

Evidence for Caution: Women and statin use

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Prologue: Evidence for Caution

This paper investigates the evidence base for the use of statin therapy in women. Statins are a class of prescription drugs designed to lower cholesterol. The leading statin drugs are Lipitor (generic name atorvastatin), Crestor (rosuvastatin), Mevacor (lovastatin), Pravacol (pravastatin), Zocor (simvastatin) and Lescol (fluvastatin). The research on this issue is exceptionally complex and cannot be fully addressed in this short document. For the purposes of this review, we explore three fields of inquiry:

1. Benefit: Key Issues in the Evaluation of Statin Benefit

- representation of women in primary and secondary prevention trials
- extrapolation of benefit from men
- cholesterol levels as a risk factor for coronary vascular disease in women
- other modifiable cardiovascular risk factors
- age and life stage

2. Safety: Key Issues in the Evaluation of Statin Safety

- general release of Serious Adverse Events data, total mortality, total cardiovascular events, or incidence of cancer and disaggregation for women
- data from the Adverse Drug Reaction reporting system
- data on concomitant use of statins and hormonal drugs
- research on the prescription of statins for women of childbearing potential (WOCBP); miscarriage, birth defects and breast-feeding
- vulnerability of women to exercise intolerance
- burden of care in relation to statin-impaired family members

3. Representation: Key Issues in the Evaluation of Information Representation

- conflict of interest (COI)
- marketing strategies and awareness campaigns
- representation of cardiac risk for women
- statistical representations including relative risk (RR), absolute risk (AR) and number needed to treat (NTT)

Our review of these fields identifies a troubling disjuncture between the widespread use of statin medication for women and the evidence base for that usage. What we found instead was evidence for caution.

A. Background

Cardiovascular Disease: The Difference between Women and Men

There are significant differences in the way heart disease manifests in men and women. Women experience different symptoms that span a wider range. Women's heart attack symptoms are less likely to be recognized and less likely to be acted on by women themselves and by healthcare workers.¹ Women may not receive timely emergency treatment and usually have a higher risk of death after a heart attack. This is especially true for younger women.²

In Canada, conditions like hypertension, diabetes and depression pose greater risks for women than for men. And populations such as Aboriginal women and South Asian women tend to be more vulnerable to these health conditions.³

Women are also more vulnerable to health risks from medications. A review conducted by the US General Accounting Office of 10 prescription drugs withdrawn from the market (January 1997 to December 2000) indicated that eight of these posed greater health risks for women than men, in four cases because they were prescribed more often to women, and in the other four for reasons unknown. Six of these eight drugs caused heart problems in women.⁴

While heart disease is the leading cause of death for women, it is mediated by age. In Canada, it is not until women are in their 80s that heart disease becomes the number one cause of death.⁵ Women between the ages of 30 and 79 are most likely to die of cancer, not heart disease.⁶ For men, on the other hand, heart disease and stroke are much more likely to occur at a younger age. The death rate due to heart disease among women is currently only about half that for men.⁷ Thus the issue of age must be kept in mind when assessing the impact of heart disease on Canadian women.

Age is also very important when assessing the impact of sudden cardiac death (SCD), which represents just under two-thirds of all heart and stroke deaths.⁸ For ages 35 and under, sudden cardiac death is very rare and occurs in less than one percent of the male and female population. For ages 35-64, men die about three times more frequently than women of sudden cardiac death. At ages 65 to 74, male deaths are double those of female. At ages greater than 85, the death rates for men and women are the same.⁹

In Canada: "Cardiovascular diseases affect men and women differently. More men than women die from ischemic heart disease and acute myocardial infarction but more women than men die from congestive heart failure and cerebrovascular disease."¹⁰

In the recent past, these differences were explained by theories of hormonal variations between men and women. This explanatory model was part of the sequence of events leading to the widespread prescription of estrogenic drugs for menopausal women (Hormone Therapy—HT) for cardio-protective reasons.¹¹ However, in 2002, the groundbreaking Women's Health Initiative tested the hypothesis that HT was cardio-protective and found the opposite to be true.¹² After four decades of use, the HT consensus has been

replaced by recommendations for severe restrictions on its use. And most recently, additional evidence has emerged with regard to its negative impact in relation to breast cancer.¹³

Questions raised by the HT experience provide a powerful incentive to ask questions about any form of widespread drug therapy for women. Current emphasis on cholesterol control and the use of cholesterol-lowering drugs invites investigation into how cardiac risk is portrayed for women, and the evidentiary basis for pharmaceutical interventions.

Cholesterol

Cholesterol is a sterol alcohol (C₂₇H₄₅OH) that is carried through the body in packages called lipoproteins. Cholesterol is vital to the body and necessary for many crucial functions including: brain function; hormone development including stress hormones, sugar-regulating hormones, and sex hormones; and signal transmission from one nerve cell to another. It is a crucial component of cell wall membranes, regulating structure and signalling functions within the body including key pathways linked to cell division and cancer. It is critical during pregnancy for foetal development and is an essential component of breast milk.¹⁴

“Good” and “Bad” Cholesterol Model

Our review of popular culture sources, including television, print advertisements, and websites suggests the following commonplace model linking cholesterol to heart disease. Cholesterol lowering is usually described in terms of adjusting two types: low-density lipoprotein (LDL), often called “bad cholesterol,” and high-density lipoprotein (HDL) called “good cholesterol.” The model links statin use to cardio-protection and posits that increased levels of LDL cause increases in plaque formation (a build-up of lipoprotein and other debris) on the arterial linings. Plaque build-up (atherosclerosis) is related to blockages in the arteries and then to coronary heart disease or stroke. Conversely, HDL is described as “good” cholesterol because it pulls cholesterol out of the arteries, thereby reducing plaque build-up. Statin drugs are administered to reduce LDL levels and Total Cholesterol (TC), and to increase HDL cholesterol.

This model, however, represents an oversimplification of very complex processes and interactions. A thorough multidisciplinary endeavour, assessing the history of its construction and acceptance into popular culture, would be useful, but is beyond our scope.

Cholesterol and Risk Factors for Heart Disease

Although there are multiple modifiable and non-modifiable risk factors associated with cardio-vascular disease (CVD), such as age, sex/gender, smoking, diet and weight, family history, stress¹⁵ and socio-economic factors,¹⁶ cholesterol has become the most prominent and feared risk factor for both women and men,¹⁷ perhaps because it is the most easily modifiable.

By contrast, there is no pill for the effects of air pollution, which is a substantial risk factor for heart disease, especially for women. Research on close to 66,000 post-

menopausal women in 36 US cities indicates that fine particulate matter is significantly associated with the development of atherosclerosis and heart disease, such that for every increase of 10 micrograms per cubic meter of pollution the risk of a cardiovascular event rises by 24% and the risk of cardiac death rises by 76%. The authors note that women are more vulnerable to the effects of particulate air pollution than men.¹⁸

The abatement of air pollution is a modifiable risk factor, but one that is societal rather than personal, complex to assess and to implement. Other interventions with regard to modifiable risk factors also require sustained personal and social spending and may not be as easy to implement as pill-taking. We assume that this is one element in the popularity of statin use.

Interest in the relationship between cholesterol levels and CVD began in the 1950s with the Framingham study.¹⁹ The Framingham study determined that high cholesterol levels, among many other risk factors, increased risk of heart disease for young and middle aged men. Their findings, however, did not extend to women or the elderly.²⁰ In fact, “higher total cholesterol levels significantly correlate with an increased risk of death from coronary heart disease only through the age of 60...[and] the risk of death from causes other than coronary heart disease *increases* significantly with *lower* total cholesterol levels for men and women after they reach the age of 50.”²¹

For a variety of reasons (discussed below) cholesterol has come to represent a virtual disease state in itself, rather than one risk factor among many, and has distracted from grappling with other risk factors that are strong indicators of cardiovascular disease²² and cardiovascular risk.²³

The “cholesterolization” of cardiovascular disease²⁴ – that is, emphasis on a single risk factor – intensified with the development of the 2001 American cholesterol guidelines.²⁵ These, followed by the revised 2004 National Cholesterol Education Program (NCEP) cholesterol guidelines,²⁶ urged that individual cholesterol levels be monitored from age 20 and that acceptable levels be significantly lower than was previously advised for both primary and secondary prevention of CVD in both women and men.

The Use of Statins to Reduce Cholesterol Levels

A class of drugs called fibrates was prescribed from the 1960s to the 1980s to lower cholesterol. However, both an important World Health Organization study and a University of Helsinki study found that this method of lowering cholesterol increased overall risk of death by 47% and 21% respectively and was associated with an elevated risk of cancer.²⁷ Interest in lowering cholesterol through medication declined until 1987 when a new class of drugs called statins was introduced.

The first statin was Merck’s Mevacor and was approved for use by both Health Canada and the US Food and Drug Administration (FDA) in 1987. Since then, six additional statins have been approved for sale in Canada, one of which, Baycol was voluntarily withdrawn from the market in 2001, after it was linked to at least 50 deaths worldwide caused by rhabdomyolysis, a very serious and potentially fatal muscle disorder.

It has been estimated that 3 million Canadians take a statin drug every day.²⁸

Statin are the most widely prescribed drug in the world. In 2006, 23.6 million prescriptions for statins were dispensed in Canada at a cost of \$2 billion (CDN).²⁹ Statin sales are only predicted to increase, with projected earnings of \$30 to \$33 billion (US) worldwide in 2007.³⁰ Lipitor is the top selling pharmaceutical in Canada. Worldwide sales reached \$12.9 billion (US) in 2005.³¹ Based on an assessment of 2006 data for six Canadian provinces, including Alberta, Saskatchewan, Ontario, Quebec, New Brunswick, and Nova Scotia (see table below), a total of 17,749,370 statin prescriptions were dispensed in that year. About half of those prescriptions were for women ranging in age from 15 to over 75 years old.

Table 1: Statin Prescriptions 2006 for Six Canadian Provinces³²

Age	2005 Population of women*	2006 Statin prescriptions	Estimated number of women on statins**	% of women on statins
15-19	841,722	2,310	266	0.03
20-24	880,746	5,730	659	0.07
25-29	883,087	11,026	1,267	0.14
30-34	893,371	26,133	3,004	0.34
35-39	950,774	62,878	7,227	0.76
40-44	1,108,567	163,991	18,850	1.70
45-49	1,060,069	357,204	41,058	3.87
50-54	932,566	622,480	71,549	7.67
55-59	815,101	899,083	103,343	12.68
60-64	622,327	1,022,355	117,512	18.88
65-69	501,298	1,062,110	122,082	24.35
70-74	450,164	1,130,550	129,948	28.87
75+	969,348	2,747,775	315,836	32.58
Total:	11,103,505	8,381,261***	963,363	8.83

* Includes all women over the age of 15 in the provinces of Alberta, Saskatchewan, Ontario, Quebec, New Brunswick, and Nova Scotia.³³

** This number was derived based on the conservative assumption that one prescription lasts six weeks.

*** The totals for the age groups do not add up to the grand total due to the presence of unspecified ages in the IMS data source.

