# Cost-Effectiveness Analysis of Rosuvastatin Versus Atorvastatin, Simvastatin, and Pravastatin from a Canadian Health System Perspective

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## ABSTRACT

**Objective:** The primary objective of this study was to assess the cost-effectiveness of the most commonly prescribed doses of rosuvastatin, atorvastatin, simvastatin, and pravastatin for managing various lipid parameters in patients with hypercholesterolemia over a 1-year time horizon from a Canadian health care perspective.

**Methods:** Incremental cost-effectiveness ratios (ICERs) were estimated for branded rosuvastatin compared with branded atorvastatin, generic simvastatin, and generic pravastatin in patients with hypercholesterolemia in terms of percent reduction in low-density lipoprotein cholesterol (LDL-C) and total cholesterol (TC)/high-density lipoprotein cholesterol (HDL-C) ratio, as well as in TC, HDL-C, triglycerides (TG), apolipoprotein (Apo) B, the ApoB/ApoA-I ratio, and attainment of the Canadian LDL-C goal. The pharmacoeconomic model was constructed for a 1-year time horizon using efficacy data from a randomized, open-label trial including 2268 adults and the wholesale acquisition costs of branded rosuvastatin and atorvastatin and generic simvastatin and pravastatin in British Columbia.

**Results:** The most commonly prescribed doses of each of the 4 statins in British Columbia were as follows: rosuvastatin 10 mg (75.8% of all rosuvastatin doses); atorvastatin 10 and 20 mg (46.4% and 35.3%, respectively, of all atorvastatin doses); simvastatin 20 and 40 mg (42.5% and 31.8%, respectively, of all simvastatin doses); and pravastatin 20 and 40 mg (55.0% and 34.1%, respectively, of all pravastatin doses). Rosuvastatin 10 mg was dominant (ie, was more effective at a lower cost) relative to atorvastatin 10 and 20 mg, simvastatin 20 and 40 mg, and pravastatin 40 mg in terms of reductions in LDL-C, TC/HDL-C ratio, TC, ApoB, and ApoB/ApoA-I ratio, increases in HDL-C, and attainment of the LDL-C goal. Compared with pravastatin 20 mg, the ICER per percent reduction in LDL-C, TC/HDL-C ratio, TC, TG, ApoB, or ApoB/ApoA-I or increase in HDL-C ranged from $3.89 to $26.07; the value for 1 additional patient achieving the LDL-C goal was $419.75. When the statin doses were aggregated based on the Canadian statin-utilization pattern, rosuvastatin was dominant relative to atorvastatin on all effectiveness measures evaluated. When rosuvastatin was compared with generic simvastatin and pravastatin, the annual costs for 1 additional patient achieving the LDL-C goal were $144.51 and $373.91, respectively. Based on the sensitivity analysis, rosuvastatin was associated with the highest probability of cost-effectiveness compared with the other statins over a broad range of monetary values per unit of clinical effect.

**Conclusion:** When percent changes in lipid parameters and rates of LDL-C goal attainment were considered in patients with hypercholesterolemia in British Columbia, rosuvastatin 10 mg was more cost-effective than the most frequently used doses of atorvastatin (10 and 20 mg), generic simvastatin (20 and 40 mg), and generic pravastatin (20 and 40 mg). (*Clin Ther.* 2008;30:1345–1357) © 2008 Excerpta Medica Inc.

**Key words:** rosuvastatin, atorvastatin, simvastatin, pravastatin, LDL-C, TC/HDL-C, ApoB/ApoA-I, Canadian LDL-C goals, cost-effectiveness analysis.

## INTRODUCTION

Cardiovascular disease (CVD) is the leading cause of death in Canada, and its economic impact in terms

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of direct and indirect costs has been estimated at ~$20 billion per year.[1,2] Due to the aging of the Canadian population, the cardiovascular burden on the population and the health care system is expected to increase over time. Reducing blood levels of low-density lipoprotein cholesterol (LDL-C) is highly recommended for the prevention of cardiovascular morbidity and mortality events.[3–5] Currently, the most effective treatment options for lowering cholesterol levels are 3-hydroxy-3-methylglutaryl coenzyme A-reductase inhibitors (statins).[3,5] Thus, statin therapy represents one of the largest prescription drug expenses in Canada, accounting for a total cost of $1.6 billion in 2007.[6]

During the past decade, there has been an emphasis on components of the lipid profile other than LDL-C that can contribute to cardiovascular risk. Several studies have found that low levels of high-density lipoprotein cholesterol (HDL-C),[7] elevated triglyceride (TG) levels,[8] and high concentrations of TG-rich lipoproteins can contribute to CVD.[9] In addition, recent clinical and epidemiologic studies have found that the apolipoproteins ApoA-I and ApoB may be independent cardiovascular risk factors.[10,11] Measurement of apolipoproteins has recently been added to some lipid management guidelines,[12] including the Canadian guideline.[3]

Six statins are currently marketed in Canada. The most commonly prescribed are rosuvastatin, atorvastatin, simvastatin, and pravastatin. According to PharmaStat data,[13] the mean annual utilization of statins in 2007 was 58.8% for atorvastatin, 16.8% for simvastatin, 14.4% for rosuvastatin, and 7.7% for pravastatin. Individual statins have been reported to have different magnitudes of effect on the lipid parameters that are clinically important in the arteriosclerosis process. As new and effective statins are introduced, it is important for health care professionals and payers to assess the clinical and economic implications of these agents based on individual patient and payer needs.[14] The lower acquisition costs of the generic forms of pravastatin and simvastatin available in Canada have substantially lowered the cost of managing dyslipidemia. However, further assessment is needed to determine whether the use of generics is a cost-effective treatment option.

The goal of this study was to perform an economic evaluation comparing commonly used statins in terms of important lipid-profile parameters from a Canadian health system perspective. Specifically, the primary objective was to assess the cost-effectiveness of the most commonly prescribed doses of rosuvastatin, atorvastatin, simvastatin, and pravastatin in patients with hypercholesterolemia in British Columbia in terms of reductions in LDL-C and the total cholesterol (TC)/HDL-C ratio (the primary and secondary targets, respectively, recommended for the management of dyslipidemia in the 2006 Canadian lipid guidelines[3]) and rates of attainment of Canadian LDL-C goals.[3] TC, HDL-C, TG, ApoB, and ApoB/ApoA-I were also investigated in this study because there is increasing clinical evidence for the additional value of these parameters as predictors of CVD risk.[3,7,8,12] Finally, the estimated overall cost-effectiveness of aggregated doses of rosuvastatin, atorvastatin, simvastatin, and pravastatin were compared based on dose-utilization patterns in British Columbia.

## MATERIALS AND METHODS

### Efficacy

Efficacy data were extracted from STELLAR (Statin Therapies for Elevated Lipid Levels compared Across doses to Rosuvastatin),[15] a multicenter, randomized, open-label, parallel-group trial including 2268 adults with hypercholesterolemia. To date, STELLAR is the only randomized trial to have compared the relative efficacy of most available doses of rosuvastatin, atorvastatin, simvastatin, and pravastatin head to head. Details of the trial design and patient population have been published previously.[15,16] Briefly, the trial consisted of a 6-week dietary lead-in period and a 6-week randomized treatment period. Patients who were compliant with the diet and met lipid criteria after the first 6 weeks were randomized to receive rosuvastatin 10, 20, 40, or 80 mg; atorvastatin 10, 20, 40, or 80 mg; simvastatin 10, 20, 40, or 80 mg; or pravastatin 10, 20, or 40 mg taken orally once daily for 6 weeks. The percent changes in LDL-C and the TC/HDL-C ratio, and the proportion of patients reaching Canadian LDL-C targets, as well as HDL-C, TC, TG, ApoB, and the ApoB/ApoA-I ratio, were assessed from baseline to 6 weeks in the intention-to-treat population.

The Canadian guidelines used in the STELLAR trial specify 4 risk categories (low, moderate, high, and very high) based on an estimated coronary artery disease risk over a 10-year period and suggest corresponding LDL-C goals of <5, <4, <3, and <2.5 mmol/L.[17] Because the maximum LDL-C reduction with statins

is usually achieved within 4 to 6 weeks,[18,19] maximum treatment effects were assumed to be achieved within the first 6 weeks of treatment.

### Costs

This analysis employed 2007 drug costs for branded rosuvastatin, branded atorvastatin, generic simvastatin, and generic pravastatin, and dose-utilization patterns for each statin in British Columbia.[13] Annual acquisition costs of rosuvastatin, atorvastatin, simvastatin, and pravastatin were based on the 2007 wholesale acquisition costs in British Columbia.[20] Similar rates of adverse events[21] and monitoring were assumed across statins; thus, the associated costs were not included in the analysis. All costs were calculated in Canadian dollars.

### Pharmacoeconomic Analysis

This analysis was conducted from the perspective of a health care system (payer) in the Canadian province of British Columbia. The decision-analytic model was used to assess cost-effectiveness ratios (**Figure 1**). The model was constructed using efficacy data from the STELLAR trial and drug wholesale acquisition costs in British Columbia over a 1-year time horizon. Thus, no discounting was applied. The results of the STELLAR trial after 6 weeks were carried forward for comparison after 52 weeks, as there are data indicating that the results of STELLAR would remain constant over 1 year of continuous treatment.[18,19] It was assumed that adherence would have no important impact on the relative effectiveness and cost-effectiveness results for the different statins, and adherence was not

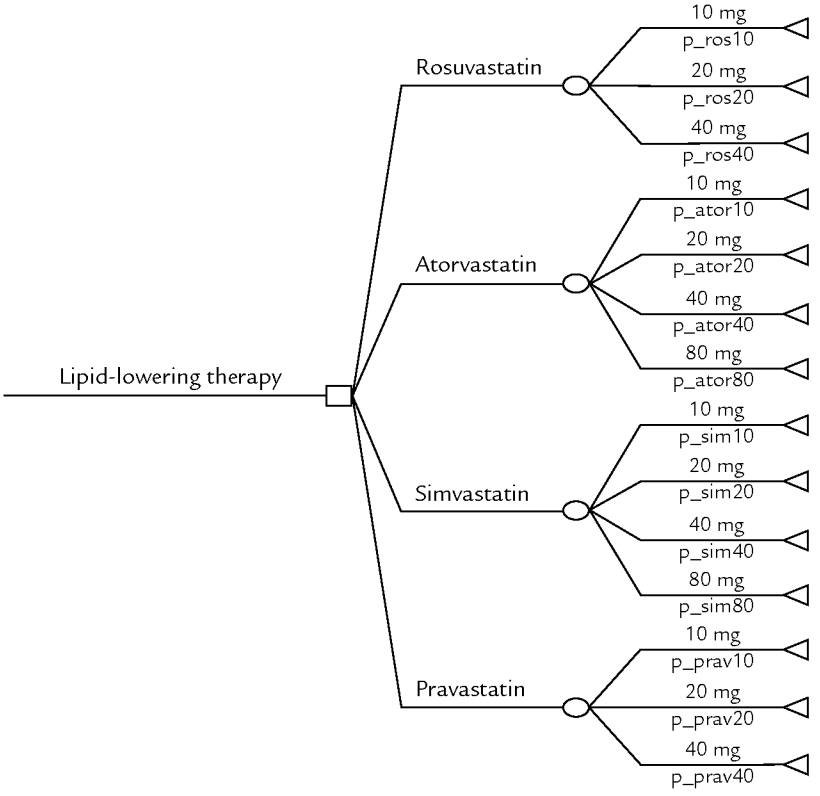


Figure 1. Decision-tree model for the cost-effectiveness comparison of rosuvastatin (ros), atorvastatin (ator), simvastatin (sim), and pravastatin (prav) in the management of lipid parameters in patients with hypercholesterolemia over a 1-year time horizon from a Canadian health system perspective. For the aggregated statin estimates, the dose-specific cost and effectiveness estimates were weighted by the proportion (p) that each dose of a particular statin represents relative to overall dispensing of that statin in British Columbia.

included in the model. It was assumed that all patients continued the prescribed statin and dose for the period of the analysis.

Annual cost-effectiveness ratios for all doses of rosuvastatin, atorvastatin, simvastatin, and pravastatin were estimated in terms of the cost per percent reduction in LDL-C and TC/HDL-C and per patient attaining the Canadian LDL-C goal. Annual cost-effectiveness ratios were estimated for percent reductions in TC, TG, ApoB, and ApoB/ApoA-I, and increases in HDL-C. In addition, incremental cost-effectiveness ratios (ICERs) were calculated for all parameters to estimate the cost of the additional benefit for rosuvastatin 10 mg compared with the most commonly used doses of the other statins.

Individual dose-utilization patterns for each statin dose in British Columbia[13] were employed to estimate an individual statin-specific (aggregated across dose strengths) cost-effectiveness estimate. The result for the aggregated doses of each statin was a weighted calculation derived by multiplying the proportion of each dose dispensed in the province of British Columbia by either the annual cost or the effect on the lipid parameter. As all statins and doses are generally priced differently, with higher prices for higher doses, the aggregated dose calculations helped determine the relative cost of each statin as a whole based on real-world utilization.

