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Harriet Rosenberg a, Danielle Allard b

a Health and Society Program, Division of Social Science, York University, Toronto, Ontario, Canada
b Faculty of Information Studies, University of Toronto, Toronto, Ontario, Canada

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ORIGINAL ARTICLE

Women and statin use: A women’s health advocacy perspective

HARRIET ROSENBERG1 & DANIELLE ALLARD2

1 Health and Society Program, Division of Social Science, York University, Toronto, Ontario, Canada, and 2 Faculty of Information Studies, University of Toronto, Toronto, Ontario, Canada

Abstract

This paper is based on a longer report on the benefits, safety and modalities of information representation with regard to women and statin use, situated within the historical context of Women’s Health Movement which has advocated for unbiased, appropriate medical research and prescribing for women based on the goals of full-disclosure, informed consent, evidence-based medicine and gender-based analysis. The evidence base for prescribing statins for women, especially for primary prevention is weak, yet Canadian data suggest that half of all prescriptions are for women. Safety meta-analyses do not disaggregate for women; do not consider female vulnerability to statin induced muscle problems, and women-centred concerns such as breast-cancer, miscarriage or birth defects are under-researched. Many trials have not published their non-cardiac serious adverse event data. These factors suggest that the standards of full-disclosure, informed consent, evidence-based prescribing and gender-based analysis are not being met and women should proceed with caution.

Key words: Statins, women, cholesterol lowering

For four decades the women’s health movement has advocated for unbiased, appropriate medical research and prescribing for women based on the goals of full-disclosure, evidence-based medicine and gender-based analysis. Women’s “knowledge advocacy” has led to bodies of investigatory, watchdog, and advice literature dedicated to the critical examination of biomedical practices as applied to women.

Within this critical historical framework, women’s health advocates are turning their attention to the cholesterol hypothesis and statin use for women. For example, in the United States, the National Women’s Health Network’s 2007 overview has concluded not only that statins are over-sold, but also that their benefits have not been sufficiently proven to justify such large-scale use (1).

The authors of Our Bodies, Ourselves, the worldwide multi-million publication, also express strong reservations about statin therapy. Their research questions the emphasis on cholesterol levels as a premier indicator of heart disease risk for women, the evidence base for statin use, and raises concerns about conflict-of-interest in the U.S. cholesterol guidelines. They caution: “Women and health care providers are being misled by such guidelines, which often are developed by experts with financial ties to drug makers (2).” An overview of the Center for Medical Consumers’ newsletters indicates that their analysis of primary prevention trials does not demonstrate evidence of benefit to women from statin therapy and concern that consumers do not have the full story of harm because virtually all the major trials are industry sponsored and have not released their non-cardiac data despite repeated requests by scientists to do so (3).

In Canada, Women and Health Protection and the Canadian Women’s Health Network have also expressed grave reservations about the promotion of statins to women. Women and Health Protection commissioned a report to investigate the evidence base for claims of benefit and safety concerning women and statin use. An adapted version of that report, entitled Evidence for Caution: Women and Statin Use (4) appears below.
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 and are less likely to be recognized or acted on. In general, women have a higher risk of death after a heart attack, especially younger women. In Canada, it is not until women are in their 80s that heart disease becomes the number one cause of death. Women between the ages of 30 and 79 are most likely to die of cancer. Heart disease and stroke in younger people are much more likely to occur in men and the death rate due to heart disease among women is currently only about half that for men.

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 hormonal drugs for menopausal women (5). However, in 2002, the Women’s Health Initiative found that Hormone Therapy was not cardio-protective for women—indeed the opposite was true. Current emphasis on cholesterol control and the use of cholesterol-lowering drugs invites similar investigation.

Cholesterol

Cholesterol is vital to the body and necessary for many crucial functions including: brain function, hormone development, bile salt production and digestion, Vitamin D synthesis, cell wall structure, and nerve cell signal transmission. It is critical in foetal development and an essential component of breast milk. Nevertheless, cholesterol is popularly portrayed as a virtual pathogen and high cholesterol as a disease in itself. While there are many modifiable and non-modifiable risk factors associated with cardiovascular disease, such as age, sex, smoking, diet and weight, family history, stress, socio-economic factors, and air pollution, high cholesterol is considered the most important.

Cholesterol lowering in women

In 2003, an AHRQ review of healthcare research on women and heart disease stated that there was insufficient evidence to determine whether lowering lipid levels by any method reduced the risk of heart attack or stroke because women were under-represented in trials. Other US research indicates that high cholesterol in women is not a risk factor, either for coronary death, sudden cardiac death or all-cause mortality (6,7).

In women over 50, low cholesterol is a risk factor for cancer and early death. Prospective research on seniors in Italy found that for women, elevated LDL cholesterol was associated with longevity and inversely associated with heart disease. Likewise, an Austrian study, which compared cholesterol and health outcomes for over 80 000 women and 67 000 men over a 15-year period, found that high cholesterol in women was not a predictor of cardiovascular events or stroke after age 50; whereas, low cholesterol was associated with higher death rates from cancer, liver disease, and mental illness. Their research confirmed five previous studies (including Framingham), which found that high cholesterol was not a strong predictor of cardiovascular problems in older women (and men). Thus the hypothesis of cardiac benefit to women of all ages through cholesterol-lowering drugs requires careful scrutiny.

Statin trials and women: A meta-analysis by Walsh and Pignone

In a meta-analysis Walsh and Pignone evaluated data for women from clinical trials of statins and non-statin drugs (8). They, like previous analysts, found a weak evidence base and failures to disaggregate data for women in key trials. Indeed, 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 ALLHAT (Table I).

Walsh and Pignone’s analysis did not find a high quality evidence based rationale for statin therapy for primary prevention and did not find that the

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

Table I. Representation of women in key primary prevention statin trials (derived from Walsh and Pignone).
Evidence extant demonstrated that lowering cholesterol reduced mortality. They concluded that in primary prevention, lipid lowering does not affect total or CHD mortality, and that current evidence is insufficient to determine if it may reduce non-fatal events. Their result is crucial because 75% of female users are in this category.

Earlier evaluations of primary prevention benefit for women

Similar results came from the Therapeutics Initiative review that included a total of 10,990 women (9). Also, Abramson’s detailed analysis of the ALLHAT primary prevention trial, which included men and women who were targeted to reduce cholesterol levels in line with 2001 US guidelines with statin therapy, did not find mortality benefit, either for women or men, or seniors with or without heart disease (10). Additionally, problems of extrapolating benefit from male-centred trials to women are of concern. For example, US guideline writers cite the WOSCOPS trial as evidence, despite the fact that it did not contain women.

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 claimed advantages for high dosage statins and an “aggressive lipid lowering strategy” based on the PROVE-IT trial, which compared different statins at different dosages. The press, advertisers, and many physicians stated that this and other research demonstrated that there were primary prevention benefits for ultra-low LDL levels. Advertising for Crestor, often featuring women contained downward pointing arrows and repeated statements that “it’s all about the numbers.” Additionally, the 2004 US National Cholesterol Education Program (NCEP) widely used guidelines recommended aggressive lipid lowering for primary prevention in women.

However, meticulous reviews of the science behind the influential 2004 NCEP guidelines add considerable evidence for caution with regard to aggressive interventions. Hayward and colleagues scrutinized all the published medical research that was used to claim an evidence based benefit for ultra-low LDL cholesterol levels (11). Their meta-analysis (data for women not disaggregated) found that, for high risk primary prevention, the evidence underpinning the US guidelines did not substantiate the 2004 pronouncement “…that for every 1% reduction in LDL-C levels relative risk for major CHD events is reduced approximately 1%.”

Women and secondary prevention trials

Walsh and Pignone’s overview identified five secondary prevention statin trials with information on women (Table II). Despite requests from researchers, only three of the trials have released data for all-cause mortality (4S, PLAC 11, LIPID) and these showed no evidence of a reduction. HPS, with approximately half the total number of women in secondary trials, has not released coronary mortality data separately from events. In those trials that released data coronary mortality was reduced. Walsh and Pignone are among many scientists and health advocates to urge the release of non-coronary adverse event data to help clarify the association between lowering cholesterol mortality and other serious adverse events. They concluded that for women with known cardiovascular disease, treatment of hyperlipidemia is effective in reducing CHD events, CHD mortality, non-fatal myocardial infarction, and revascularization, but that it does not affect total mortality.

Similarly, Abramson’s assessment of three secondary prevention trials that included women found that the 4S and the CARE trials showed a reduction of non-fatal events in women, but not of total mortality (12), whereas the LIPID trial failed on both outcomes. Overall, 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% or about 0.8% per year, but no effect was seen for total mortality.

In 2002, the PROSPER trial looked at high risk seniors after age 70. The study included

![Table II. Representation of women in key secondary prevention statin trials (derived from Walsh and Pignone).](image-url)
approximately 3000 women and 2500 men. After about three years, total mortality for both men and women was similar in the placebo group (10.5%) and the treatment group (10.3%) as was the number of non-fatal events, both for men and women.

Assessing the safety of statins

Statins have commonly been described as so safe they should be in the drinking water. Evaluating the safety of statin therapy for women is particularly difficult; however, little research has explicitly proceeded from a gender-based perspective. An example of this failure 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 report 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, but did suggest in a brief phrase that small-framed or frail women might be vulnerable. Another recent safety review by Armitage did not disaggregate for women either (13), and neither of them commented on the failure of most key statin trials to publish non-cardiac adverse event data.

Below we focus on several hallmark issues of concern to women, but our full report discusses the issues of adverse events reporting, post-marketing surveillance, conflict-of-interest and the impacts of impairments and burden of care on women who look after statin impaired partners.

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. Exercise is thus an important element in women’s cardiac health and concerns that statins may lead to exercise intolerance is a hallmark issue.

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 myopathy and weakness suggested that women may be especially at risk. The authors raised important concerns about whether exercise is actually contraindicated for people weakened by statin exposure. They describe statin-impaired patients who presented 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.” (14) The tendency of physicians to discount patient reports of possible statin adverse events is pronounced and may result in low reporting rates and contribute to delays in the identification of ADRs (15). Furthermore, discontinuation of statins may not resolve muscle and cognitive impairments.

Breast cancer

There is a body of literature from animal studies and from the use of pre-statin cholesterol-lowering drugs in humans which points to an association between low cholesterol and cancer. Several problems have made research into determining the relationship between cancers and statins difficult, including: 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 statistical 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 6) under-representation of women in meta-analyses.

Concern associating breast cancer and statin exposure emerged in relation to two trials. The PROSPER study (ages over 70) reported a 25% statistically significant increase of new cancers over-all, including more first breast cancer diagnoses in the treatment (n=18) than in the placebo group (n=11), but gave no data on cancer recurrences or deaths. The CARE study, which included younger women (average age 61), reported a 12-fold statistically significant increase in the incidences of breast cancer in statin users when compared to the placebo.

A meta-analysis of breast cancer in seven clinical trials and nine observational studies in 2005 by Bonovas and colleagues assessed whether statin exposure enhances protection from breast cancer or whether it increases the risk. They found a neutral effect, (the PROSPER trial was not included) but urged 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.
Statins and concomitant use of hormonal drugs

Another issue of concern for women is the combined effects of taking statins with hormone therapy or oral contraceptives. This area is under-researched, particularly with respect to cancer. Hormone therapy drugs lower cholesterol. Prior to 2002, concomitant use of statins and hormones was advised, but current guidelines now list hormone therapy as contraindicated for prevention of cardiovascular disease. There is reason for concern because an 8–9 year long study of 13,592 Saskatchewan (Canada) women exposed to statins and Hormone Therapy by Beck et al. found a statistically significant doubling of breast cancer (16).

