not yet been published that demonstrate the value of rosuvastatin in improving anything except surrogate cholesterol markers.
Determining which statin to choose represents a therapeutic challenge. Very few trials have compared statins to each other in reducing negative outcomes. The PROVE-IT trial tested the efficacy of aggressive lipid lowering therapy with atorvastatin 80mg/day with standard therapy with pravastatin 40mg/day in patients post-acute coronary syndrome (Cannon et al, 2004). Atorvastatin significantly reduced the primary composite endpoint. However, because non-equivalent dosing of the drugs were used, the study only shows differences that aggressive versus standard care can achieve. In a 5 year retrospective cohort study published by Zhou et al. researchers followed survival and cardiac event rates of >18,000 post-MI patients on 5 different statins (Zhou et al, 2005). They found no significant difference in recurrence of MI or death between patients taking any of the statins. The authors concluded that the different statins are equally effective at secondary prevention of MI when given in a “real life” situation. As there is no clearly superior statin, neither the Canadian nor the American guidelines specify a recommended agent.

Dosing Strategies
The 2 dosing strategies that are predominately found in published trials; they are fixed dose and targeted LDL reduction.

Fixed Dose
Randomized controlled trials using fixed doses of Atorvastatin 10mg (Sever et al, 2003), fluvastatin 80mg (40mg given twice daily) (Serruys et al, 2002), pravastatin 40mg (Shepherd et al, 2002; Sacks et al, 1996; LIPID Study Group, 1998) and simvastatin 40mg (Heart Protection Study Collaborative Group, 2004) have all shown positive impacts on clinical endpoints. Fixed dosing strategies reduce the need for serum lipid monitoring as there is no dosage titration. Fixed and titrated dosing strategies have not been compared in directly, and the fixed dosing strategy is not supported by either the Canadian or American Guidelines. In a recent report by the National Cholesterol Education Program in the United States, authors commented on the concept of simplifying the guidelines to apply standard statin doses to all high risk patients. The authors stated, “In the view of NCEP, this suggestion represents an oversimplification that will lead to undertreatment of many patients. It does not take advantage of the strong database supporting the log-linear relationship between LDL levels and CHD risk” (Grundy et al, 2004).

Targeted LDL Reduction
This methodology is advocated in both the Canadian and American guidelines. (Genest et al 2003; Grundy et al, 2004) The strategy employs risk stratification with the Framingham Risk Calculations to stratify patients into target groupings. Different lipid targets are employed for different target groupings and drug therapy is directed at reaching those lipid targets. The trials that support this methodology include the ALLIANCE and the GREACE trial wherein an atorvastatin titration regimen was compared to “usual care”. The “usual care”
arm did not require patients to take any cholesterol lowering therapy at any particular dose. Both these trials found reductions in important cardiovascular endpoints including cardiac death and non-fatal MI (Koren et al, 2004; Athyros et al, 2002).

Key Findings

- All statins except rosuvastatin have proven value in the reduction of important clinical endpoints.
- Equivalent LDL reduction can be achieved by appropriate dosing of the different statins and no statin has been proven more effective than another in reducing important clinical endpoints when given in equivalent doses.
- Both the fixed dosing and target LDL reduction dosing strategies have been shown effective in reducing important clinical endpoints. The targeted LDL reduction strategy is recommended in the Canadian guidelines.
Safety and Drug Interactions

Drug Interactions
The majority of clinically significant drug interactions between statins and other agents are a result of a metabolic interaction involving the cytochrome P450 enzyme system. Simvastatin, lovastatin and atorvastatin are metabolized primarily through the 3A4 isoenzyme of the cytochrome P450 system, while a majority of fluvastatin and 10% of rosuvastatin metabolism is handled by the 2C9 isoenzyme (Hefland et al, 2004). These agents are susceptible to interaction with agents that affect these isoenzymes. Table #4 outlines agents that inhibit these enzyme systems and thus can increase plasma concentrations of the statins, making them more likely to cause adverse events.

Table #4: Inhibitors of the Cytochrome P450 3A4 and 2C9 Isoenzymes (Hefland et al, 2004)

<table>
<thead>
<tr>
<th>3A4</th>
<th>2C9</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clarithromycin*</td>
<td>Amiodarone</td>
</tr>
<tr>
<td>Erythromycin*</td>
<td>Azole Antifungals (ex. Itraconazole)</td>
</tr>
<tr>
<td>Cyclosporine*</td>
<td>Cimetidine</td>
</tr>
<tr>
<td>Nefazodone*</td>
<td>Fluoxetine</td>
</tr>
<tr>
<td>Itraconazole*</td>
<td>Fluvoxamine</td>
</tr>
<tr>
<td>Fluconazole</td>
<td>Metronidazole</td>
</tr>
<tr>
<td>Ketoconazole</td>
<td>Omeprazole</td>
</tr>
<tr>
<td>Protease Inhibitors</td>
<td>TMP/SMX</td>
</tr>
<tr>
<td>(ex. indinavir)</td>
<td>Zafirlukast</td>
</tr>
</tbody>
</table>

*Published reports of rhabdomyolysis when combined with statin therapy.