Statin belongs to the group of medications known as HMG CoA reductase inhibitors. They work by blocking 3-hydroxy-3-methylglutaryl (HMG) coenzyme A reductase, an enzyme in the liver that is required in the early stages of cholesterol synthesis.

All statins lower cholesterol and the actual differences among medications within this class of drugs have been called into question. Recent research has found that, although they are differently indicated (approved by Health Canada to achieve different benefits), there is not a considerable practical difference among them.³⁴ For example, among patients who have already experienced heart attacks, the incidence of another heart attack or death from any cause is similar for five different statin brands at doses that all reduce cholesterol to different degrees.³⁵

Key events in the 20-year history of statin use in Canada include:

1987 – Mevacor (lovastatin), manufactured by Merck, is the first statin approved by Health Canada and the FDA.

1988 - 1997 Pravachol (pravastatin), Zocor (simvastatin), Lescol (fluvastatin), Baycol (cerivastatin), and Lipitor (atorvastatin) are approved by Health Canada and the FDA. Lipitor is an immediate success; it lowers cholesterol levels more dramatically than other statins to date.

2000 – Canadian recommendations for dyslipidemia management are released.

2001 – NCEP Cholesterol guidelines are released.

2001 – Baycol is voluntarily withdrawn from the Canadian and US market in August because of reports of fatal cases of rhabdomyolysis.

2002 – US Clinical Advisory issues alert for increased risk of statin-associated myopathy for advanced age, especially women over 80 and small body frame and frailty.³⁶

2003 – Crestor (rosuvastatin), by AstraZeneca, is approved. Crestor lowers cholesterol more aggressively than other statins including Lipitor. It earns \$30.7 million CDN during its first year on the market.³⁷

2003 – Revised Canadian cholesterol guidelines urge more aggressive cholesterol lowering.

2004 – NCEP cholesterol guidelines are updated to also urge more aggressive cholesterol lowering.

2004 – Zocor Heart Pro is approved for “behind the counter” sales in low doses in UK pharmacies.

June and November 2004 – Health Canada releases a Crestor Public Health Advisory. The advisory warns of rhabdomyolysis, particularly for Asian patients.³⁸

2005 – AstraZeneca makes significant changes to Crestor warning labels and releases a Canadian public advisory letter that includes a greater range and severity of adverse events.³⁹

January 2005 – Merck applies to the US FDA to sell Mevacor over the counter. The application is denied.

March 2005 – Health Canada releases another Crestor Health Advisory⁴⁰ warning of rhabdomyolysis particularly for Asian patients. It advises that all prescriptions should be for the lowest possible dose.

July 2005 – Health Canada releases an advisory on all statin drugs stating that all statin manufacturers should update their safety information about the risks of rhabdomyolysis. The advisory also warns that pregnant women and women of childbearing age should not take statins without consulting their physicians.⁴¹

We are unaware of any research about the impact of Health Canada advisories on how decisions are made to prescribe statins. One US study on statin prescribing behaviour suggests that prescriptions that go beyond the indications of guidelines may be commonplace,⁴² perhaps also signalling that decision-making with regard to statin use may not take advisory information into account.

B. Assessment of Benefits

Cholesterol Lowering in Women

In 2003, the US agency that reviews the quality of healthcare research produced a report on women and heart disease stating that there was insufficient evidence to determine whether lowering lipid levels by any method reduced the risk of heart attack or stroke in women, because women were under-represented in trials.⁴³ Other research (described below) has found that low cholesterol, especially in women over 50, is associated with higher levels of cancer and early death.

According to US research, high cholesterol in women is not a statistically significant risk factor for sudden cardiac death. On the other hand, smoking is one of the most important predictors of sudden cardiac death in women.⁴⁴

Prospective research on seniors in Italy found that there was no benefit of low LDL cholesterol in older women. For 1,887 women (average age 73), elevated LDL cholesterol was in fact associated with greater longevity and fewer cardiac events for over 11 years, a period of research about twice as long as most drug trials.⁴⁵

An Austrian study (also prospective), which compared cholesterol levels and health outcomes for over 80,000 women and 67,000 men over a 15-year period, found that high cholesterol in women over the age of 50 was not a predictor of cardiovascular problems or stroke, but was for women under the age of 50. Their research confirmed five previous studies (including the Framingham study), which found that high cholesterol was not a strong predictor of cardiovascular problems in older women (and men.) Low cholesterol at over age 50 was associated with higher death rates from cancer, liver disease and mental illness in the Austrian study. The authors titled their paper “Why Adam is not Eve” and concluded that their research contributed to the strong body of literature indicating that women are both physiologically and sociologically different from men and research must recognize both categories of difference.⁴⁶

Primary and Secondary Prevention:

In this paper we use two terms to discuss the risk of heart disease and stroke in women and appropriateness of statin intervention strategies relating to these two categories of prevention.

Primary Prevention describes a population of people without established heart disease who are nevertheless considered to be at risk for developing heart disease or stroke. These risks are usually expressed as being low, medium and high and are found in guidelines addressed to physicians to guide treatment or in various public advertisements and awareness campaigns. The majority of statin drugs prescribed in Canada are for primary prevention.

Secondary Prevention describes a population of people who have established heart problems, who have had a heart attack, stroke, unstable angina or a vascular blockage of some kind. These are people for whom the risk of another episode is demonstrably greater than those in the primary prevention category.

The drug trials described below are conventionally divided into primary and secondary prevention trials. That distinction has been blurred in some trials and subsequent meta-analyses requiring readers to be alert to statistical problems which over-estimate the effects of statin interventions. (Abramson and Wright, 2007)

Trials and Women: A Meta-Analysis by Walsh and Pignone

One of the most in-depth reviews of women and statin trials was undertaken in 2004 by Walsh and Pignone.⁴⁷ Their meta-analysis evaluated data from every significant clinical trial about cholesterol-lowering drugs (both statins and non-statin drugs) and women. They, like previous analysts, found a weak evidence base and failures to disaggregate data for women in key trials.⁴⁸

Of the over 1,500 articles vetted, only 21 clinical trials on lowering cholesterol included women and only nine published their results by sex. Almost two thirds of the women came from only two studies, HPS and ALL-HAT, and these trials have raised controversies (discussed below). Walsh and Pignone contacted trialists and were able to obtain some additional unpublished data.

Table 2: Representation of women in key primary prevention statin trials (derived from Walsh and Pignone)⁴⁹

Trial/Date	Number of women	Total participants	% women	Average age of women
ACAPS 1992 to 94	445	919	48%	61
AFCAPS/TexCAPS 1998 to 2001	997	6,605	15%	62
HPS 2002 to 03	1,816	5,963	30%	N/A
ALLHAT 2002	5,051	10,355	49%	N/A
ASCOT 2003	1,942	10,305	19%	N/A
TOTAL	10,251	34,147	30%	-

Walsh and Pignone’s analysis did not find a high quality evidence based rationale for statin therapy in women without known cardiac disease (primary prevention) and did not find that the evidence extant demonstrated that lowering cholesterol reduced mortality. Their conclusion was:

For women without cardiovascular disease, lipid lowering *does not affect total or CHD mortality*. Lipid lowering may reduce CHD events, but *current evidence is insufficient to determine this conclusively* (emphasis added).⁵⁰

They note that, because women have a lower risk of cardiovascular disease than men at any given age, the number of women needed to treat (NNT) to prevent a coronary event would be double the number of men, or 140 women per year for primary prevention.⁵¹

Previous Evaluations of Primary Prevention Benefit for Women

It is crucial to assess the validity of primary prevention trials and their use as a basis for prescribing to women because 75% of female users are in this category.⁵²

In addition to the work of Walsh and Pignone, other evidence casting doubt on primary prevention statin use for women includes the Therapeutics Initiative⁵³ review of primary prevention trials,^a which looked at a total of 10,990 women. This overview also found no evidence that statin therapy reduced cardiovascular events in women.

A detailed analysis of the ALLHAT⁵⁴ primary prevention trial, which included men and women who were targeted to reduce cholesterol levels in line with 2001 US guidelines for statin therapy,⁵⁵ did not find benefit in terms of a decrease in overall risk of death for women and men or for seniors, with or without heart disease.⁵⁶

Additionally, problems of extrapolating benefit from male-centred trials to women have been noted. For example, a key primary prevention trial that US guideline writers cite as evidence of benefit for treatment of women did not, in fact, include any women (WOSCOPS).⁵⁷

Primary Prevention and the “Lower is Better” Hypothesis

After the publication of Walsh and Pignone’s work, new studies and a new statin (Crestor) emerged that were associated with the ostensible advantages of high dosage statins and an “aggressive lipid lowering” strategy based on the PROVE-IT trial, which compared different statins at different dosages.⁵⁸ The press, advertisers and many physicians claimed that this and other research demonstrated that there were primary prevention benefits for ultra-low LDL levels. Advertising for the then new drug Crestor prominently featured downward pointing arrows and repeated statements that “it’s all about the numbers.”

In addition, the 2004 US NCEP widely used guidelines recommended aggressive lipid lowering for primary prevention in women. However, recent meticulous reviews of the science behind the influential 2004 NCEP guidelines add considerable evidence for caution⁵⁹ with regard to aggressive interventions.

^a These trials include PROSPER, ALLHAT-LLT, ASCOTT-LLA, AFCAPS, but not WOSCOPS (no women in trial population) (Therapeutics Initiative. Do statins have a role in primary prevention? Therapeutics Letter. 2003, 48).

The work of Hayward and colleagues, published in 2006, assessed the primary prevention strategy of cholesterol lowering by scrutinizing all the published medical evidence that was used to claim an evidence-based benefit for ultra-low LDL cholesterol levels.⁶⁰ Their meta-analysis (data for women not disaggregated) found that, for high risk primary prevention, the evidence behind the US guidelines did not substantiate the 2004 pronouncement "...that for every 1% reduction in LDL-C [low-density lipoprotein cholesterol] levels relative risk for major CHD events is reduced approximately 1%."⁶¹

Despite widespread belief in a smooth mathematical correlation between LDL-C lowering and equivalent risk reduction for patients, Hayward and colleagues found that no studies were of sufficient quality to prove the hypothesis. They state that "...current clinical evidence does not demonstrate that titrating lipid therapy to achieve proposed LDL cholesterol levels is beneficial or safe."⁶² They note that achieving these targets is very difficult and increases risks of serious side effects.

Another 2006 study also looked at lipid lowering for primary prevention for people at moderate to moderately high risk. The research of Thavendiranathan and colleagues⁶³ (which does not disaggregate for women) found a 1.7% reduction in risk with statin use for non-fatal heart attacks, stroke, and for angioplasty and bypass surgery over a 4.3-year period, and no decline in the overall death rate, nor a reduction of deaths from coronary problems.

If we agree with this research indicating that the "lower is better" proposition is not evidence-based for primary prevention, we must also assume that that message must urgently be re-evaluated for women.⁶⁴

Women and Secondary Prevention Trials

Walsh and Pignone's⁶⁵ overview identified five secondary prevention statin trials with information on women.

Table 3: Representation of women in key secondary prevention statin trials (derived from Walsh and Pignone)

Trial/Date	Number of women	Total participants	% women	Average age of women
4S 1994 to 97	827	4,444	19%	61
PLAC11 1995	22	151	15%	N/A
CARE 1996 to 99	576	4,159	14%	61
LIPID 1998 to 2003	1,516	9,014	17%	62
HPS 2002 to 2003	3,266	14,573	22%	N/A
TOTAL	6,207	32,341	19%	

Only three of the above trials have released data for all-cause mortality (4S, PLAC 11, LIPID) and these show no evidence of overall reduction of mortality with statin use. The total number of women in the statin-exposed group was 1,173, with 102 deaths. The placebo group included 1,192 women and there were 103 deaths. Death from coronary disease based on data released from all of the above except HPS (with approximately half the women) was, however, reduced with statin use. The authors urge the release of non-coronary heart disease data to help clarify the association between lowering cholesterol and mortality.

Walsh and Pignone's meta-analysis in relation to women with previous cardiovascular problems (secondary prevention) found a reduction in events. Twenty-six women would have to be treated for one year to prevent one event.

Their conclusion is that:

For women with known cardiovascular disease, treatment of hyperlipidemia [high cholesterol] is effective in reducing CHD events, CHD mortality, non-fatal myocardial infarction, and revascularization, but it does not affect total mortality.⁶⁶

As with primary prevention, any understanding of benefit based on data from trials of people with established heart problems must be understood in light of the failure of many trials to release full data on adverse events, or all-cause mortality.

Abramson's⁶⁷ assessment of three secondary prevention trials that included women found that the 4S (1994-1997) and the CARE (1996-1999) trials also showed a reduction of recurrence in coronary heart disease events in women taking a statin drug, but not a decrease in the number of overall deaths. The third study, LIPID (1998-2003), failed to show a statistically significant reduction of coronary heart events.

Overall, Abramson found that the benefit to women with some form of heart disease was slight. Over approximately a five-year period, the rate of cardiac events was lowered from 17.92% to 14.06%⁶⁸ or about .8 % per year. Statin use was not associated with avoiding premature death from any cause.⁶⁹

In terms of the benefit of cholesterol lowering and statin use with regard to overall death rates in women, Walsh and Pignone conclude:
"For the trials reporting total mortality,^b lipid lowering did not appear to have a beneficial effect for women with or without previous cardiovascular disease over the 2.8 to 6-year study period in the available trials, although a longer length of follow-up may be necessary to find a reduction in mortality."⁷⁰

^b Some trials did not report total mortality, but only heart disease-related deaths.

Seniors and Trials

Careful analysis is required to assess the purported benefit of statin use for elders. For example, the famous Framingham long-term research project has been cited by US guideline writers as support for the concept that high cholesterol is a major risk factor for people over age 70. However, the Framingham study actually stated that physicians should be cautious about cholesterol lowering for older men and women once they reach the age of 65, especially in the absence of trials that showed benefit.⁷¹

In 2002, the PROSPER trial looked at high risk seniors (primary prevention) and those who already had some form of heart disease (secondary prevention) over the age of 70.⁷² The study included approximately 3,000 women and 2,500 men. It showed that, over the approximately three year period of the trial, the number of deaths from all causes for both men and women was the same for those taking a placebo (306 people, 10.5%) and those taking a statin (298 people, 10.3%).⁷³ No statistically significant reduction of cardiac events was observed for either men or women.⁷⁴

The mortality rate for women, from all causes, in the PROSPER trial cannot be deduced from the published material. The reporting of cardiac events confusingly combines fatal and non-fatal outcomes: these combined data show no benefit either.^c Thus, no apparent impact on morbidity or mortality for women over 65 was established in this trial.

Interpreting “Mortality” and “Events”

The use of mortality data and events data to calculate the benefit or harm of statin therapy requires some explanation. Events are usually presented as myocardial infarction, unstable angina, sudden cardiac death, coronary revascularization (e.g., bypass surgery, angioplasty) or stroke. Analysts of statin trials use mortality as an unequivocal indicator: either the drug prolongs life or it does not. But even this indicator is complicated because many of the trials have not released all-cause mortality data; hence, the phrase “for trials reporting total mortality” in the meta-analysis by Walsh and Pignone discussed above. Critical research points to the obvious problems raised in trials that show a decrease in coronary death but no overall decrease in mortality. In other words, has a decline in heart/stroke death been negated by an equal number of deaths or even an increase in deaths from other causes? The absence of improved overall mortality in some trials must also be viewed within the context of reports of decline of cardiac events. However, this calculus requires more fine-grained research. The published trial data do not allow us to interpret the lived impact of heart attack and stroke events. Are all events presumed to be severe and disabling in the short-term and the long-term? Are the potential risks of adverse outcomes from life-long statin use offset by the benefits of reducing these heart and stroke events? We are unaware of research that addresses these comparative quality of life issues.

^c Figure 3, Shepard et al, 2002: 1627 shows that 186 (12.22%) statin-exposed women had CHD death, non-fatal MI and fatal or non-fatal strokes. The placebo group had 194 such events (12.89%).

C. Assessment of Safety

Statins have commonly been described as “so safe they should be in the drinking water.”⁷⁵ Evaluating the safety of statin therapy for women in particular is exceptionally difficult. Very little research has explicitly proceeded from a gender-based perspective. An example of this failure to consider the importance of gender is found in the 2005 US National Lipid Association’s Safety Assessment Task Force that reviewed statin safety and published a multi-part 97-page assessment, based on reviews of hundreds of studies about muscle, liver, kidney and cognitive adverse events. This project did not disaggregate data for women or assess any research with regard to women-specific adverse events.⁷⁶

Our overview will focus on what we call **hallmark issues of concern** to women and point to areas where further research is urgently needed.

Unavailability of Serious Adverse Event Trial Data

Any research on the safety of statins for women must be put into the context of an overall assessment of safety to the general population. However, that has proven to be very difficult, as noted above, because of reporting practices from the major drug trials.

In Canada, trials are legally required to collect data about Serious Adverse Reactions. A Serious Adverse Reaction is defined as “requiring inpatient hospitalization or prolongation of existing hospitalization, causes congenital malformation, results in persistent or significant disability or incapacity, is life-threatening or results in death.”⁷⁷

Analysts have pointed out that only two of 14 key statin drug trials have fully reported serious adverse events data.⁷⁸ It is important to note that these “data were collected but have not been published or released to research scholars despite explicit repeated requests to do so.”⁷⁹

This failure to fully disclose all adverse events has been noted in an earlier analysis of statin and cholesterol-lowering trials by Law et al⁸⁰ who surveyed 164 trials of statins and LDL cholesterol and found that only 48 of them released information on participants with one or more adverse symptoms.

Thus analysts have been forced to rely on mortality statistics, as described above, to establish a consistent and representative indicator of harm; but these death statistics are clearly not the whole story. Any calculation of the benefit of lifetime statin usage cannot be undertaken without a full release of adverse event data for both women and men of all ages.

Adverse Events in the Post Marketing Context

Since 2004, Dr. Beatrice Golomb and colleagues at UC San Diego have been compiling information on statin-related outcomes, including problems with cognition, mood and behaviour (violence and aggression.) Their work has found associations between aggressive behaviour and statin use not seen in clinical trials that were not designed to

pick up quality-of-life impacts outside of the cardiac domain.⁸¹ She found that some statin users who had mood and memory problems also had muscle problems and weakness.⁸² She has estimated that, while clinical trials may report 1-7% of patient adverse events, their research work indicates that the number of adverse events with statin use may be closer to 15%.⁸³

“An unexplained disturbing event must be taken as the equivalent of a yellow traffic light: as a signal to proceed with caution and be prepared to stop. If the patient thinks the drug has caused the problem, it very often has. Patients should be routinely asked for their opinion.”⁸⁴

Dr. Andrew Herxheimer

There are many on-line groups of former statin users, and/or their partners, who state that their experiences have resulted in cognitive and memory impairments, including amnesia, episodes of depression, mood problems, especially extreme irritability, peripheral neuropathy, muscle pain and exercise intolerance, weakness and fatigue, blood sugar problems, and the unmasking of underlying genetic conditions (e.g. Parkinson’s Disease) that are disabling or life-altering.

An 86-page overview has been compiled by Hope,⁸⁵ which includes adverse events as published by statin manufacturers in product monographs and on websites, patient websites and discussion group sites and an extensive bibliography of medical journal research. The conditions that are addressed in this bibliographic review are as follows: nerve damage; chronic pain and chronic fatigue; cognitive impairments, including memory problems; joint/muscle problems; as well as rhabdomyolysis; kidney and liver damage; lupus-like symptoms; extreme irritability and violent behaviour; immune system depression and infection; erectile dysfunction; birth defects; and cancer.

Adverse event: Any untoward medical occurrence that may present during treatment with a pharmaceutical product but which does not necessarily have a causal relationship with this treatment.⁸⁶

Adverse reaction: Any undesirable or unwanted consequence of a preventive, diagnostic, or therapeutic procedure or regimen.⁸⁷

Statin Adverse Reaction Reporting

In Canada, all suspected adverse reactions, including Serious Adverse Reactions (SARs), are collected and monitored using the Canadian Adverse Drug Reaction Monitoring Programme (CADRMP). Adverse reactions (ARs) are reported to the Canadian Adverse Reaction Database voluntarily by health professionals and laypersons. Pharmaceutical manufacturers are required to report serious adverse reactions to the Adverse Reaction Database under the Food and Drugs Act and Regulations. These are reactions that have been reported to the manufacturers by either health professionals or laypeople.

It is estimated that in Canada, in 1999, approximately 3% to 5% of ARs were reported.⁸⁸ Others argue that approximately 1% of ARs get reported in the US.⁸⁹ Given the unreliability of voluntary AR reporting and the difficulty in interpreting causal relationships between ARs in the database and actual incidents, because of lack of

specificity in describing events or potential causal mechanisms, the following table must be examined cautiously and interpreted as under-representative.

Table 4: Data from the Canadian Adverse Reaction Database (as of November 25, 2006)

	Lipitor	Crestor	Mevacor	Pravachol	Lescol	Zocor	Baycol*	Total
Total AEs**	3,163	547	302	535	111	967	193	5,818
Total women's AEs	1,426	255	160	244	57	451	97	2,690
AEs in women aged 0 to 50	178	47	9	6	1	43	7	291
AEs in women aged 51 to 65	505	114	19	16	8	151	29	842
AEs in women aged 66 to 99	628	94	25	31	10	207	43	1,038
Total deaths***	122	7	8	19	1	32	6	195
Total women's deaths***	51	1	3	8	0	16	3	82

*Baycol was withdrawn from the market in 2001 because it was linked to fatal cases of rhabdomyolysis, including at least one in Canada.

**The database does not allow us to disaggregate serious from non-serious outcomes.

***Full title of database field is "Died and the drug may be contributory."

According to the database there have been close to 6,000 potential statin-related adverse reactions in Canada. Of these, almost one half have been reported for women. There are 195 database entries into the category "died and drug have been contributory," and 42% of these are for women.

Adverse Events Specific to Women: Issues Requiring Research

a) Exercise Intolerance

Research on exercise, diet and smoking cessation indicates that these activities far outstrip cholesterol lowering in protecting women from heart disease and stroke, especially if physicians offer counselling to their patients.⁹⁰ In the treatment of type 2 diabetes, a major risk factor for heart disease and stroke, such non-drug interventions surpass statin interventions in effectiveness.⁹¹

Exercise is thus an important element in women's cardiac health and concerns that statins may cause muscle problems and lead to exercise intolerance are of signal importance. A comparison of statin treatment and mild exercise over a one-year period in people with diabetes reveals that statins prevented 1 death in 250 diabetic patients, while walking for at least two hours a week prevented four deaths in formerly inactive diabetics.⁹²

There is a large body of literature on muscle disorders and statin therapy, but very little that concentrates on women specifically. Tomlinson and Mangione's review of statin-induced muscle problems (myopathy) and weakness suggests that women may be especially at risk.⁹³ The authors raise important concerns about whether exercise is

actually contraindicated for people weakened by statin exposure.⁹⁴ They describe statin-impaired patients who present with conditions that undermine activities of daily life, including: balance problems, peripheral neuropathy causing weakness in hands and grip problems, difficulty navigating stairs or rising from a seated position without using arms to assist, and leg pain. Recent research supports the perspective that statins interfere with exercise, indicating a population of as many as 25% of users who experience “muscle fatigue, weakness, aches, and cramping due to statin therapy and potentially dismissed by patient and physician.”⁹⁵

The only known treatment for statin-induced myopathy is discontinuation of statin use⁹⁶ and research by Needham and colleagues⁹⁷ amongst others, suggests that discontinuation does not always resolve impairments if an immune system myopathy is triggered. Other research suggests that statin exposure may unmask underlying genetic disorders and contribute to the persistence of muscle problems after statin exposure has ceased.⁹⁸ One example may be vulnerability to Parkinson’s disease. A nine-year Dutch study indicates that women over 55 with high cholesterol appear to be at decreased risk for Parkinson’s disease.⁹⁹ Forthcoming large-scale prospective studies in the US are underway to shed additional light on the possible associations between statin-exposure and Parkinson’s disease.¹⁰⁰

b) Women and Cancer

There is a history of association between drug-induced cholesterol lowering and cancer from other cholesterol-lowering drugs, as noted above for fibrates. Newman and colleagues’ animal studies found that all lipid-lowering drugs classified as fibrates and statins cause cancer in rodents “...at doses that are close to those given to humans.”¹⁰¹ Thomas and Huley acknowledge that extrapolation from animal studies to humans can be controversial, but conclude that “research suggests that long-term preventative use of these drugs without [the presence of] arterial disease should be avoided.”¹⁰²

Our review of three meta-analyses that assess statin exposure and cancer risk found the following problems: 1) failure to report cancer data in large scale trials; 2) conflation of incidents and deaths as events or inconsistent reporting of either; 3) exclusion of large numbers of women from analysis for standardization reasons, e.g. differential inclusion of new or recurrent cancers; 4) failure to disaggregate by sex for all cancers; 5) breast cancer assumed to be female only; and finally 6) concern about under-representation of women in these meta-analyses.

For example:

- Dale and colleagues’ review of 26 trials is based on a population of 27% women and includes only five trials with data on breast cancer. Their methodology further reduced the database for women by excluding the ALLHAT study (with close to 5,000 women) when calculating incidences of cancer. They found a non-statistically significant 33% excess of breast cancer in the statin-exposed population.

- A 2006 primary prevention trials meta-analysis by Thavendiranathan and colleagues notes that only three of the seven major trials they examined have fully released cancer data.
- These two meta-analyses urge caution, given the short duration of statin trials and the long latency period for most cancers.
- Cholesterol Treatment Trialists (CTT) meta-analysis of 14 key statin trials by Bagnett and colleagues¹⁰³ has also not fully released all cancer data. It did release data of first incidence of any cancer that was non-fatal, but did not include deaths from any cancer recurrence.¹⁰⁴ In figure 8,¹⁰⁵ the trialists noted a non-statistically significant excess of breast cancer with cholesterol lowering, but in a footnote, they indicate that data from the ASCOT-LLA trial, with close to 2,000 women (9% of all women in the 14 trials) were excluded because they provided data on fatal cancers only.

A true gender analysis of cancer risk is not possible from these meta-analyses because the trials on which they are based have not disclosed all relevant information and because sex was not disaggregated for the six types of cancers assessed.

c) Breast Cancer

The issue of breast cancer and statin exposure is largely a woman-specific issue. However, the problems described above have made research into this crucial question very difficult. Concern associating breast cancer and statin exposure emerged in relation to two trials:

- The PROSPER study¹⁰⁶ (ages over 70) reported a 25% statistically significant increase of new cancers overall, and did not release data on cancer recurrences or deaths. There were more first breast cancer diagnoses in the statin-exposed group than in the placebo group, for a total of 18 in the statin-exposed group and 11 in the placebo group.¹⁰⁷
- The CARE study,¹⁰⁸ which included younger women (average age 61), reported a 12-fold statistically significant increase in the incidence of breast cancer in statin users when compared to the placebo group.

A meta-analysis of breast cancer in seven clinical trials and nine observational studies in 2005 by Bonovas and colleagues¹⁰⁹ assesses whether statin exposure enhances protection from breast cancer or increases risk. They found a neutral effect. They assessed breast cancer mortality of diagnoses or non-fatal breast cancer during trials. They did not cite analytical concerns with standardization of reporting and terminology as later meta-analyses of all cancer types did, but they did exclude the PROSPER study from their assessment, for reasons not specified. They, like the other meta-analyses cited above, urge caution given the long latency of cancer and the relatively short follow-up periods of trials.

Overall, the clinical trial data on women and breast cancer indicates a hallmark signal for further analysis that can only be meaningful if all elements of breast cancer data, including incidences, recurrences and deaths, are released from all trials.

d) Statins and Concomitant Use of Hormonal Drugs

Another issue of concern for women is the combined effects of taking statins with Hormone Therapy (HT) or oral contraceptives (OC). This area is under researched, particularly with respect to all cancers, including breast cancer.

HT and Statins

Hormonal drugs themselves lower cholesterol. Prior to 2002, concomitant use of statins and HT was advised.^d For example, in the 1997 “Update for Women,” Davidson and co-authors discussed in positive terms the benefits of “combined therapy.”¹¹⁰ They started from a position that unquestioningly assumed cholesterol lowering for post-menopausal women would afford cardio-protection, and that HT was beneficial in this effort. Other studies of that time period also praised combining statins with HT to improve lipid levels.^e

The history of combined statin and HT use prior to the 2002 findings of the Women’s Health Initiative study on the dangers of hormonal exposure in menopausal women has yet to be written. We now know that women were actually placed at greater risk by the use of hormonal therapies; indeed, current cholesterol guidelines list HT as contraindicated for prevention of CVD in women.¹¹¹ We are unaware of any current publications on the health impacts of combined HT and statin exposure.

We have found one Canadian study that does investigate concomitant statin-HT use and breast cancer outcomes in the 1990s. Researchers in Saskatchewan^{112f} found that statin users were more likely than controls to have used HT and that there was “a statistically significant doubling of breast cancer risk in long-term [over 6 years] HT users who also used statins.”¹¹³ Their data indicate that 56.3% of statin-exposed women had also used HT.

It is difficult to assess the extent of statin use by women also taking HT. IMS data for six Canadian provinces indicate that, in 2006, 4,290,804 statin prescriptions were dispensed

^d Rossouw cited in Jacques, E. (Hormone replacement therapy and cardiovascular disease: Review Article, *Current Opinion in Lipidology*. 1999, 10(5): 429- 434) noted the “well known effects on LDL-cholesterol, HDL-cholesterol, and triglycerides in women.” See also Baal V. M. et al (Cardiovascular disease risk and hormone replacement therapy (HRT): A review based on randomised controlled studies in postmenopausal women. *Current Medicinal Chemistry*. 2000, 17(5): 499-517) who also note “improved lipid profile.” Both articles express concern about the HERS study which demonstrated the unanticipated result of increased risk of CVD in women.

^e In 1998, Sbarouni, E. et al (The effect of hormone replacement therapy alone and in combination with simvastatin on plasma levels of hypercholesterolemic postmenopausal women with coronary artery disease. *Journal of the American College of Cardiology*. 1998, 32: 1244-1250) recommended the usage of combined statin and HRT for postmenopausal women with heart disease. They argued that the HRT seemed to increase survival rates for women with ischaemic heart disease partly due to changes in lipid levels.

^f Beck et al assessed 13,592 Saskatchewan women exposed to statins (based on provincial health plan records) and compared them with a non-exposed group of 53,880 women for up to 8.5 years. The average follow-up time was 4.2 years.

to women 46 and over. For that same time period, 3,781,638 prescriptions were dispensed for HT¹¹⁴. (See Table 5 below).

Oral Contraceptives and Statins

An indicator that combined oral contraceptive-statin use occurs comes from research by AstraZeneca, the manufacturer of Crestor. They investigated the combined use of their drug and oral contraceptives to ascertain whether pharmacological efficacy was impacted by concomitant use. They found no interaction concerns.¹¹⁵ This short-term investigation did not address the question of the long-term impact of co-administering statins and oral contraceptives. Since both drugs are usually taken for many years, it is important to know what the long-term health outcomes might be.