No such risk was found by AstraZeneca in a short duration study where oral contraceptives were used with their statin drug Crestor. However, a 2008 U.S. print advertisement for Crestor notes that concomitant use of Crestor and birth control pills with ethinyl estradiol or norgestrel should be discussed with a health care professional. Despite lack of evidence for efficacy and safety, young women are being prescribed both birth control pills and statins, signalling to advocates the need for urgent research into long term combined use.

Miscarriage and birth defects

It has been estimated that between 500,000 and 800,000 women of childbearing age in the US were taking statins in 2004. It is therefore important to understand that younger women who may become pregnant while taking statins are faced with risks of miscarriage, birth defects, and infant development problems.

Hearings were held (2004) in the US on an application by Merck to determine whether Mevacor should be sold over-the-counter. Vigorous opposition came from representatives from the March of Dimes, the Organization of Teratology Information Services, and researchers Edison and Muenke among others. Testimony at the hearings indicated that half of all pregnancies are unplanned, that a woman might unknowingly already be pregnant while being exposed to a statin, and that, given increasing maternal age, there is an expanded age-range of risk of pregnancy while exposed to statins.

The research on statins and birth defects is also a hallmark signal for caution. In 2004, Edison and Muenke published their assessment of 22 cases of babies born with birth defects whose mothers had been taking statins in their first trimester (17). They included facial malformations, intrauterine foetal death, and severe intrauterine growth restriction. There were five central nervous system anomalies and five limb deficiencies. Two anomalies with limb deficiencies also had multiple malformations, including anomalies of three or more of the following: vertebral, anal, cardiac, tracheo-esophageal, and renal structures. They estimated that the latter malformations occur in between one in 50,000 to one in 500,000 cases in non-statins-exposed pregnancies. That only 6,636 pregnant women may have been exposed to statins in the US in the year 2000 is a strong indication that these malformations were caused by statin exposure. Larger databases may detect higher rates of foetal exposure and the need for more studies to track this tip-of-the-iceberg issue. Other research indicates that isolated placenta cells are harmed by exposure to the statin simvastatin, and may result in miscarriage and birth defects linked to impaired implantation.

Low cholesterol levels in infant formula raise 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 g of edible milk, while some formulas have only 1 or 2 mgs of cholesterol. Health Canada has therefore issued an advisory against lowering cholesterol through statin use while breast-feeding.

Credibility scale for gender-based analysis

It has been suggested that the best way to gauge the value of scientific research is not statistical significance but credibility. For example, some studies have found statistically significant elevated breast cancer rates with statin exposure and others have not. A goal for gender based analysis would be to proactively initiate credible research that squarely addresses the possible statin-cancer link. Women’s health advocates are also concerned about biases in research which fail to proactively pursue the hallmark issues described above, the proliferation of poor quality research (“popcorn studies”) which seem to be designed to confuse rather than shed light on crucial issues, and the shaping of prescribing practices not linked to evidence but to industry persuasion practices.

In terms of statin research on women, advocates ask that evidence based medicine be combined with gender based analysis to develop a credibility scale which would reassess past trials, undertake new research, and issue unbiased guidelines. This model should report number needed to treat and absolute risks; should not extrapolate from research done on men; should identify and support research for hallmark issues of specific concern to women, and include important sub-group analysis of women by gender.
age, socio-economic status, physical condition, ethnicity and race.

The Canadian government already supports gender-based analysis recognizing that it results in better evidence. The Canadian Institutes for Health Research, the Government of Canada’s health research funding agency, has also recently introduced guidelines based on gender analysis for researchers and peer reviewers (18). The US Agency for Healthcare Research and Quality has made similar recommendations (19).

Conclusion

The lessons learned from the Women’s Health Movement suggest 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. A 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 a 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. She should feel confident that information about any risks will be explained to her in meaningful and accessible language. With regard to women and statin use, these expectations have not been met. Instead we have found a pattern of overestimation of benefit and underestimation of harm.

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We dedicate this paper to the memory of Barbara Seaman, a founder of the women’s health movement, whose life’s work has inspired our efforts.

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