Higher rates of muscle-related adverse effects have also been found when statin therapy is combined with fibrates. The exact mechanism of the interaction is not known. This interaction has been most commonly documented when statins are combined with gemfibrozil. In pharmacokinetic studies of rosuvastatin plus gemfibrozil, the area under the curve and maximum drug concentration of rosuvastatin were approximately doubled (McKenney, 2005). Researchers did not find any increase in blood levels when rosuvastatin was combined with fenofibrate; however, all fibrates have been linked individually with myopathic adverse events. As such if the benefits of combination therapy is felt to outweigh the potential risk, use of fenofibrate is preferred (Genest et al, 2003; McKenney, 2005).

Safety
Statins as a class are generally considered a safe class of drugs, with their most severe adverse events occurring very rarely (McKenney, 2005). The most commonly identified adverse effects for drugs in this class include gastrointestinal upset (diarrhea or constipation), dyspepsia, headache, skin rash and nausea. The event rates for these adverse effects are generally <10% and are self-limiting. The rare and more severe toxicities related to statin therapy...
include myotoxicity, hepatic toxicity and nephropathy are of greater concern to clinicians.

Myopathy
Myopathy refers to a muscle related complaints that range in severity from myagia (mild muscle pain and tenderness) to rhabdomyolysis (severe pain, CK>10x upper limit of normal and associated nephropathy). All statins can cause myopathy and all statins (except fluvastatin) have been linked to fatal cases of rhabdomyolysis (Jamal et al, 2004). The incidence rates of fatal rhabdomyolysis are extremely low, between 0.04-1.9 events per 1 million prescriptions for statins currently on the market (Jamal et al, 2004). An incident rate of 3.16 per 1 million prescriptions was seen with cerivastatin before it was removed from the market. The incidence rates of myopathy in general are believed to be linearly related to blood concentration of the statin as opposed to the degree of LDL reduction (McKenney, 2005). Therefore, higher doses of all of the statins carry greater risk of adverse muscle reactions.

There is substantial debate over the comparative safety of statins with respect to myopathy. In a statin class review conducted by the Oregon Evidence-based Practice Centre, researchers looked at 53 head-to-head comparison trials and, “...did not find any difference in rates of muscle toxicity between statins.” (Helfand et al, 2004). This review of literature included information on atorvastatin, fluvastatin, pravastatin, simvastatin and lovastatin, but not rosuvastatin. The myopathy rates of rosuvastatin have been heavily scrutinized by the public and regulatory authorities after the 80mg dose was withdrawn from testing due to high rates of rhabdomyolysis (McKenney, 2005). A post-marketing analysis of adverse events related to rosuvastatin was published very recently in Circulation. The analysis looked at adverse event reports submitted to the United States Food and Drug Administration (FDA) (Alsheikh-Ali et al, 2005). When compared with simvastatin, pravastatin and atorvastatin, the rhabdomyolysis and non-rhabdomyolysis adverse muscle event rates were significantly higher with rosuvastatin. It has been argued that the event rates in rosuvastatin may be comparatively over-reported because of heightened media attention to its adverse event profile.

Higher then normal rhabdomyolysis rates with rosuvastatin have been noted by Health Canada and, as a result, the following contraindications have been added to the Crestor monograph (Health Products and Food Branch, 2005):
Contraindication of the 40mg once daily dose in patients with pre-disposing risk factors for myopathy/rhabdomyolysis such as:
- Personal or family history of hereditary muscular disorders
- Previous history of muscle toxicity with another “statin”
- Concomitant use of a fibrate or niacin
- Severe hepatic impairment and Alcohol abuse
- Severe renal impairment (CrCl<30mL/min/1.73m²)
- Hypothyroidism
- Asian patients
- Situations where an increase in rosuvastatin plasma levels may occur

**Hepatic Toxicity**
Similar to muscle toxicity, all statins have been associated clinically significant hepatic toxicity. An increase in liver transaminase levels 3 times the upper limit of normal although normally asymptomatic is considered clinically significant. Elevated liver enzymes are routinely managed by discontinuing or reducing the dose of statin, the development of fullminant hepatic failure from statin therapy is extremely rare (Chalasani, 2005). A database tracking the world-wide incidence of adverse events related to lovastatin estimates the risk of fulminant liver failure attributable the drug to be approximately 2 in one million patients.

Meta-analysis of liver toxicity in 13 studies (49,275 patients) determined that statins as a class did not significantly increase the risk of increase liver function tests (Denes et al, 2004). When each statin was analysed individually, the difference in rates between simvastatin, lovastatin, pravastatin and placebo did not reach significance, but the rates in fluvastin did. However, this increase in risk was largely driven by an unusually low rate of enzyme elevation in the placebo population; further, the absolute risk increase was small (0.85%) translating in a number needed to harm of 118 patients. The authors also admit the results of the meta-analysis only apply to low-moderate doses of statins and that research on the safety of newer statins (atorvastatin and rosuvastatin) as well as high-dose therapy is required.

In the Oregon Evidence-based Practice Centre review of 53 head-to-head statin trials, the incidence of hepatic toxicity was also measured (Helfand et al, 2004). The review found that the elevation in transaminase levels occurred in approximately 1% of patients on chronic statin therapy. Out of these trials, one comparative trial found higher rates of elevated liver enzymes in the atorvastain 80mg/day group compared to the simvastatin 80mg/day. This information, coupled with data from 2 placebo controlled trials that found hepatic toxicity rates of 2% and 2.5% with atorvastatin 80mg/day has lead to some concerns about the safety of this dose. None of the elevations in liver function tests resulted in long-term hepatic toxicity in any of the trials considered in the review. The conclusion of the Oregon reviewers was that there is not enough evidence to determine if any statin is better or worse for causing hepatic toxicity.

**Key Findings**
- Cautious use of certain cytochrome P450 isoenzyme inhibitors with statins is warranted as they may increase the risk of adverse events including rhabdomyolysis.
- Combining statin therapy with fibrates can increase the risk of myopathy, if these groups are to be combined, the use of fenofibrate over gemfibrozil is recommended.
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### Appendix A: Primary Prevention Lipid Lowering RCTs: Study Descriptions

<table>
<thead>
<tr>
<th>Trial</th>
<th>ASCOT-LLA&lt;sup&gt;1&lt;/sup&gt;</th>
<th>A/FCAPS/TexCAPS&lt;sup&gt;2&lt;/sup&gt;</th>
<th>WOSCOPS</th>
<th>ACAPS&lt;sup&gt;4&lt;/sup&gt;</th>
<th>PROSPER&lt;sup&gt;6&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Design</strong></td>
<td>Sub-study of ASCOT trial, placebo controlled, randomized, double blinded</td>
<td>Randomized, double blind, placebo controlled</td>
<td>Randomized, placebo controlled trial</td>
<td>Randomized, double blind, placebo controlled</td>
<td>Randomized, double blind, placebo controlled</td>
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<td>Funding Source</td>
<td>Pfizer, Sevier Research Group, Leo Laboratory</td>
<td>Merck &amp; Co</td>
<td>Bristol Myers Squibb</td>
<td>Merck, Sharp &amp; Dohme, Dupont</td>
<td>Bristol-Myers Squibb</td>
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<tr>
<td><strong>Intervention</strong></td>
<td>Atorvastatin 10mg/day</td>
<td>Lovastatin 20mg/day, dose titrated to 40mg if LDL&gt;2.84 after 3 months</td>
<td>Pravastatin 40mg</td>
<td>Lovastatin 20-40mg/day +/- low dose warfarin</td>
<td>Pravastatin 40mg/day</td>
</tr>
<tr>
<td><strong>Inclusion</strong></td>
<td>- Hypertensives - Age 40-79 - No-lx of CHD - Minimum 3 CV risk factors - Non-fasting TC ≤ 6.5 (untreated with statin)</td>
<td>- Men aged 45-73 - Women aged 55-73 - Non prior history of CVD - TC 4.65-6.82 - LDL 3.36-4.91 - HDL≤1.16 men, ≤ 1.22 fem - TG ≤ 4.52 - LDL3.23-3.34 if TC/HDL &gt;6</td>
<td>Age 45-64 Male LDL&gt;4 TC&gt;6.5</td>
<td>- Men and women aged 40-79 - Early carotid atherosclerosis - LDL 4.13-4.89 with 0-1 coronary risk factor - LDL 3.36 – 4.12 with any number of risk factors</td>
<td>- Men and women aged 70-82 - Pre existing vasc disease (stable angina, intermittent clauditation, stroke, TIA, MI, arterial sx, amputation for vascular disease) &gt;6 months before study, or - Pts with 1 or more risk factors (smoking, dm, htn), and TC 4-9, TG&lt;6</td>
</tr>
<tr>
<td><strong>Exclusion</strong></td>
<td>- Previous MI - Current angina - Recent CVA - Fasting TG&gt;4.5 - Heart failure - Uncontrolled arrhythmias - Heme/biochem abnormalities</td>
<td>- Uncontrolled HTN - Secondary hyperlipidemia - Type I or II diabetes that was managed with insulin or HA1c&lt;10%</td>
<td>- History of MI - Abnormal ECG - Atrial fibrillation - No arrhythmia - Stable Angina if hospitalized in previous year</td>
<td>- History of MI, stroke or angina - TG &gt; 4.5</td>
<td>-MMSE&lt;24 - CHF - Serum Cr &gt;200 - Cancer with past 5 years - Atrial Fibrillation or other significant arrhythmia</td>
</tr>
<tr>
<td><strong>Duration</strong></td>
<td>3.3 years (median)</td>
<td>5.2 years (average follow-up)</td>
<td>4.9 years (mean)</td>
<td>34.1 months (mean)</td>
<td>3.2 years (mean)</td>
</tr>
<tr>
<td><strong>Population Age</strong></td>
<td>Tx: 63.1 (mean) Pl: 63.2 (mean)</td>
<td>Tx: 58 (mean) Pl: 58 (mean)</td>
<td>Tx 55.1 years Pl 55.3 years</td>
<td>Average of Tx and Pl 61.7 years</td>
<td>Tx: 75.4 (mean) Pl: 75.3 (mean)</td>
</tr>
<tr>
<td><strong>Population Sex distribution</strong></td>
<td>Male: 8363 (81.2%) Female: 1942 (18.8%)</td>
<td>Male: 5608 (84.9%) Female: 997 (15.1%)</td>
<td>Male: 100%</td>
<td>Male: 473 (51.5%) Female: 446 (48.5%)</td>
<td>Male: 2804 (48.3%) Female: 3000 (51.7%)</td>
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<td><strong>No Previous CHD</strong></td>
<td>Tx: 100% Pl: 100%</td>
<td>Tx: 100% Pl: 100%</td>
<td>Tx: 100% Pl: 100%</td>
<td>Tx: 100% Pl: 100%</td>
<td>Tx: 54.8% Pl: 56.8% (no angina, MI, PVD, CVD)</td>
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<tr>
<td><strong>Sample Size</strong></td>
<td>Tx: 5168 Pl: 5137</td>
<td>Tx: 3304 Pl: 3301</td>
<td>Tx: 460 Pl: 459</td>
<td>Tx: 2891 Pl: 2913</td>
<td></td>
</tr>
<tr>
<td><strong>Primary Endpoint</strong></td>
<td>Combined non-fatal MI and fatal CHD</td>
<td>Incident of 1&lt;sup&gt;st&lt;/sup&gt; major coronary even (fatal MI, UA, sudden cardiac death)</td>
<td>Non-fatal MI or Death from CHD</td>
<td>Changes in Ultrasound Determined Early Carotid Arteriosclerosis</td>
<td>Combined endpoint of death from cor hrt disease, non-fatal MI, fatal and non-fatal stroke</td>
</tr>
<tr>
<td><strong>Secondary Endpoint</strong></td>
<td>All cause mortality, total CV mortality, fatal and non-fatal stroke/HF, total coronary endpoints, total CV event</td>
<td>Coronary revascularization procedure, fatal or non-fatal MI/CV event/coronary event, CV mortality, CHD mortality</td>
<td>Major atherosclerotic events, safety, ∆ lipids.</td>
<td>Each part of primary endpoint analyzed separately</td>
<td></td>
</tr>
</tbody>
</table>
### Appendix B: Secondary Prevention Lipid Lowering RCTs: Study Descriptions