It is difficult to assess the extent of statin use by women of childbearing age. IMS data for six Canadian provinces indicate that, in 2006, 5,752,416 statin prescriptions were dispensed to women between the ages of 15 and 45. For that same time period, 7,706,295 prescriptions were dispensed for oral contraceptives.

The Saskatchewan study found that 13.5% of statin-exposed women had also used oral contraceptives.¹¹⁶ The findings of their study with regard to breast cancer risk for concomitant use are complex, and limited by data collection problems; they could only designate ever/never usage of oral contraceptives and the duration of their follow-up was short. It would be prudent to initiate research that takes longer exposure times and concomitant usage into consideration to assess breast cancer or other health risks.

Table 5: Prescriptions for statins, oral contraceptives and hormone therapy filled at retail pharmacies in six Canadian provinces in 2006¹¹⁷

Age	Statin Prescriptions	Oral Contraceptive Prescriptions	Hormone Therapy Prescriptions
15-19	2,310	1,341,171	X
20-24	5,730	2,043,157	X
25-29	11,026	1,667,688	X
30-34	26,133	1,093,072	X
35-39	62,878	710,168	X
40-44	163,991	525,512	X
45-49	357,204	325,527	X
50-54	622,480	X	996,220
55-59	899,083	X	1,127,528
60-64	1,022,035	X	759,615
65-69	1,062,110	X	413,134
70-74	1,130,550	X	238,857
75+	2,747,775	X	246,284
Total	8,381,261*	7,942,869*	4,471,471*

*The totals for the age groups do not add up to the grand total due to the presence of unspecified ages in the IMS data source.

e) Miscarriage, Birth Defects, and Breast Feeding

Younger women who do not use oral contraception while taking statins are faced with a different set of issues. Statin exposure is associated with risks of miscarriage for pregnant women, and birth defects and infant development problems if used by breast-feeding mothers.

It has been estimated that between 500,000 and 800,000^g women of childbearing age in the US were taking statins in 2004. It is difficult to determine the equivalent Canadian figure.

In 2004, hearings were held in the US on an application by Merck to determine whether Mevacor should be sold over-the-counter (OTC), without a prescription. The issue of birth defects arose. In their testimony, Merck noted that there were seven cases of birth defects in 105 statin-exposed pregnancies; but they denied a causal link.¹¹⁸

That perspective was vigorously opposed by representatives from the March of Dimes, the Organization of Teratology Information Services (OTIS) and researchers Edison and Muenke. Those opposed to OTC selling of statins stated that half of all pregnancies are unplanned, that a woman might unknowingly already be pregnant while being exposed to a statin¹¹⁹ and that, given increasing maternal age, there was an expanding risk of pregnancy while exposed to statins.¹²⁰ A Merck representative acknowledged that possibility and referred to statin usage for younger women as “off-label,” in contradistinction to women aged 55 and over who were the appropriate age group for statin use; nevertheless, their own data indicated that one half million young women were taking statins in the US.

In July of 2005, Health Canada issued an advisory on statins indicating that, before taking drugs from this class, women should tell their doctors or pharmacists if they “are pregnant, intend to become pregnant, are breast-feeding or intend to breast feed.” Work by Schwartz and colleagues suggest that this advisory may be insufficient, because physician awareness of birth defect risk associated with drugs like statins is quite low.¹²¹

The research on statins and birth defects signals the need for caution. In 2004, Edison and Muenke¹²² published their assessment of 22 cases (released from the FDA pursuant to a Freedom of Information Act request) of babies born with birth defects whose mothers (aged 20 to 44) had been taking statins in their first trimester. The authors estimated that in the year 2000, a maximum 6,636 births may have been exposed to statins in the US and possibly 104,775 worldwide.¹²³ The birth defects described were severe in some cases, combining more than one problem. There were five central nervous system anomalies and five limb deficiencies. Two with limb deficiencies also had multiple malformations, including anomalies of three or more of the following: vertebral, anal,

^g This range of numbers was achieved from 500,000 (Merck cited in Mechcatie, E. Panel rejects OTC version of statin. *OB GYN News*. 2005, 40(4) and 800,000 (Schwarz, EB et al Prescription of teratogenic medications in United States ambulatory practices. *The American Journal of Medicine*. 2005, 118: 1240-1249).

cardiac, tracheo-esophageal, and renal structures (collectively called VACTERL patterns in the literature).¹²⁴ They estimated that the latter malformations are exceptionally rare in non-statin-exposed pregnancies: between one in 50,000 to one in 500,000 cases. Other problems included facial malformations, intrauterine foetal death and severe intrauterine growth restriction.

Their work strongly implicates the complex influence that cholesterol-lowering drugs exert on foetal development during first trimester gestation. They state an expectation that larger databases may detect even higher rates of foetal exposure and the need for a range of studies to track this tip-of-an-iceberg issue.

Kenis et al¹²⁵ have demonstrated damage to the newly formed human embryo, and adverse effects to the placenta which may result in miscarriage and birth defects linked to impaired implantation, associated with the inhibition of cholesterol needed for cell metabolism, hormone regulation, the initiation of DNA synthesis and other cell functions mediated by cholesterol. US FDA data, cited by the French drug bulletin *La revue Prescrire*,¹²⁶ indicates that 45 of 214 statin-exposed pregnancies ended in miscarriage, and five in intrauterine death.

Low cholesterol levels in infant formula have raised concerns about the development of infant central and peripheral nervous systems, and formation of bone, bile and hormonal systems. Breast milk is estimated to have 14 mg of cholesterol per 100 grams of edible milk, while some formulas have only 1 or 2 mgs of cholesterol.¹²⁷ Health Canada has issued an advisory against lowering cholesterol through statin use while breast-feeding.

We have been unable to locate Canadian data for the distribution of birth defects or rates of miscarriage with statin use.

f) Burden of Care

We have found no systematic research about increased burden of care on men and women who are the spouses, partners and children of statin-impaired family members and loved ones. We have received personal communications about experiences of humiliation and frustration in consulting with physicians to assess statin impairments, and financial deprivation as careers and businesses are lost.¹²⁸ These stresses are currently not being addressed by medical or social science research, but are extremely significant to women as principal caregivers, who are themselves at risk from care burn-out.^{129 130}

D. Information Representation

Issues of statin safety and benefit are further complicated because they are mediated by a variety of information transfer frameworks that shape how safety or benefit are portrayed and perceived. These influences may inflate how benefit is understood, obscure meaningful investigation into drug safety, and shape decision-making processes. In this section, we examine some of the context of information transfer that has had the effect of overstating statin benefits, and diverting attention from discussions of other cardiac risk factors and possible short and long-term adverse outcomes of statin use.

Marketing to Women

Although the data above indicate a weak evidence base for statin use by women, especially for primary prevention, our research indicates that large numbers of women of childbearing age may be taking statins. Health Canada has, as noted, issued an advisory about women of childbearing age, and product monographs also caution against prescribing to this group. The data is also weak in establishing benefits of statin use for older men or women, yet this too is a high prescription population.

One influence on prescribing practices is direct-to-consumer advertising (DTCA).¹³¹ Although DTCA is illegal in Canada, it occurs as a spill-over from exposure to American media and advertising on television and in magazines readily available in Canada.

Other advertisements appear in Canada in the guise of “disease awareness” campaigns. DTCA, in this form, is strongly opposed by many critics who argue that it creates false consumer need based on overstated descriptions of benefit, while minimizing harm. An example of this with regard to women is a recent television advertisement featuring a raging bull charging a slim young woman, portraying her as being in grave danger because she is unaware of the risks of high cholesterol. A previous version of this form of indirect advertising is the notorious “toe tag” ad that drew condemnation for conflating failure to have cholesterol tests with certain death.

In the US, a class action lawsuit challenging the targeting of women for statin use has been launched against Pfizer. The complaint alleges that Pfizer violated consumer protection laws against deceptive advertising.¹³² The complainants seek reimbursement for women, seniors and third party payers “who bought Lipitor unnecessarily as a result of Pfizer’s marketing and promotional campaign.”¹³³

Statin marketing also occurs through the activities of seemingly independent health advocacy groups who have links to funding from the pharmaceutical industry. These subsidies and donations raise serious concerns about conflict of interest and the reliability of the data that health advocacy groups use to educate the public. One example is the link between the Canadian Heart and Stroke Foundation and the donations they receive from several manufacturers of statin drugs.

A recent Canadian Heart and Stroke Foundation awareness campaign, aimed at intensifying concern about heart disease in women, conflated age-related statistics giving the impression that women of all ages are at imminent risk for heart attacks or strokes and thus candidates for preventive drug therapy. Yet, as indicated above, heart disease does not become the most significant cause of death for Canadian women until they are in their 80s. Thus, the statement from the Heart and Stroke Foundation that, “Heart disease and stroke are responsible for more female deaths in Canada than any other disease”¹³⁴ is technically correct but an overstatement implying that women of all ages are at equal risk.

Conflict of Interest and Cholesterol Guidelines

Meta-analyses discussed above have indicated the need for a cautious approach with regard to primary prevention intervention strategies found in guidelines that have urged

aggressive lowering of cholesterol. In addition to concerns about the evidence base for these guidelines, questions of conflict of interest (COI) have arisen because of the financial ties between guideline writers and the pharmaceutical industry.

COI is defined as occurring “when a person or organization has a primary moral obligation to act on behalf of another and, at the same time, has an interest with a third party that could interfere with proper judgment in the first place.”¹³⁵ Seven of the nine physicians who wrote the 2004 US NCEP guidelines had significant undisclosed financial ties to pharmaceutical industries that were revealed through the press after publication. Within Canada, the guideline writers have acknowledged their financial links to statin drug manufacturers.

Analysts¹³⁶ are concerned about cholesterol guidelines, especially with regard to primary prevention, for other reasons, including:

- Over-emphasis on lowering cholesterol has minimized interventions in relation to other risks of CVD, resulting in reduced public awareness, advocacy efforts and support for critically important issues such as routine exercise, smoking cessation, weight control, environmental causes of CVD, and social determinants of health.
- If fully implemented, the Canadian guidelines would result in another \$250 million in drug costs.¹³⁷
- The evidence base for statin use by women is weak and has resulted in requests by a number of physicians and health advocates that the US guidelines be re-evaluated.¹³⁸

Data Disclosure

Meaningful decision-making is impeded if all the relevant information is not disclosed. As we noted above, attempts to assess the safety of statin use by women is compromised not only by the under-representation of women in key trials, but also by the overall absence of crucial adverse event information for both men and women. Most recently, Abramson and Wright have noted the urgent need for full disclosure of “total mortality, total serious adverse events, total incidences of cancer and total cardiovascular events”¹³⁹ in 12 of 14 key statin trials moderated by the Cholesterol Treatment Trialists.

Another area of concern with regard to transparent information transfer relates to advisories. Health Canada’s advisories do not publish relevant trial information¹⁴⁰ or citations to other material that serve as the underpinnings for advisories. This information gap hinders the ability of health professionals and consumers to interpret their import. The US FDA, on the other hand, has a more transparent process that enables consumers and health care professionals to examine all the important aspects of the decision-making process on the FDA website.¹⁴¹

Statistical Representations

The language used in presenting statistical data to the public is also important in meaningful decision-making with regard to statin use. Clearing up confusion over the term “significance” and understanding what is credible research are important elements for enabling women to decide whether statin drugs are useful or not.¹⁴²

Clinical trials that are aimed at the eventual licensing of a drug must show regulators data that reach statistical significance. But statistical significance, which means that an outcome did not occur by chance, does not necessarily reflect meaningfulness in real-life contexts; it may obscure important information about harm or may not ask the questions that are important to drug users. We have called these “**hallmark**” issues: important areas for further research for which statistical analyses may not have reached significance.

Furthermore, there are many possible statistical biases that may spuriously inflate benefit. Ioannidis’¹⁴³ research cautions against “**significance-chasing**” as a marker, noting that positive results are preferentially published over negative results and that disconfirming results may only be published much later, as we have seen with research on Hormone Therapy for menopausal women. Our attempts to assess possible links between statin exposure and breast cancer serve as an example of this problem. Other sources of distortion noted by Ioannidis include conflict of interest, which may encourage selective analysis or re-framing of studies to obscure findings.

Many statin studies report large statistical advantages in statin use by citing relative risk (RR) percentages. For example, the influential WOSCOPS trial¹⁴⁴ (which was based on following 6,600 high risk men and no women) was described as a milestone in favour of statin therapy because the statin users had 31% fewer heart attacks than the non-exposed group. This number was statistically significant. However, looking at the figures a different way elucidates that for every 100 men who took a statin (Pravachol), there were 1.1 heart attacks per year, while those who were given a placebo had 1.6 heart attacks. The difference between these two numbers can of course be expressed as a 31% advantage, which gives the impression of enormous benefit; whereas, the previous comparison implies a much more modest advantage.

Number Needed to Treat

A better method for deciding whether to use a drug is NNT, or **Number Needed to Treat**, because it offers a more credible information framework for decision-making. Thus, the actual number of heart attacks or deaths prevented by taking a statin using an NNT approach in the WOSCOPS case reveals that 100 men had to take Pravachol for two full years in order to prevent one heart attack. In order to prevent one death, 100 men would have to take this drug for 5.5 years.¹⁴⁵ The cost of drug treatment for all those men would be US\$336,000. Additionally, as noted above, these methods of calculation do not include an assessment of possible harm to the drug user or burden-of-care costs to their caregivers.

Using Canadian guidelines, Manuel and colleagues have estimated that, over all risk categories, to prevent one cardiac death 154 people would have to be treated for five years.¹⁴⁶

To prevent one cardiac death amongst low-risk people, 23,000 would have to take statins for five years.¹⁴⁷

The use of relative risk values is also related to the issue of credibility of research conclusions. If we look at a trial of lower risk people with mildly elevated LDL levels, which included 997 women (15%),¹⁴⁸ we find that the relative risk ratio demonstrated a statistically significant 37% advantage to participants who had used a statin. In NNT terms this datum is less impressive: 100 people would have to take the drug for 2.5 years to prevent one cardiac event. Overall, statin use did not save lives.

Credibility Scale for Gender-based Analysis (GBA)

Ioannidis suggests that rather than using statistical significance as the only marker of importance, a better way to gauge the value of scientific research is by looking at **credibility**. Low credibility findings would be consigned to the bottom of a pyramid like-structure; whereas, the most relevant, well-executed high priority research would be at the apex.

In terms of statin research on women, a credibility scale could be combined with Gender-based Analysis (GBA) guidelines in place in Health Canada since 1993,¹⁴⁹ which are sensitive to gender issues and could be used to reassess the value of trials, new research and guidelines. This model would:

- employ the credibility pyramid model as described above;
- report using NNT and absolute risk formats for data representation;
- would not extrapolate from men;
- would identify and support research for hallmark issues of specific concern to women;
- would include important sub-groups of women by age, socio-economic condition, physical condition, ethnicity and race.

These expectations are espoused by Health Canada. Since 1993, Health Canada has stated its commitment to support the protection of women's health through the promotion of GBA. They argue that, "By using GBA, Health Canada can improve its understanding of sex and gender as determinants of health, and how they interact with other determinants. This knowledge will help ensure that proposed policies, programs and legislation have intended and equitable results for all people living in Canada."¹⁵⁰

Recognizing that GBA results in better evidence, the Canadian Institutes for Health Research (CIHR), the Government of Canada's health research funding agency, has also recently introduced GBA guidelines for researchers and peer reviewers.¹⁵¹

Applying GBA to research on statins would improve the evidence base that women and their physicians are using to make decisions about statin use.

Furthermore, we agree with the recommendation from the US Agency for Healthcare Research and Quality which states that, "we recommend that in addition to demanding participation of women and minorities in research, the National Institutes of Health, Federal Drug Administration, and other funding sources should insist that primary and secondary outcome data by subgroup [women and minorities] be published or archived."¹⁵²

E. Conclusion

We have assessed the impact of statin use on women starting from the assumption that if a woman is put on a drug for the rest of her life, the reasons for doing so must be based on the highest quality, most credible data possible. There must be solid evidence of advantage over harm and careful analysis of any serious adverse outcomes that may arise immediately or with years or decades of use or when used in conjunction with other drugs commonly prescribed for women. In other words, a Canadian woman should be able to take a pill, safe in the knowledge that its benefits and safety were tested on women like her. She should embark on long-term commitment to a drug therapy with the understanding that she is highly likely to derive a clear advantage in terms of health and longevity and also feel confident that information about any risks will be explained to her in meaningful and accessible language.

These expectations have not been met. Instead we have found a pattern of overestimation of benefit and underestimation of harm. Below are recommendations that address strategies to remedy the situation.

F. Recommendations for Health Canada

Health Canada has a number of roles to play in assisting physicians and women to make informed decisions about statin use and in collecting accurate data and supporting independent research.

In accordance with its commitment to Gender-based Analysis, we recommend that Health Canada, in conjunction with the CIHR, the partners of the Bureau of Women's Health and Gender Analysis (the Centres of Excellence for Women's Health and affiliated research Working Groups, and the Canadian Women's Health Network) and other relevant entities, support the following:

- Funding should be made available for high quality and sufficiently powered gold-standard independent statin trials specifically designed for women and sensitive to issues of age, socio-economic status, ethnicity and race.
- An independent Post-Marketing Review Process should be instituted to reassess statin trials that have not released all serious adverse event data and address post-approval safety issues.
- Guidelines based on these trials should be reassessed by an independent research institute in light of released data.
- Health Canada should maintain a database on statin exposure and birth defects.
- A Credibility Scale Template for Gender-based Analysis should be supported, based on the following issues:
 - functioning of cholesterol and its role throughout a woman's life cycle;
 - research on combined use of statins and estrogenic drugs (oral contraceptives and hormone therapy);

- research on statin exposure and birth defects, miscarriage and breast-feeding;
- research on statins and cancer in women;
- research on the impact of cholesterol lowering and statin use for women of colour, First Nations women, differently-abled women and additional research for Asian women about whom advisories have been released.
- Independent funding should also be made available for non-drug therapies and education programmes for the prevention and treatment of heart disease that focus on issues other than cholesterol lowering.
- Health Canada has released several advisories on statins. It should make this process more transparent, citing its sources, including relevant communications between itself and the pharmaceutical industry that underpin these advisories. The US FDA has a more transparent process that enables health care professionals and consumers to examine all the important aspects of the decision-making process on the FDA website.¹⁵³ A process for following up on the effectiveness of advisories should also be established.
- Many of the conflict of interest issues have been more fully addressed in a previous Women and Health Protection publication by Sharon Batt.¹⁵⁴ Based on her findings, patients, citizen groups, and stakeholder groups should be required to make their pharmaceutical affiliations publicly known and to prominently display them on all of their publications and at educational events.
- Health Canada should not approve over-the-counter statin sales.
- Support for independent comprehensive pharmaco-epidemiology of harm is warranted, to more systematically capture adverse reactions in light of the large population of users.

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- ¹ Goff DC Jr, Sellers DE, McGovern PG et al. Knowledge of heart attack symptoms in a populations survey in the United States: The REACT Trial. *Arch Internal Medicine*, 1998; 158:2329-2338.
- ² Zheng Z, Croft JB, Giles W, et al. Sudden cardiac death in the United States, 1989-1998. *Circulation*. 2001; 104:2158.
- ³ Statistics Canada. *Women in Canada: A gender-based statistical report*. 2006:58.
- ⁴ Heinrich, J et al. Drug safety: Most drugs withdrawn in recent years had greater health risks for women. US General Accounting Office -01-286R Letter. 2001. Online at: www.gao.gov/new.items/d01286r.pdf Downloaded April 10, 2007.
- ⁵ Statistics Canada, 2006:57.
- ⁶ Statistics Canada, 2006:58.
- ⁷ Statistics Canada, 2006:58.
- ⁸ de Lorgeril M & Salen P. Cholesterol lowering and mortality: Time for a new Paradigm? *Nutrition, Metabolism & Cardiovascular Diseases*. 2006; 16:387-390.
- ⁹ See Table 3. Zheng et al, 2001:2163
- ¹⁰ Heart and Stroke Foundation of Canada. *The growing burden of disease and stroke in Canada*. 2003. Online at: www.cvdinbase.ca/cvdbook/CVD_En03.pdf. Downloaded April 10, 2007.
- ¹¹ Krieger N et al. Hormone replacement therapy, cancer controversies and women's health: historical epidemiological, biological, clinical, and advocacy perspectives. *J Epidemiol Community Health*. 2005; 59:740-748.
- ¹² Writing Group for the Women's Health Initiative Investigators. Risk and benefits of estrogen plus progestin in healthy postmenopausal women. Principal results from the Women's Health Initiative randomized controlled trial. *JAMA* 2002; 288:321-333.
- ¹³ Clarke CA et al. Recent declines in hormone therapy utilization and breast cancer incidences: Clinical and population-based evidence. *Journal of Clinical Oncology*. 2006; Nov. Online at: <http://jco.ascopubs.org/cgi/reprint/24/33/e49.pdf> Downloaded April 10, 2007.
- ¹⁴ Abramson J. *Overdosed America: The broken promise of American medicine*. New York: Harpercollins, 2004: 132 and see also section C.e) Miscarriage, Birth Defects, and Breast Feeding below.
- ¹⁵ Abramson, 2004:131-132.
- ¹⁶ Raphael D. Bridging the gap between knowledge and action on the social determinants of cardiovascular disease: How one Canadian community effort hit – and hurdled – the lifestyle wall. *Health Education*. 2003; 103(3):177-189.
- ¹⁷ Moynihan R & Cassels A. *Selling sickness: How the world's biggest pharmaceutical companies are turning us all into patients*. Vancouver: Greystone Books, 2005.
- ¹⁸ Miller KA, Siscovick DS et al. Long-term exposure to air pollution and incidence of cardiovascular events in women. *NEJM*. 2007; 356(5):447-458: 456.
- ¹⁹ Kannel WB. The role of cholesterol in coronary atherogenesis. *Medical Clinics of North America*. 1976; 58:363-379.
- ²⁰ Ravnskov U. *The cholesterol myths*. Washington: New Trends, 2000.
- ²¹ Abramson, 2004:134.
- ²² Kanjilal S, Gregg, EW, Cheng YJ, Zhang P, Nelson DE, Mensah G, and Beckles GL. Socioeconomic status and trends in disparities for 4 major risk factors for cardiovascular disease among US adults, 1971-2002. *Archives of Internal Medicine*. 2006; 166(21):2348-2355.
- ²³ Daviglius Daviglius M et al. Favourable cardiovascular risk profile in young women and long term risk of cardiovascular and all-cause mortality. *JAMA*; 2004, 292(13):1588-1592.
- ²⁴ Term coined by Aasim Hasany, Medical Anthropology student, University of Toronto, 2006.
- ²⁵ Expert Panel on the Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive summary of the third report of the National Cholesterol Education Program (NCEP) on

the Expert Panel on the Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). JAMA. 2001; 285:2486-2497.

²⁶ Grundy SM, Cleeman MI, Merx NB, et al. Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel Guidelines. Circulation, 2004; 110:227-239.

²⁷ Abramson, 2004:133.

²⁸ Carey E. Statin drugs must carry health warning. Toronto Star. January 13, 2006.

²⁹ Kirkey S. Cholesterol drug no preventative for women, study says. Montreal Gazette. January 23, 2007.

³⁰ IMS Health Canada. News release: IMS health forecasts 5 to 6% growth for global pharmaceutical market in 2007. Online at:

www.imshealth.com/web/content/0,3148,77303623_63872702_77770096_79210240,00.html

Downloaded April 10, 2007.

³¹ IMS Health Canada. Drug treatment insights: cholesterol reducers among the world's top prescribed medication. 2006.

³² IMS. Estimated number of prescriptions dispensed from Canadian retail pharmacies for statins for women by 5-year age cohorts. 2006. [unpublished data set].

³³ Statistics Canada Demography Division. Annual demographic statistics. Ottawa: Ontario, 2005. no 90-212.

³⁴ Zhou Z et al. Effectiveness of statins for secondary prevention in elderly patients after acute myocardial infarction: an evaluation of class effect. CMAJ. 2005; 172(9):1187-1194; Hayward RA, Hofer TP and Vijan S. Narrative review: lack of evidence for recommended low-density lipoprotein treatment targets: A solvable problem. Annals of Internal Medicine. 2006; 145(7):520-530; Thavendiranathan P, Baqai A, Brookhart MA and Choudry NK. Primary prevention of cardiovascular diseases with statin therapy. Archives of Internal Medicine. 2006; 166(21):2307-2313.

³⁵ Wright JM. Are the benefits of statins a class effect? CMAJ. 2005; 172(9):1195-1196.

³⁶ Pasternak RC et al. ACC/AHA/NHLBI Clinical advisory on statins. Journal of the American College of Cardiology. 2002; 40(3):562-72: 570.

³⁷ IMS Health Canada News. Retail prescriptions grow at record level in 2003. 2003.

³⁸ Health Canada. Warning: Updated safety information about Crestor. 2004. Online at: www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/2004/2004_34_e.html Downloaded April 10, 2007.

³⁹ AstraZeneca. Public Advisory. 2005. Online at:

www.astrazeneca.ca/documents/en/news/FINALPACRESTOR%20March%208%202005%20AZ%20v10.0.pdf Downloaded April 10, 2007.

⁴⁰ Health Canada. Health Canada advises patients about the risks of CRESTOR® (rosuvastatin). 2005. Online at: www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/2005/2005_10_e.html Downloaded April 10, 2007.

⁴¹ Health Canada: Health Canada advises consumers about important safety information on statins. July 12, 2005. Online at: www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/2005/2005_77_e.html Downloaded April 10, 2007.

⁴² Smith MA, Cox ED, Bartell JM. Overprescribing lipid lowering agents. Qual Saf Health Care. 2006; 15:251-257.

⁴³ Napoli M. Statin treatment guidelines: 198 to 1 odds that the drug won't help. 2006. Online at: www.medicalconsumers.org/pages/statin-treatmentguidelines.htm Downloaded April 10, 2007;

Grady D et al. Results of systematic review of research on diagnosis and treatment of coronary heart disease in women. Agency for Healthcare Research and Quality. US Department of Health and Human Services. May 2003. www.ahrq.gov Publication no. 03-E035.

- ⁴⁴ Albert CM, Chae CU, Grodstein F et al. Prospective study of sudden cardiac death among women in the United States. *Circulation*. 2003; 107:2096-2101.
- ⁴⁵ See Figure 1 (p. 2161) Tikhonoff V. et al. Low-density lipoprotein cholesterol and mortality in older people. *Journal of the American Geriatrics Society*. 2005; 53:2159-2164.
- ⁴⁶ Ulmer H, Kelleher C, Diem G et al. Why Eve is not Adam: Prospective follow-up in 149,650 women and men of cholesterol and other risk factors related to cardiovascular and all-cause mortality. *Journal of Women's Health*. 2004; 13(1):41-53.
- ⁴⁷ Walsh JME & Pignone M. Drug treatment of hyperlipidemia in women. *JAMA*. 2004; 291:2243-2252.
- ⁴⁸ Walsh & Pignone, 2004: 2245-2247.
- ⁴⁹ Adapted from Table 1, Walsh & Pignone, 2004:2246.
- ⁵⁰ Walsh & Pignone, 2004:2243.
- ⁵¹ Walsh & Pignone, 2004:2250.
- ⁵² See Table 3. Savoie E & Kazanjian A. Utilization of lipid-lowering drugs in men and women: A reflection of the research evidence? *Journal of Clinical Epidemiology*. 2002; 55:95-101.
- ⁵³ Therapeutics Initiative. Do statins have a role in primary prevention? *Therapeutics Letter* 48. 2003. Online at: www.ti.ubc.ca/PDF/48.pdf Downloaded April 10, 2007.
- ⁵⁴ ALLHAT officers. Major outcomes in high risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blockers vs diuretic: The antihypertensive and lipid-lowering treatment to prevent heart attack trial (ALLHAT). *JAMA*. 2002; 288(23):2981-2297.
- ⁵⁵ Abramson, 2004:144-145.
- ⁵⁶ Abramson, 2004:144.
- ⁵⁷ Abramson, 2004.
- ⁵⁸ Cannon C et al. Intensive vs. moderate lipid-lowering with statins after acute coronary syndromes (PROVE IT). *New England Journal of Medicine*. 2004; 350(15):1495-1504.
- ⁵⁹ Hayward RA, Hofer TP and Vijan S. Narrative review: lack of evidence for recommended low-density lipoprotein treatment targets: A solvable problem. *Annals of Internal Medicine*. 2006; 145(7):520-530.
- ⁶⁰ See, for example, Cannon et al, 2004; Baigent C et al. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90 056 participants in 14 randomized control trials. *Lancet*. 2005; 366:1267-1278.
- ⁶¹ Hayward et al, 2006: 520.
- ⁶² Hayward et al, 2006: 520.
- ⁶³ Thavendiranathan et al, 2006.
- ⁶⁴ Abramson J & Wright J. Are lipid-lowering guidelines evidence-based? *The Lancet*. 2007; 369 (January 20):168-169.
- ⁶⁵ Walsh & Pignone, 2004.
- ⁶⁶ Walsh & Pignone, 2004:2243.
- ⁶⁷ Abramson, 2004.
- ⁶⁸ Calculated from Table 3, Walsh and Pignone, 2004:2249.
- ⁶⁹ See Table 3, Walsh & Pignone, 2004:2249.
- ⁷⁰ Walsh & Pignone, 2004: 2249.
- ⁷¹ Abramson, 2004:141.
- ⁷² Shepherd J. et al. Pravastatin in elderly individuals at risk of vascular disease (PROSPER): a randomized controlled trial. *The Lancet*. 2002; 360(23):1623-1630.
- ⁷³ See Table 2, Shepard et al, 2002:1625.
- ⁷⁴ Shepard et al, 2002: 1626.

- ⁷⁵ Roberts M. Statin-fortified drinking water. BBC News Online, August 1, 2004. Online at: <http://news.bbc.co.uk/2/hi/health/3931157.stm> Downloaded April 10, 2007.
- ⁷⁶ Bays H. Statins, cardiovascular disease and drug safety—2005. *American Journal of Cardiology*. 2006; 97 (8A):1C-94C.
- ⁷⁷ Health Canada. About adverse reaction reporting. Online at: www.hc-sc.gc.ca/dhp-mps/medeff/report-declaration/about-apropos/index_e.html Downloaded April 10, 2007.
- ⁷⁸ Abramson and Wright, 2007.
- ⁷⁹ Dr. James Wright, personal communication, April 24 2007.
- ⁸⁰ Law MR et al. Quantifying effect of statins on low density lipoprotein cholesterol, ischaemic heart disease, and stroke: Systematic review and meta-analysis. *BMJ*. 2003; 36:1423.
- ⁸¹ Golomb B et al. Conceptual foundations of the UCSD Statin Study: A randomized controlled trial assessing the impact of statins on cognition, behavior, and biochemistry. *Arch. Intern Med*. 2004; 164(2):153-162.
- ⁸² Golomb B. Severe irritability associated with statin cholesterol-lowering drugs. *QJMed*. 2004; 97:229-235.
- ⁸³ Golomb cited in Barnum B. Doubts raised on wider sales of statins: Over-the-counter marketing push for cholesterol drug. SFGate.com, 2005. Online at: www.sfgate.com Downloaded April 10, 2007.
- ⁸⁴ Andrew Herxheimer cited Cohen J. What you must know about statin drugs and their natural alternatives. Garden City, NY: Square One Publishers, 2005:82.
- ⁸⁵ Hope S. Frequently asked questions (FAQ) about statin adverse events. 2005. Online at: www.freewebs.com/stopped_our_statins/StatinFAQ_031305wTOCv4.pdf Downloaded April 10, 2007.
- ⁸⁶ Pugh MB et al (eds.). *Stedman's Medical Dictionary 28th Edition*. Baltimore, MD: Lippincott Williams & Wilkins. 2006.
- ⁸⁷ Pugh et al, 2006.
- ⁸⁸ Fuller C. Women and adverse drug reaction reporting in the Canadian context. *Women and Health Protection*. 2003. Online at: www.whp-apsf.ca Downloaded April 10, 2007.
- ⁸⁹ DES Action Canada in collaboration with Women and Health Protection. How safe are our medicines? Monitoring the risks of drugs after they become approved for marketing. 2003. Online at: www.whp-apsf.ca Downloaded April 10, 2007.
- ⁹⁰ Abramson, 2004:220-232.
- ⁹¹ Abramson, 2004:228-232.
- ⁹² Abramson, 2004:228-232.
- ⁹³ Tomlinson S & Mangione K. Potential adverse effects of statins on muscle. *Physical Therapy*. 2005; 85(5):460.
- ⁹⁴ Tomlinson & Mangione, 2005:464.
- ⁹⁵ Dirks A, Jones KM. Mitochondrial modeling and function: statin-induced apoptosis and skeletal myopathy. *Am. J Physiology*. 2006; 291:C1208-C1212.
- ⁹⁶ Dirks & Jones, 2006.
- ⁹⁷ Needham M. et al. Progressive myopathy with up-regulation of MHC-I associated with statin therapy. *Neuromuscular Disorders*. 2007; 17(1):194-200.
- ⁹⁸ Vladutiu GD et al. Genetic risk factors associated with lipid lowering drug-induced myopathies. *Muscle and Nerve*. 2006; 34(2):153-162.
- ⁹⁹ de Lau LM, Koudstaal PJ, Hofman A, Breteler MM. Serum cholesterol levels and the risk of Parkinson's disease. *American Journal of Epidemiology*. 2006; 164(10):998-1002.
- ¹⁰⁰ New study to test statin-Parkinson's link. *Medical News Today*. Jan 17, 2007. Online at: www.medicalnewstoday.com Downloaded April 10, 2007.
- ¹⁰¹ Newman TB, Huley SB. Carcinogenicity of lipid-lowering drugs. *JAMA*. 1996; 275(1):55-60.

- ¹⁰² Newman & Huley, 1996.
- ¹⁰³ Baigent et al, 2005.
- ¹⁰⁴ Baigent, 2005:1273.
- ¹⁰⁵ Baigent, 2005:1273.
- ¹⁰⁶ Shepard et al, 2002.
- ¹⁰⁷ See Table 4, Shepard et al, 2002:1628.
- ¹⁰⁸ Lewis S. et al. Effect of pravastatin on cardiovascular events in women after myocardial infarction: The cholesterol and recurrent events (CARE) trial. *J Am Coll Cardiol.* 1998; 32:140-146.
- ¹⁰⁹ Bonovas S et al. Use of statins and breast cancer: a meta-analysis of seven randomized clinical trials and nine observational studies. *Journal of Clinical Oncology.* 2005; 23(34):8606-8612.
- ¹¹⁰ Davidson MH et al. A comparison of estrogen replacement, pravastatin, and combined treatment for the management of hypercholesterolemia in postmenopausal women. *Arch Internal Med.* 1997; 157:1186-92.
- ¹¹¹ See Table 7, Hayes, 2006:1338; Genest et al, 2003.
- ¹¹² Beck P et al. Statin use and the risk of breast cancer. *Journal of Clinical Epidemiology.* 2003; 56:280-285.
- ¹¹³ Beck et al, 2003:284.
- ¹¹⁴ IMS. Estimated number of prescriptions dispensed from Canadian retail pharmacies for oral contraceptives for females. 2006. [unpublished data set].
- ¹¹⁵ Simonson SG et al. The effect of rosuvastatin on oestrogen and progestin pharmacokinetics in healthy women taking an oral contraceptive. *British Journal of Clinical Pharmacology.* 2004; 57:279.
- ¹¹⁶ See Table 1, Beck et al, 2003:282.
- ¹¹⁷ IMS. Estimated number of prescriptions dispensed from Canadian retail pharmacies for HRTs for females. 2006. [unpublished data set].
- ¹¹⁸ Merck cited in Mechatie, E. Panel rejects OTC version of statin. *OB GYN News.* 2005; 40(4).
- ¹¹⁹ Rubin R. Statins: A risk to your baby? *USA Today.* Dec 12, 2005. Online at: www.usatoday.com/news/health/2005-01-12-statins-risk_x.htm Downloaded April 10, 2007.
- ¹²⁰ Rubin, 2005.
- ¹²¹ Schwarz EB et al. Prescription of teratogenic medications in United States ambulatory practices. *The American Journal of Medicine.* 2005; 118:1240-1249.
- ¹²² Edison RJ, Muenke M. Mechanistic and epidemiological considerations in the evaluation of adverse birth outcomes following gestational exposure to statins. *American Journal of Medical Genetics.* 2004; 131A:287-298.
- ¹²³ See Table 2, Edison & Muenke, 2004.
- ¹²⁴ Edison & Muenke, 2004:293.
- ¹²⁵ Kenis I. et al. Simvastatin has deleterious effects on human first trimester placental explants. *Human Reproduction.* 2005; 20(10):2866-2872.
- ¹²⁶ Prescrire. November 2005, 25(266):748-749.
- ¹²⁷ Opitz JM, Gilbert-Barness E, Ackerman J et al. Cholesterol and development: The RSH (“Smith-Lemli-Opitz”) syndrome and related conditions. *Pediatr Path Mol Med.* 2002; 21(2):153-81.
- ¹²⁸ Laise E. The lipitor dilemma. *Smart Money: The Wall Street Journal.* Nov 2003.
- ¹²⁹ National Coordinating Group on Health Care Reform and Women. Women and home care. 2002. Winnipeg: National Coordinating Group on Health Care Reform and Women. Online at: www.cewh-cesf.ca Downloaded April 10, 2007.

- ¹³⁰ See, for comparison, Rosenberg H. From trash to treasure: Housewife activists and the environmental justice movement. In *Articulating hidden histories: Exploring the influence of Eric R. Wolf, Jane Schneider and Rayna Rapp*, eds. Pp.190-204. Berkeley: University of California Press, 1995.
- ¹³¹ Gilbody S, Wilson P. & Watt DI. Benefits and harms of direct to consumer advertising: A systematic review. *Quality and Safety in Health Care*. 2005; 14:246-250.
- ¹³² Community Catalyst. Prescription access litigation project. Online at: www.prescriptionaccess.org/index.php?doc_id=941 Downloaded April 10, 2007.
- ¹³³ ConsumerAffairs.com. Suit charges Pfizer misled seniors about Lipitor. September 29, 2005. Online at: www.consumeraffairs.com/printme.php?url=/news04/2005/lipitor_suit.html Downloaded April 10, 2007.
- ¹³⁴ Heart and Stroke Foundation. What you need to know, June 26, 2002. Online at: ww2.heartandstroke.ca/Page.asp?PageID=1562&ArticleID=1371&Src=&From=SubCategory Downloaded April 10, 2007.
- ¹³⁵ Batt S. Marching to different drummers: Health advocacy groups in Canada and funding from the pharmaceutical industry. *Women and Health Protection*, 2005:3. Online at: www.whp-apsf.ca Downloaded April 10, 2007.
- ¹³⁶ Cholesterol Guidelines Analysis Group (C-Gag). Petition to the National Institutes of Health seeking an independent review panel to re-evaluate the National Cholesterol Education Program guidelines, 2004. Online at: <http://cspinet.org/new/pdf/finalnihltr.pdf> Downloaded April 10, 2007.
- ¹³⁷ Manuel DG et al. The 2003 Canadian recommendations for dyslipidemia management: Revisions are needed. *Canadian Medical Association Journal*. 2005; 172(8):92-114.
- ¹³⁸ Abramson, 2004; Cholesterol Guidelines Analysis Group, 2004.
- ¹³⁹ Abramson & Wright, 2007:169.
- ¹⁴⁰ Mintzes B. Drug regulatory failure in Canada: The case of Diane-35. *Women and Health Protection*, 2005.
- ¹⁴¹ Mintzes, 2005.
- ¹⁴² Ioannidis J. Evolution and translation of research findings: From bench to where? *PLoS Clinical Trials*. 2006; 1(7) e36:1-6.
- ¹⁴³ Ioannidis, 2006.
- ¹⁴⁴ Shepherd J et al for the West of Scotland Coronary Prevention Study Group. Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. *N.Engl.J.Med*. 1995; 333(20):1301-1307.
- ¹⁴⁵ Abramson, 2004:136.
- ¹⁴⁶ Manuel, Douglas G., Kwong, Kelvin, Tanuseputro, Peter et al. Effectiveness and efficiency of different guidelines on statin treatment for preventing deaths from coronary heart disease: modelling study. *British Medical Journal*. 2006; 332:1419 (17 June.)
- ¹⁴⁷ Manuel et al, 2006.
- ¹⁴⁸ Downs JR et al for the AFCAPS/TexCAPS research group. Primary prevention of acute coronary events with lovastatin with men and women with average cholesterol levels: Results of AFCAPS/TexCAPS. *JAMA*. 1998; 279(20):1615-1622.
- ¹⁴⁹ Health Canada. Gender-based analysis. 2005. Online at: www.hc-sc.gc.ca/hl-vs/women-femmes/gender-sexe/index_e.html Downloaded April 10, 2007.
- ¹⁵⁰ Health Canada, 2005.
- ¹⁵¹ Canadian Institutes for Health Research. Gender and sex-based analysis in health research: A guide for CIHR peer review committees, 2006. Online at: www.irsc.gc.ca/e/32019.html Downloaded April 10, 2007.
- ¹⁵² Grady D et al. Results of systematic review of research on diagnosis and treatment of coronary heart disease in women. Agency for Health Care Research and Quality. Evidence

Report/Technology Assessment 80. 2003. Online at:
www.ahrq.gov/clinic/epesums/chdwtopsum.pdf Downloaded April 10, 2007.

¹⁵³ Mintzes, 2005.

¹⁵⁴ Batt, 2005:20.

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Copies of this publication can be downloaded from www.whp-apsf.ca/en/index.html or ordered free from:

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