### Sensitivity Analysis

We performed sensitivity analyses to determine whether the ICERs were affected by changes in statin efficacy. Monte Carlo simulation was used to vary all effectiveness inputs at once by randomly generating 1000 resamples according to the distribution around the reduction in LDL-C.[22] Because there is no price discounting in British Columbia and the associated rates of dispensing fees and wholesale charges are the same for both generic and branded drugs, statin prices were based on fixed wholesale acquisition costs and were not varied in the Monte Carlo simulation. The cost-effectiveness acceptability curve (CEAC) was plotted to display the optimal alternatives for incremental effectiveness as a function of monetary values from zero to infinity.

## RESULTS

In the STELLAR study,[16] rosuvastatin was associated with the greatest percent reduction in LDL-C and the greatest proportion of patients achieving the Canadian LDL-C goal in terms of milligram-equivalent doses and point-estimate means (**Table I**). In descending order, the proportions of patients achieving the Canadian LDL-C goal were 85% to 91% for rosuvastatin 10 to 40 mg, 68% to 86% for atorvastatin 10 to 80 mg, 66% to 82% for simvastatin 10 to 80 mg, and 44% to 65% for pravastatin 10 to 40 mg. Rosuvastatin was also associated with the greatest efficacy in terms of lipid parameters other than LDL-C reduction, including TC/HDL-C, TC, HDL-C, ApoB, and ApoB/ApoA-I.

Rosuvastatin 10 mg had the lowest annual cost per percent LDL-C reduction ($10.82), followed by simvastatin 80 mg ($11.24) and rosuvastatin 20 mg ($11.85) (**Table I**). The mean cost per patient achieving the LDL-C goal was also lowest for rosuvastatin 10 mg ($584.00), followed by generic simvastatin 10 mg ($619.39). **Figure 2** illustrates the mean annual costs and percent reductions in LDL-C for all statin doses.

ICERs for the most commonly used statin doses in British Columbia are summarized in **Table II**. Based on PharmaStat data,[13] the most frequently used doses of each of the 4 statins were as follows: rosuvastatin 10 mg (75.8% of all rosuvastatin doses); atorvastatin 10 and 20 mg (46.4% and 35.3%, respectively, of all atorvastatin doses); simvastatin 20 and 40 mg (42.5% and 31.8%, respectively, of all simvastatin doses); and pravastatin 20 and 40 mg (55.0% and 34.1%, respectively, of all pravastatin doses). Rosuvastatin 10 mg was dominant (was more effective at a lower cost) with respect to all lipid parameters except TG reduction compared with atorvastatin 10 and 20 mg, simvastatin 20 and 40 mg, and pravastatin 40 mg. Regarding the percent reduction in TG, rosuvastatin 10 mg was more effective than pravastatin 20 mg, but at a greater cost; in contrast, the percent reduction in TG was higher for atorvastatin 10 and 20 mg than for rosuvastatin 10 mg, but at a greater cost. When rosuvastatin 10 mg was compared with generic pravastatin 20 mg, the incremental cost per 1 additional percent reduction in LDL-C, TC/HDL-C, TC, TG, ApoB, and ApoB/ApoA-I and increase in HDL-C ranged from $3.89 to $26.07, and the ICER per additional patient achieving the LDL-C goal was $419.75.

The aggregate estimates across doses based on the utilization pattern for each statin in British Columbia are listed in **Table III**. Rosuvastatin was associated

Table I. Annual costs and effects on low-density lipoprotein cholesterol (LDL-C) and attainment of Canadian LDL-C goals for all doses of the 4 most commonly used statins in Canada.

| Statin and Dose | Wholesale Acquisition Cost, Can $ | Percent Decrease in LDL-C, Mean (SD) | Mean Cost per Percent Decrease in LDL-C, Can $ | Proportion of Patients Achieving LDL-C Goal, % | Mean Cost per Patient Achieving LDL-C Goal, Can $ |
|---|---|---|---|---|---|
| Rosuvastatin | | | | | |
| 10 mg | 496.40 | 45.87 (13.08) | 10.82 | 85 | 584.00 |
| 20 mg | 620.50 | 52.34 (13.64) | 11.85 | 91 | 681.87 |
| 40 mg | 726.35 | 54.96 (13.44) | 13.22 | 88 | 825.40 |
| Atorvastatin | | | | | |
| 10 mg | 605.90 | 36.73 (10.69) | 16.50 | 68 | 891.03 |
| 20 mg | 759.20 | 42.57 (14.32) | 17.83 | 78 | 973.33 |
| 40 mg | 817.60 | 47.79 (12.92) | 17.11 | 84 | 973.33 |
| 80 mg | 817.60 | 51.05 (13.94) | 16.02 | 86 | 950.70 |
| Simvastatin | | | | | |
| 10 mg | 408.80 | 28.30 (13.65) | 14.45 | 66 | 619.39 |
| 20 mg | 514.65 | 34.98 (10.70) | 14.71 | 71 | 724.86 |
| 40 mg | 514.65 | 38.81 (13.90) | 13.26 | 66 | 779.77 |
| 80 mg | 514.65 | 45.78 (11.85) | 11.24 | 82 | 627.62 |
| Pravastatin | | | | | |
| 10 mg | 350.40 | 20.13 (11.30) | 17.41 | 44 | 796.36 |
| 20 mg | 412.45 | 24.29 (11.26) | 16.98 | 65 | 634.54 |
| 40 mg | 496.40 | 29.69 (12.53) | 16.72 | 65 | 763.69 |

with the lowest mean annual costs per percent reduction in LDL-C ($11.04) and TC/HDL-C ($13.55), as well as per percent reduction in TC ($15.39), ApoB ($13.77), and ApoB/ApoA-I ratio ($12.40); it was followed by generic simvastatin ($14.05, $16.95, $19.38, $17.86, and $15.87, respectively), atorvastatin ($17.06, $20.81, $22.97, $20.93, and $19.36), and generic pravastatin ($16.92, $20.01, $23.69, $21.66, and $18.02). Rosuvastatin also had the lowest cost per percent increase in HDL-C ($64.48), followed by simvastatin ($86.34), pravastatin ($90.91), and atorvastatin ($131.28). The cost per patient achieving the LDL-C goal was also lowest for rosuvastatin ($603.46), followed by generic pravastatin ($687.23), generic simvastatin ($719.67), and atorvastatin ($934.12). Based on the ICERs, rosuvastatin was more effective and less costly than atorvastatin on all effectiveness measures evaluated, as illustrated by the cost-effectiveness plane for LDL-C reduction in **Figure 3**. Comparing rosuvastatin with generic simvastatin and pravastatin, the ICERs per percent reduction in LDL-C were $2.10 and $4.02, respectively; the corresponding ICERs for TC/HDL-C were $2.74 and $5.17; for TC, $3.04 and $5.57; and for ApoB/ApoA-1, $2.33 and $4.82. Comparing rosuvastatin with generic simvastatin and pravastatin, the incremental costs per 1 additional patient achieving the LDL-C goal were $144.51 and $373.91.

**Figure 4** shows the CEACs for LDL-C reduction with all 4 statins. The intersection of 2 lines denotes the monetary value at which the likelihood of being cost-effective passes from one statin to another. The threshold is interpreted as the point at which both therapies are optimal 50% of the time, based on a monetary value for each percent decrease in LDL-C. Rosuvastatin had the highest probability of being cost-effective compared with the other statins over a broad range of monetary values per unit of clinical effect. The CEACs for the other efficacy parameters were comparable.

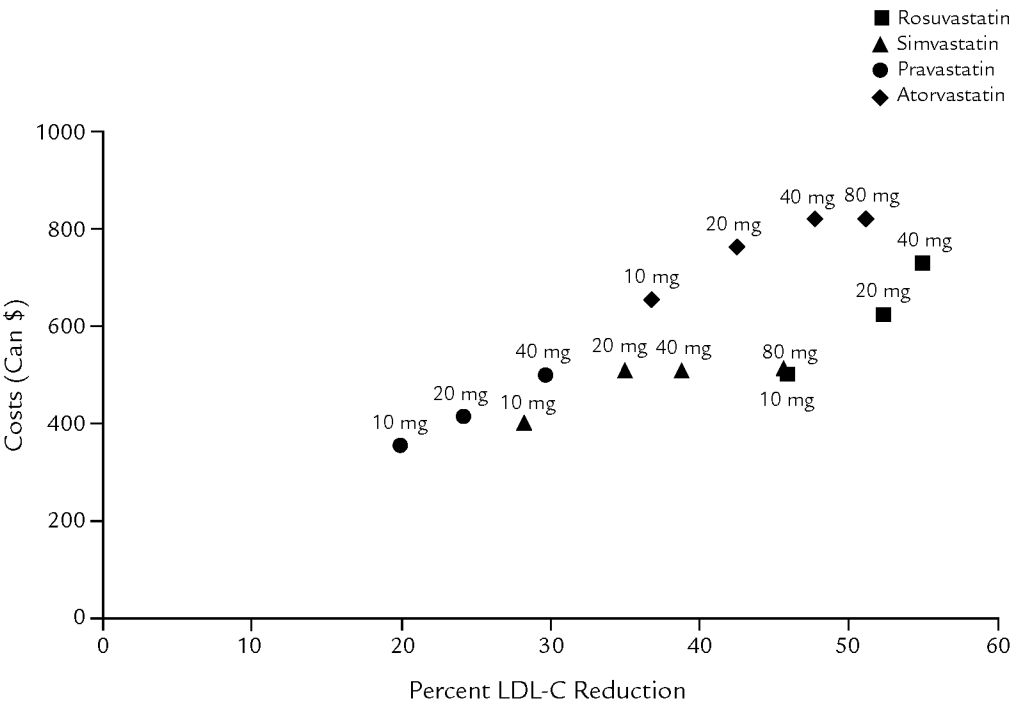


Figure 2. Mean annual costs and reductions in low-density lipoprotein cholesterol (LDL-C) per patient for all doses of the 4 most commonly used statins in British Columbia. The closer to the lower right corner, the greater the cost-effectiveness benefit (ie, the best efficacy at the lowest cost).

## DISCUSSION

This was a cost-effectiveness comparison of the most commonly used statins in patients with dyslipidemia in British Columbia over a 1-year time horizon. Rosuvastatin 10 mg was more effective in the management of various lipid parameters (LDL-C, TC/HDL-C, TC, HDL-C, ApoB, ApoB/ApoA-I) and in attaining the Canadian LDL-C goal at a lower cost (dominant) compared with atorvastatin 10 and 20 mg, simvastatin 20 and 40 mg, and pravastatin 40 mg. In the comparison of rosuvastatin 10 mg with generic pravastatin 20 mg, the incremental cost per additional percent reduction in LDL-C, TC/HDL-C, TC, TG, ApoB, and ApoB/ApoA-I and each increase in HDL-C ranged from $3.89 to $26.07; the cost for 1 additional patient achieving the LDL-C goal was $419.75. After aggregating the statin doses based on utilization patterns in British Columbia, rosuvastatin was dominant relative to atorvastatin on all effectiveness measures evaluated. In the comparison of rosuvastatin with generic simvastatin and pravastatin, rosuvastatin was more effective in terms of all lipid parameters and LDL-C goal attainment, but at a higher cost. The incremental costs per 1 additional percent reduction in LDL-C with rosuvastatin compared with generic simvastatin and pravastatin were $2.10 and $4.02, respectively, and per additional patient achieving the LDL-C goal were $144.51 and $373.91.

In this analysis, rosuvastatin was the most cost-effective of the 4 statins per unit of LDL-C reduction among patients in British Columbia and was associated with the highest proportion of patients achieving the LDL-C target recommended in the Canadian dyslipidemia management guidelines.[3,17] The results of this economic evaluation are consistent with those of analyses conducted from the European and US health care perspectives.[23–25] A recent article on the cost-effectiveness of statins in Canada supports the hypothesis that rosuvastatin may be a cost-effective treatment option even when generic pricing is taken into consideration.[26] That analysis, however, considered only LDL-C reduction and used National Cho-

Table II. Incremental cost-effectiveness ratios (ICERs) indicating the cost per additional unit effect for the most commonly used statin doses in British Columbia.

| Variable | ROS 10 mg, Mean (SD) | ATOR 10 mg, Mean (SD) | ATOR 20 mg, Mean (SD) | ICER ROS 10 mg/ ATOR 10 mg | ICER ROS 10 mg/ ATOR 20 mg |
|---|---|---|---|---|---|
| Annual cost, Can $ | 496.40 | 605.90 | 759.20 | – | – |
| Percent reduction in lipid parameters | | | | | |
| LDL-C | 45.87 (13.08) | 36.73 (10.69) | 42.57 (14.32) | ROS (D) | ROS (D) |
| TC/HDL-C | 37.36 (10.88) | 30.80 (8.97) | 34.43 (11.39) | ROS (D) | ROS (D) |
| TC | 32.89 (10.03) | 27.12 (8.27) | 31.76 (10.67) | ROS (D) | ROS (D) |
| TG | 20.06 (25.44) | 20.10 (22.35) | 22.62 (19.44) | 2737.5* | 102.7* |
| ApoB | 36.77 (12.70) | 29.42 (10.64) | 35.16 (12.39) | ROS (D) | ROS (D) |
| ApoB/ApoA-I | 40.99 (12.85) | 32.21 (11.25) | 38.24 (11.72) | ROS (D) | ROS (D) |
| Percent increase in HDL-C | 7.75 (10.07) | 5.79 (10.23) | 4.89 (12.26) | ROS (D) | ROS (D) |
| Proportion of patients achieving Canadian LDL-C goal, % | 85 | 68 | 78 | ROS (D) | ROS (D) |

| Variable | ROS 10 mg, Mean (SD) | SIM 20 mg, Mean (SD) | SIM 40 mg, Mean (SD) | ICER ROS 10 mg/ SIM 20 mg | ICER ROS 10 mg/ SIM 40 mg |
|---|---|---|---|---|---|
| Annual cost, Can $ | 496.40 | 514.65 | 514.65 | – | – |
| Percent reduction in lipid parameters | | | | | |
| LDL-C | 45.87 (13.08) | 34.98 (10.70) | 38.81 (13.90) | ROS (D) | ROS (D) |
| TC/HDL-C | 37.36 (10.88) | 24.06 (11.55) | 29.49 (10.12) | ROS (D) | ROS (D) |
| TC | 32.89 (10.03) | 25.66 (8.99) | 27.87 (11.07) | ROS (D) | ROS (D) |
| TG | 20.06 (25.44) | 17.69 (22.77) | 14.93 (26.14) | ROS (D) | ROS (D) |
| ApoB | 36.77 (12.70) | 27.33 (12.34) | 30.89 (12.55) | ROS (D) | ROS (D) |
| ApoB/ApoA-I | 40.99 (12.85) | 30.14 (13.15) | 34.97 (12.82) | ROS (D) | ROS (D) |
| Percent increase in HDL-C | 7.75 (10.07) | 6.10 (10.90) | 5.31 (9.95) | ROS (D) | ROS (D) |
| Proportion of patients achieving Canadian LDL-C goal, % | 85 | 71 | 66 | ROS (D) | ROS (D) |

(continued)

Table II. (Continued)

| Variable | ROS 10 mg, Mean (SD) | PRAV 20 mg, Mean (SD) | PRAV 40 mg, Mean (SD) | ICER ROS 10 mg/ PRAV 20 mg | ICER ROS 10 mg/ PRAV 40 mg |
|---|---|---|---|---|---|
| Annual cost, Can $ | 496.40 | 412.45 | 496.40 | – | – |
| Percent reduction in lipid parameters | | | | | |
| LDL-C | 45.87 (13.08) | 24.29 (11.26) | 29.69 (11.26) | 3.89 | ROS (D) |
| TC/HDL-C | 37.36 (10.88) | 20.43 (10.24) | 25.33 (10.36) | 4.96 | ROS (D) |
| TC | 32.89 (10.03) | 17.14 (8.87) | 21.50 (9.22) | 5.33 | ROS (D) |
| TG | 20.06 (25.44) | 7.74 (25.26) | 13.46 (22.93) | 6.81 | ROS (D) |
| ApoB | 36.77 (12.70) | 19.27 (10.58) | 22.94 (12.12) | 4.80 | ROS (D) |
| ApoB/ApoA-I | 40.99 (12.85) | 23.68 (11.10) | 26.87 (12.37) | 4.85 | ROS (D) |
| Percent increase in HDL-C | 7.75 (10.07) | 4.53 (9.59) | 5.65 (10.12) | 26.07 | ROS (D) |
| Proportion of patients achieving Canadian LDL-C goal, % | 85 | 65 | 65 | 419.75 | ROS (D) |

ROS = rosuvastatin; ATOR = atorvastatin; LDL-C = low-density lipoprotein cholesterol; D = dominant (greater effect at a lower cost); TC = total cholesterol; HDL-C = high-density lipoprotein cholesterol; TG = triglycerides; Apo = apolipoprotein; SIM = simvastatin; PRAV = pravastatin.

*ATOR 10/20 mg was more effective than ROS 10 mg in terms of TG reduction, but was associated with higher costs. The ICER for ROS 10 mg/ATOR 10 mg was so high because the difference in effect approached zero.

lesterol Education Program Adult Treatment Panel III guidelines for LDL-C targets.

Even though high levels of LDL-C are generally accepted as one of the strongest risk factors for coronary artery disease, there is increasing evidence that HDL-C and apolipoproteins play an important predictive role.[27] Evidence from several population-based studies has indicated that a low HDL-C level is an independent predictive factor for CVD.[7,28,29] Regarding apolipoproteins, results of the AMORIS[30] (Apolipoprotein-related Mortality Risk) and INTERHEART[31] studies indicated that the balance between atherogenic lipoproteins (mainly ApoB-containing particles) and antiatherogenic lipoproteins (mainly Apo-I–containing particles) is an important parameter in predicting future myocardial infarction. The present analysis included these more recently identified predictors of CVD risk and found that the costs per percent increase in HDL-C and percent reduction in ApoB/ApoA-I were lower for rosuvastatin compared with the other statins studied, both for aggregate doses and milligram-equivalent doses.

Declines in adherence to statin therapy over a 1-year period have been widely described[32–34] and would have an obvious impact on statin effectiveness. Therefore, an attempt was made to examine the magnitude of the impact of statin adherence on the cost-effectiveness estimates for statins in the present study. A 21% reduction in the LDL-C–lowering ability of statins has been reported in the real-world setting relative to clinical trials, with no significant variation in the magnitude of this reduction in efficacy among the statins studied.[35] In 2 Canadian studies, rates of filled prescriptions in patients initiating statin therapy ranged from 56% to 90% over a 1-year period.[33,34] To examine the impact of adherence decline over a 1-year period in the present analysis, we decreased the percent LDL-C reduction by 21%[35] and costs by 27% (estimated based on mean prescription rates in the 2 aforementioned Cana-

Table III. Results for the aggregated statin doses, based on the utilization pattern in British Columbia.

| Effectiveness Parameter | Cost, Can $ | Effect | Mean Cost per Effect, Can $ | ICER |
|---|---|---|---|---|
| Percent reduction in lipid parameters | | | | |
| LDL-C | | | | |
| Rosuvastatin | 518.37 | 46.96 | 11.04 | 2.10 vs simvastatin |
| Atorvastatin | 689.19 | 40.39 | 17.06 | Rosuvastatin dominant |
| Simvastatin | 493.48 | 35.12 | 14.05 | 6.39 vs pravastatin |
| Pravastatin | 432.27 | 25.55 | 16.92 | 4.02 vs rosuvastatin |
| TC/HDL-C | | | | |
| Rosuvastatin | 518.37 | 38.25 | 13.55 | 2.74 vs simvastatin |
| Atorvastatin | 689.19 | 33.12 | 20.81 | Rosuvastatin dominant |
| Simvastatin | 493.48 | 29.11 | 16.95 | 8.13 vs pravastatin |
| Pravastatin | 432.27 | 21.61 | 20.01 | 5.17 vs rosuvastatin |
| TC | | | | |
| Rosuvastatin | 518.37 | 33.69 | 15.39 | 3.04 vs simvastatin |
| Atorvastatin | 689.19 | 30.01 | 22.97 | Rosuvastatin dominant |
| Simvastatin | 493.48 | 25.47 | 19.38 | 8.45 vs pravastatin |
| Pravastatin | 432.27 | 18.25 | 23.69 | 5.57 vs rosuvastatin |
| TG | | | | |
| Rosuvastatin | 518.37 | 20.72 | 25.02 | 4.97 vs simvastatin |
| Atorvastatin | 689.19 | 21.95 | 31.39 | 138.35 vs rosuvastatin |
| Simvastatin | 493.48 | 15.69 | 31.46 | 9.99 vs pravastatin |
| Pravastatin | 432.27 | 9.58 | 45.13 | 7.72 vs rosuvastatin |
| ApoB | | | | |
| Rosuvastatin | 518.37 | 37.64 | 13.77 | 2.49 vs simvastatin |
| Atorvastatin | 689.19 | 32.93 | 20.93 | Rosuvastatin dominant |
| Simvastatin | 493.48 | 27.62 | 17.86 | 7.96 vs pravastatin |
| Pravastatin | 432.27 | 19.96 | 21.66 | 4.86 vs rosuvastatin |
| ApoB/ApoA-I | | | | |
| Rosuvastatin | 518.37 | 41.82 | 12.40 | 2.33 vs simvastatin |
| Atorvastatin | 689.19 | 35.59 | 19.36 | Rosuvastatin dominant |
| Simvastatin | 493.48 | 31.11 | 15.87 | 8.57 vs pravastatin |
| Pravastatin | 432.27 | 23.99 | 18.02 | 4.82 vs rosuvastatin |
| Percent increase in HDL-C | | | | |
| Rosuvastatin | 518.37 | 8.04 | 64.48 | 10.76 vs simvastatin |
| Atorvastatin | 689.19 | 5.25 | 131.28 | Rosuvastatin dominant |
| Simvastatin | 493.48 | 5.71 | 86.34 | 63.48 vs pravastatin |
| Pravastatin | 432.27 | 4.76 | 90.91 | 26.18 vs rosuvastatin |
| Attainment of Canadian LDL-C goal, % | | | | |
| Rosuvastatin | 518.37 | 86 | 603.46 | 144.51 vs simvastatin |
| Atorvastatin | 689.19 | 74 | 934.12 | Rosuvastatin dominant |
| Simvastatin | 493.48 | 69 | 719.67 | 1070.18 vs pravastatin |
| Pravastatin | 432.27 | 63 | 687.23 | 373.91 vs rosuvastatin |

ICER = incremental cost-effectiveness ratio; LDL-C = low-density lipoprotein cholesterol; TC = total cholesterol; HDL-C = high-density lipoprotein cholesterol; TG = triglycerides; Apo = apolipoprotein.

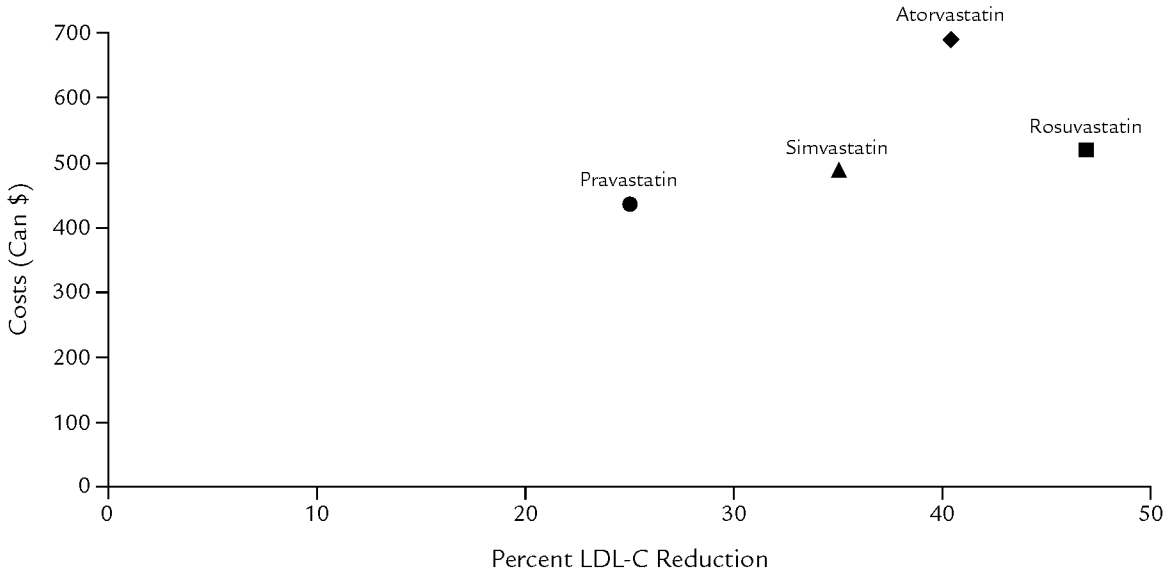


Figure 3. Mean annual costs and reductions in low-density lipoprotein cholesterol (LDL-C) for aggregated doses of each statin based on utilization patterns in British Columbia. Branded rosuvastatin was dominant (ie, had a greater effect at a lower cost) to branded atorvastatin. Generic simvastatin and pravastatin were associated with lower costs than the branded agents, but had a lesser effect on LDL-C.

dian studies[33,34]). The results indicated that the ICER values decreased by ~7%, but this did not change overall cost-effectiveness. Nonetheless, future studies should more systematically examine the impact of decreased adherence on real-world reductions in LDL-C and the associated cost-effectiveness implications.

The study findings should be interpreted in light of several limitations. The study used efficacy data from a 6-week randomized clinical trial and assumed that efficacy would be unchanged over the 52-week study period. This assumption was supported by previous publications suggesting that the maximum LDL-C reduction is achieved after 4 to 6 weeks of treatment and that efficacy remains constant over a 1-year period of continuous treatment.[18,19] Based on evidence suggesting no important differences in adverse events among the statins investigated,[21] these measures were not expected to influence the relative cost-effectiveness results and were not included in the analysis. Furthermore, as with any economic analysis, the results may not be generalizable to areas beyond British Columbia.

The dose-comparison analysis assumed that all patients would continue the same statin and dose over the time horizon of 1 year. Only drug costs (and not the cost of treatment monitoring) were included in the model. Ory et al[36] reported that only a small proportion (12.3%) of patients had a change in their statin regimen (a titration event) over a 1-year follow-up period, supporting the use of such a fixed-dose model. Although titration may be associated with increased costs for laboratory testing and physician visits, it would not be likely to change the overall cost-effectiveness ranking of the alternatives, as the main cost driver was annual drug costs.

The primary focus of this study was the cost-effectiveness of the most commonly used doses of rosuvastatin, atorvastatin, simvastatin, and pravastatin. From a health system perspective, it would also be important to understand the cost-effectiveness of individual statins as a whole based on the distribution of each dose used in clinical practice.[13] Therefore, the results of the statin-level aggregated analysis in this study complement those of the dose-to-dose comparisons, indicating the cost-effectiveness of rosuvastatin in the management of lipid parameters in patients with dyslipidemia.

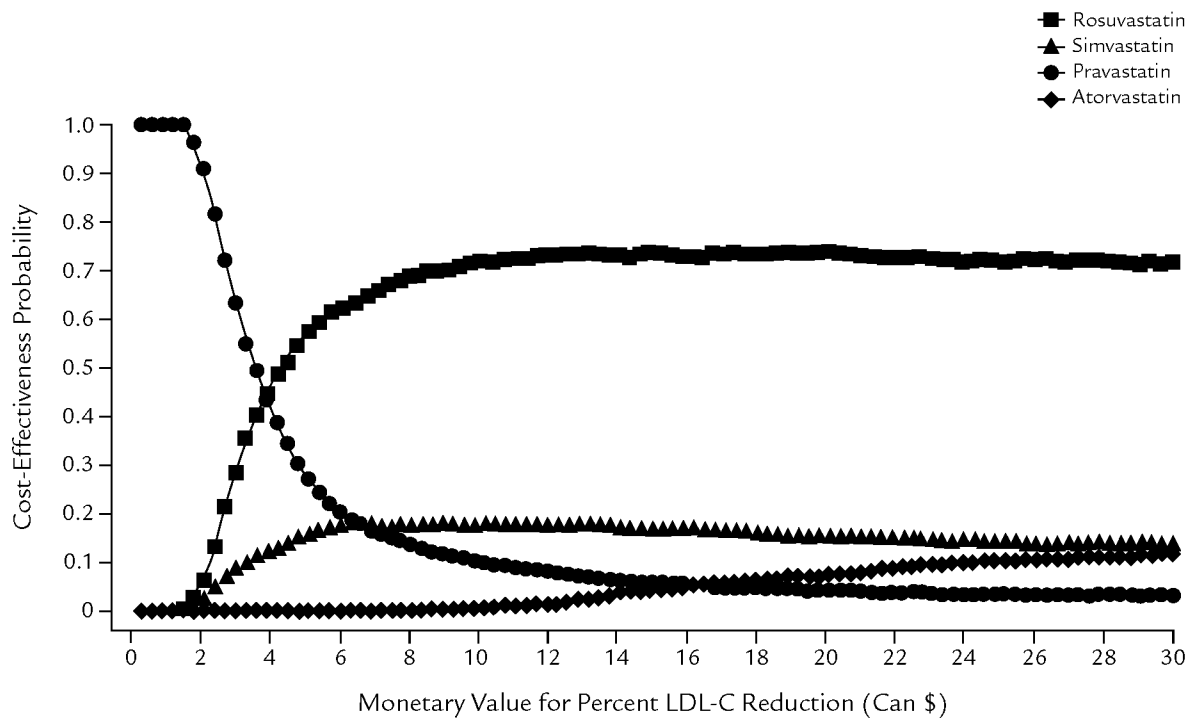


Figure 4. Cost-effectiveness acceptability curves for the 4 statins. The intersection of 2 lines illustrates the monetary value at which the likelihood of being cost-effective passes from one statin to another. The threshold is interpreted as the point at which both therapies are optimal 50% of the time, based on a monetary value for each percent decrease in low-density lipoprotein cholesterol (LDL-C).

## CONCLUSIONS

Rosuvastatin was associated with the lowest mean cost per percent improvement in all lipid parameters, including LDL-C, TC/HDL-C, TC, HDL-C, TG, ApoB, and ApoB/ApoA-I, compared with the other commonly used statins in British Columbia. In comparisons of the most commonly used statin doses in British Columbia, rosuvastatin 10 mg was associated with greater effectiveness at lower costs for most effectiveness measures evaluated compared with branded atorvastatin 20 and 40 mg, generic simvastatin 20 and 40 mg, and generic pravastatin 40 mg. Compared with generic pravastatin 20 mg, rosuvastatin 10 mg was more effective with respect to the percent reduction in TG, but at a higher cost. Given its drug-acquisition cost in Canada and its effectiveness in managing various lipid parameters and helping patients attain Canadian LDL-C goals, rosuvastatin 10 mg was the most cost-effective statin compared with the most frequently used doses of atorvastatin, generic simvastatin, and generic pravastatin.

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## REFERENCES

1. Choi BK, Pak AW. A method for comparing and combining cost-of-illness studies: An example from cardiovascular disease. *Chronic Dis Can.* 2002;23:47–57.
2. Age-standardized mortality rates by selected causes, by sex [Statistics Canada Web site]. http://www40.statcan.ca/l01/cst01/health30a.htm. Accessed May 3, 2008.
3. McPherson R, Frohlich J, Fodor G, et al. Canadian Cardiovascular Society position statement—Recommendations

for the diagnosis and treatment of dyslipidemia and prevention of cardiovascular disease [published correction appears in *Can J Cardiol.* 2006;22:1077]. *Can J Cardiol.* 2006; 22:913–927.
4. Baigent C, Keech A, Kearney PM, et al, for the Cholesterol Treatment Trialists' (CTT) Collaborators. Efficacy and safety of cholesterol-lowering treatment: Prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins [published correction appears in *Lancet.* 2005;366: 1358]. *Lancet.* 2005;366:1267–1278.
5. National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). Third Report of National Cholesterol Education Program (NCEP) Expert Panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel III) final report. *Circulation.* 2002;106: 3143–3421.
6. IMS Canada. Canadian Drug Store and Hospital Purchases Audit. December 2007.
7. Espinosa-Larrañaga F, Vejar-Jalaf M, Medina-Santillán R, for the Latin American Group. The importance of low serum levels of high-density lipoprotein cholesterol (HDL-C) as a cardiovascular risk factor. *Diab Vasc Dis Res.* 2005;2 (Suppl 1):S1–S8.
8. Yuan G, Al-Shali KZ, Hegele RA. Hypertriglyceridemia: Its etiology, effects and treatment. *CMAJ.* 2007; 176:1113–1120.
9. Fruchart JC, Nierman MC, Stroes ES, et al. New risk factors for atherosclerosis and patient risk assessment. *Circulation.* 2004;109(Suppl 1): III15–III19.
10. Thompson A, Danesh J. Associations between apolipoprotein B, apolipoprotein AI, the apolipoprotein B/AI ratio and coronary heart disease: A literature-based meta-analysis of prospective studies. *J Intern Med.* 2006;259:481–492.
11. Walldius G, Jungner I. The apoB/apoA-I ratio: A strong, new risk factor for cardiovascular disease and a target for lipid-lowering therapy—a review of the evidence. *J Intern Med.* 2006;259:493–519.
12. Faergeman O. Introduction: Apolipoproteins and guidelines for prevention of cardiovascular disease. *J Intern Med.* 2006;259:434–436.
13. PharmaStat [Brogan Inc Web site]. http://www.broganinc.com/english/products/pstat.html. Accessed June 9, 2008.
14. Russell MW, Huse DM, Miller JD, et al. Cost effectiveness of HMG-CoA reductase inhibition in Canada. *Can J Clin Pharmacol.* 2001;8:9–16.
15. Jones PH, Davidson MH, Stein EA, et al, for the STELLAR Study Group. Comparison of the efficacy and safety of rosuvastatin versus atorvastatin, simvastatin, and pravastatin across doses (STELLAR* Trial). *Am J Cardiol.* 2003;92:152–160.
16. McKenney JM, Jones PH, Adamczyk MA, et al, for the STELLAR Study Group. Comparison of the efficacy of rosuvastatin versus atorvastatin, simvastatin, and pravastatin in achieving lipid goals: Results from the STELLAR trial. *Curr Med Res Opin.* 2003;19:689–698.
17. Fodor JG, Frohlich JJ, Genest JJ Jr, McPherson PR. Recommendations for the management and treatment of dyslipidemia: Report of the Working Group on Hypercholesterolemia and Other Dyslipidemias. *CMAJ.* 2000;162:1441–1447.
18. Olsson AG, Istad H, Luurila O, et al, for the Rosuvastatin Investigators Group. Effects of rosuvastatin and atorvastatin compared over 52 weeks of treatment in patients with hypercholesterolemia. *Am Heart J.* 2002;144:1044–1051.
19. Brown WV, Bays HE, Hassman DR, et al, for the Rosuvastatin Study Group. Efficacy and safety of rosuvastatin compared with pravastatin and simvastatin in patients with hypercholesterolemia: A randomized, double-blind, 52-week trial. *Am Heart J.* 2002;144:1036–1043.
20. *PPS Buyers Guide.* Moncton, Canada: PPS Pharma; 2007.
21. Shepherd J, Vidt DG, Miller E, et al. Safety of rosuvastatin: Update on 16,876 rosuvastatin-treated patients in a multinational clinical trial program. *Cardiology.* 2007;107:433–443.
22. O'Brien BJ, Briggs AH. Analysis of uncertainty in health care cost-effectiveness studies: An introduction to statistical issues and methods. *Stat Methods Med Res.* 2002;11:455–468.
23. Hirsch M, O'Donnell JC, Jones P. Rosuvastatin is cost-effective in treating patients to low-density lipoprotein-cholesterol goals compared with atorvastatin, pravastatin and simvastatin: Analysis of the STELLAR trial. *Eur J Cardiovasc Prev Rehabil.* 2005;12:18–28.
24. Ohsfeldt RL, Gandhi SK, Fox KM, et al. Effectiveness and cost-effectiveness of rosuvastatin, atorvastatin, and simvastatin among high-risk patients in usual clinical practice. *Am J Manag Care.* 2006;12(Suppl 15): S412–S423.
25. Miller PS, Smith DG, Jones P. Cost effectiveness of rosuvastatin in treating patients to low-density lipoprotein cholesterol goals compared with atorvastatin, pravastatin, and simvastatin (a US analysis of the STELLAR Trial). *Am J Cardiol.* 2005; 95:1314–1319.
26. Tran YB, Frial T, Miller PS. Statin's cost-effectiveness: A Canadian analysis of commonly prescribed generic and brand name statins. *Can J Clin Pharmacol.* 2007;14:e205–e214.
27. Sniderman AD, Jungner I, Holme I, et al. Errors that result from using the TC/HDL C ratio rather than the apoB/apoA-I ratio to identify the lipoprotein-related risk of vascular disease [published correction appears in *J Intern Med.* 2006;260:186]. *J Intern Med.* 2006;259:455–461.

28. Turner RC, Millns H, Neil HA, et al. Risk factors for coronary artery disease in non-insulin dependent diabetes mellitus: United Kingdom Prospective Diabetes Study (UKPDS: 23). *BMJ.* 1998;316:823–828.
29. Barter P, Gotto AM, LaRosa JC, et al, for the Treating to New Targets Investigators. HDL cholesterol, very low levels of LDL cholesterol, and cardiovascular events. *N Engl J Med.* 2007;357:1301–1310.
30. Walldius G, Aastveit AH, Jungner I. Stroke mortality and the apoB/apoA-I ratio: Results of the AMORIS prospective study. *J Intern Med.* 2006; 259:259–266.
31. Yusuf S, Hawken S, Ounpuu S, for the INTERHEART Study Investigators. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): Case-control study. *Lancet.* 2004;364:937–952.
32. Benner JS, Pollack MF, Smith TW, et al. Association between short-term effectiveness of statins and long-term adherence to lipid-lowering therapy. *Am J Health Syst Pharm.* 2005;62:1468–1475.
33. Perreault S, Blais L, Dragomir A, et al. Persistence and determinants of statin therapy among middle-aged patients free of cardiovascular disease. *Eur J Clin Pharmacol.* 2005;61:667–674.
34. Lachaine J, Rinfret S, Merikle EP, Tarride JE. Persistence and adherence to cholesterol lowering agents: Evidence from Régie de l'Assurance Maladie du Québec data. *Am Heart J.* 2006;152:164–169.
35. Frolkis JP, Pearce GL, Nambi V, et al. Statins do not meet expectations for lowering low-density lipoprotein cholesterol levels when used in clinical practice. *Am J Med.* 2002;113: 625–629.
36. Ory C, Fontes C, Williams SA, et al. An evaluation of the factors associated with statin dose management and low-density lipoprotein-cholesterol goal attainment. *Dis Manag Health Outcomes.* 2006;14:37–44.

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