<table>
<thead>
<tr>
<th>Trial</th>
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<th>Inclusion</th>
<th>Exclusion</th>
<th>Duration</th>
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<th>Population Sex Distribution</th>
<th>Previous CHD</th>
<th>Sample Size</th>
<th>Primary Endpoint</th>
<th>Secondary Endpoints</th>
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<tbody>
<tr>
<td>4S</td>
<td>Randomized, double blind, placebo controlled</td>
<td>Merck Research Laboratories</td>
<td>Simvastatin 20mg/day, dose titrated to 40mg if TC &gt;5.2 at 6 or 18 weeks</td>
<td>Patients aged 21-75</td>
<td>- Premenopausal females - UA/Prinzmetal angina - Planned cardiac surgery - Tx arrhythmias/unTx Afib - Severe CHF, MI in last 6mo - Valvular HD, hx stroke, ↓ hepatic fxn, hx etoh abuse</td>
<td>5.4 years (median)</td>
<td>Male: 3617 (81.4%) Female: 827 (18.6%)</td>
<td>Tx: 100% Pl: 100%</td>
<td>2221 Pl: 2223</td>
<td>Tx: 59 (mean) Pl: 59 (mean)</td>
<td>All Cause Mortality</td>
<td>Major coronary events (CHD death, non-fatal MI, or resuscitated cardiac arrest)</td>
</tr>
<tr>
<td>CARE</td>
<td>Randomized, double blind, placebo controlled</td>
<td>Bristol-Myers Squibb</td>
<td>Pravastatin 40mg/day</td>
<td>Patients aged 50-70</td>
<td>- History of MI or agina pectoris - TC 5.5 – 8 - TG ≤ 2.5 - Postmenopausal women - Fasting blood glucose &gt;12.2mmol/L - LVEF&lt;25% - Symptomatic HF - Chronic liver or renal disease - ↑ liver enzymes, tx w/niacin, fibrates, or cyclosporin - Inflammatory muscle disease - Fem w/child bearing potential - Severe HF, or other disease that limit long term therapy - Clinically significant medical or surg event w/in 3months of study entry</td>
<td>5 years (median)</td>
<td>Male: 3583 (86.2%) Female: 576 (13.8%)</td>
<td>Tx: 100% Pl: 100%</td>
<td>2081 Pl: 2078</td>
<td>Tx: 59 (mean) Pl: 59 (mean)</td>
<td>Fatal CHD or nonfatal MI</td>
<td>Major coronary events (CHD death, non-fatal MI, or resuscitated cardiac arrest)</td>
</tr>
<tr>
<td>HPS</td>
<td>Randomized, double blind, placebo controlled</td>
<td>Merck &amp; Co</td>
<td>Simvastatin 40mg/day</td>
<td>Patients aged 40-80</td>
<td>- Men and women aged 40-80 - TC ≥ 3.5 - Presence of coronary disease - Or, occlusive disease of non-cardiac vessels (ex. CNS) - Or, diabetic (type I or II) - Or, maile &gt;65 w/ treated htn</td>
<td>5 years (mean)</td>
<td>Male: 15454 (75.3%) Female: 5082 (24.7%)</td>
<td>Male: 1516 (17%) Female: 1516 (17%)</td>
<td>10269 Pl: 10267</td>
<td>Tx: 62 (median) Pl: 62 (median)</td>
<td>All Cause Mortality, death from coronary heart disease, death from all other causes</td>
<td>Major coronary events, major vascular events, fatal and non-fatal stroke</td>
</tr>
<tr>
<td>LIPID</td>
<td>Randomized, double blind, placebo controlled</td>
<td>Bristol-Myers Squibb</td>
<td>Pravastatin 40mg/day</td>
<td>Patients aged 65-80</td>
<td>- Men and women aged 65-80</td>
<td>6.1 years (mean)</td>
<td>Male: 1256 (78%) Female: 344 (22%)</td>
<td>Male: 1256 (78%) Female: 344 (22%)</td>
<td>800 Pl: 800</td>
<td>Tx: 58 (mean) Pl: 58 (mean)</td>
<td>Death from CHD</td>
<td>death from all-cause/CV, death from CHD or non-fatal MI, non-fatal MI, stroke, revasc, days in hosp, Δ lipids</td>
</tr>
<tr>
<td>GREACE</td>
<td>Randomized, prospective, open-label trial</td>
<td>Independent</td>
<td>Atorvastatin 10mg, titrated up to 80mg as needed vs “usual care”</td>
<td>Patients aged 35-70</td>
<td>- History of MI, or -&gt;70% stenosis of at least 1 coronary artery - LDL&gt;2.6 and TG &lt;4.5</td>
<td>3 years</td>
<td>Male: 13386 (65%) of total population</td>
<td>Male: 13386 (65%) of total population</td>
<td>4512 Pl: 4502</td>
<td>TX: 100% Pl: 100%</td>
<td>Total and coronary mortality, non-fatal MI, UA, CHF, revascularization and stroke</td>
<td>Safety and cost effectiveness of atorvastatin</td>
</tr>
</tbody>
</table>