Title: Discontinuation of Statin Therapy in Primary Prevention Patients who Have Achieved Normal Lipid Levels: Guideline and Clinical Effectiveness Review

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Context and policy issues:

Coronary heart disease (CHD) is a major cause of morbidity and mortality in North America. HMGCoA reductase inhibitors (also known as statins) can be prescribed to lower a patient’s risk of developing CHD. It is approved for the treatment of dyslipidemia in addition to dietary modifications when response to dietary and other non-pharmacologic measures have not had adequate impact on lipid levels. The statins currently approved for use in Canada include atorvastatin, fluvastatin, lovastatin, pravastatin, rosuvastatin, and simvastatin.

Patients can be prescribed statins for primary prevention of cardiovascular disease. That is, a patient with dyslipidemia who is at risk of cardiovascular disease. Some patients taking statins for primary prevention achieve normal lipid levels when statin therapy is added to diet modification. It is unknown whether normal lipid levels can be maintained by diet modification alone if statin therapy is discontinued.

Research question:

Can normal lipid levels be maintained with diet modification alone in patients taking statin therapy for primary prevention of cardiovascular disease if statin therapy is discontinued?

Methods:

A limited literature search was conducted on key health technology assessment resources, including PubMed, The Cochrane Library (Issue 4, 2007), University of York Centre for Reviews.
and Dissemination (CRD) databases, ECRI, EuroScan, international HTA agencies, and a focused Internet search. Results include articles published between 2002 and the present, and are limited to English language publications only. Filters were applied to limit the retrieval to health technology assessments, systematic reviews, meta-analyses, practice guidelines, randomized controlled trials, and observational studies.

Abstracts and full articles were scanned (by one reviewer) for mention of the effect of discontinuation of statin therapy on lipid levels. Studies that focused on subgroups of patients such as those with renal disease, metabolic syndrome, diabetes, and familial hypercholesteremia were excluded.

**Summary of findings:**

No relevant health technology assessments, systematic reviews, systematically conducted meta-analyses, randomized controlled trials, or guidelines were found. Two observational studies were found that addressed statin discontinuation.

In 2006, Li and colleagues\(^3\) published a case series report that included 17 patients with hyperlipidemia taking pravastatin. The 11 women and 6 men were given 40 mg/day of pravastatin for six weeks, upon which treatment was abruptly terminated to track the changes in plasma inflammatory markers. C-reactive protein and interleukin-6 were measured immediately before receiving the statin, immediately after termination of the statin therapy and the first, third, and seventh day after statin therapy was discontinued. Lipid levels were measured at the first day of statin therapy, immediately after six weeks of statin therapy, and on the seventh day after statin therapy was discontinued. Findings were presented as mean±standard deviation.

After six weeks of treatment, pravastatin significantly reduced total cholesterol (6.88±0.36 versus 5.7±0.23, \(p<0.01\)) and low density lipoprotein cholesterol (LDL-C) (4.28±0.25 versus 3.06±0.14, \(p<0.01\)) from baseline and significantly increased high density lipoprotein cholesterol (HDL-C) (1.09±0.88 versus 1.22±0.09, \(p<0.05\)) from baseline. The authors reported that after the seventh day of pravastatin being terminated, there were no changes of lipid parameters. However, the authors do not report any data or \(p\) values for these outcome measures.

Significant improvements compared to baseline were reported following six weeks of pravastatin for C-reactive protein (0.28±0.16 versus 0.20±0.08, \(p<0.01\)) and interleukin-6 (8.4±0.6 versus 6.7±0.4, \(p<0.01\)). When measured seven days following discontinuation of pravastatin, these values increased significantly (i.e., rebounded) when compared to the values at the end of six weeks of pravastatin (\(p<0.01\)). At seven days post statin discontinuation, values were similar to the baseline values reported for these two outcomes.

The authors concluded that six weeks of pravastatin significantly modified the lipid profile and decreased two inflammatory markers and that discontinuation of pravastatin therapy induced a rebound phenomenon in these inflammatory markers. However, the outcomes measured have limited applicability of the impact of statin discontinuation on cardiovascular events. In addition, the sample size was quite small and the study design, not being randomized in design, is more susceptible to bias.

One study by Puccetti et al.\(^4\) in 2003 assessed the effects of statin discontinuation in 18 patients previously taking cerivastatin. The patients opted to maintain their diet regimen but not replace cerivastatin, which was withdrawn from the market, with another statin. Findings were presented as mean±standard error.
Patient compliance to the diet was verified by an ad hoc questionnaire and body weight. The daily diet consisted of 1700±100 Kcal, 35 grams of fiber, <200 mg/day of cholesterol, and 30.0% of total calories from fat, 55.0% from carbohydrates, and 15.0% from proteins. Of importance is that these patients, prior to statin treatment, failed to lower their LDL-C by more than 25.0% by dietary modification, which was deemed an ineffective change.

The authors reported that the patients experienced significantly increased LDL-C levels after 28 days of statin therapy cessation (2.84±0.19 at start of cessation compared to 4.19±0.21 after 28 days, p<0.05) as well as 60 days after cessation (2.84±0.19 at start of cessation compared to 4.44±0.23 after 60 days, p<0.001). Statistically significant increases were also seen in the total cholesterol, oxidized low density lipoprotein, P-selectin after 60 days of statin therapy discontinuation (all p<0.01, compared to baseline). As well, platelet aggregation increased after 14 days of cessation (30.4±2.8 to 31.6±2.3 at start of cessation compared to 56.8±4.1 to 59.7±3.8 after 14 days, p<0.05) and this difference continued until 60 days post cessation (30.4±2.8 to 31.6±2.3 at start of cessation compared to 69.1±5.2 to 65.1±5.4 at 60 days p<0.01).

The authors concluded that the raised platelet count alongside the increased LDL-C after discontinuation of statin therapy could contribute to the increased chance of experiencing a cardiovascular event. However, the conclusion is speculative as it is based on intermediary measures. This study was vulnerable to bias as it was not a randomized controlled study and no blinding occurred. In addition, the sample size was small and the last follow-up period reported was 60 days, which is short term. It was unclear whether this study included patients taking cerivastatin for primary or secondary prevention, however, the reported mean lipid levels of the patients fell within the healthy target levels published by the Public Health Agency of Canada.5

Conclusions and implications for decision or policy making:

Two observational studies were identified that assessed the short-term effects of sudden withdrawal of a statin therapy. Neither of these study designs was such that the patients had to achieve normal lipid levels prior to the discontinuation of statin therapy in a controlled, physician-guided manner. Therefore, the summarized studies have limited applicability to the research question for this CADTH report.

In one study, the statin therapy was abruptly discontinued to monitor the effects on two specific inflammatory markers. While patients followed the American Heart Association Step I diet four weeks prior to and during the study, it was not explicitly stated that the patients maintained their diet after the statin therapy was terminated. In the second study, discontinuation of statin therapy was a result of the prescribed statin being withdrawn from the market. The diet was monitored post hoc but no details were reported on how well the diet was adhered to.

While several peer-reviewed articles assessed the effectiveness of statin therapy as an adjunct to diet modification, none investigated whether statin therapy could be successfully discontinued from patients who experienced success in achieving normal lipid levels. Thus, it is impossible to determine whether patients can maintain normal lipid levels by persevering diet modifications alone, after statin therapy has been discontinued.
References:


