STATIN'S COST-EFFECTIVENESS: A CANADIAN ANALYSIS OF COMMONLY PRESCRIBED GENERIC AND BRAND NAME STATINS

Yvan BL Tran[1,2], Tony Frial[1], Paul SJ Miller[3]

[1]AstraZeneca Canada Inc, Mississauga, Canada, [2]Leslie Dan Faculty of Pharmacy, University of Toronto, Toronto, Canada, [3]AstraZeneca UK Limited, Macclesfield, United Kingdom

Corresponding Author: yvan.tran@utoronto.ca

ABSTRACT

Background
Generic statins may be considered as a compelling treatment option for managing dyslipidemia, due to their reduced cost, compared to their brand name equivalent. However, further assessment is needed to determine whether using a particular generic statin is more cost-effective relative to other brand-name statins.

Objective
The purpose of this study is to compare the cost-effectiveness of the most commonly prescribed statins in Canada with respect to 1) lowering low-density lipoprotein cholesterol level (LDL-C) and 2) achieving National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) LDL-C goal.

Methods
The study was conducted from the perspective of Canadian payers over a 1-year time horizon. Clinical data were obtained from the STELLAR trial (n=2268) in which patients received fixed doses of rosuvastatin, atorvastatin, simvastatin and pravastatin. Brand and generic drug costs were based on wholesale acquisition costs. Relative cost-effectiveness was assessed using the net monetary benefit approach (NMB), which allows probabilistic cost-effectiveness comparison of the various treatment options over a wide range of willingness-to-pay (WTP) values for a unit of clinical effect.

Results
Rosuvastatin 10mg was the most cost-effective statin over the largest range of WTP values. Pravastatin 10mg was cost-effective when the clinical outcomes had little or no monetary value. Rosuvastatin 20mg was more cost-effective at the highest end of the WTP spectrum.

Conclusion
The result of this analysis provides evidence that prescribing generic statins in Canada does not necessarily translate into the most cost-effective option for treating dyslipidemia; especially as the monetary value of 1% decrease in LDL-C or patients achieving NCEP ATP III target increases.

Key Words*: Statin, cost-effectiveness, generic, cardiovascular disease, cholesterol*

In 2003, cardiovascular diseases (CVD) were the leading cause of all death in Canada, for which it has been the underlying cause of about one in three deaths.[1] The economical impact of CVD in terms of direct and indirect costs is estimated to be about $20 billion per year.[2] In the advent of the ageing Canadian population, CVD burden on the population and the healthcare system will only increase over time.

Dyslipidemia is considered an important independent risk factor for CVD, for which the control of low-density lipoprotein cholesterol

(LDL-C) constitutes a primary objective in its optimal management.[3-5]

The efficacy and safety of 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors (statins) in reducing LDL-C and CVD-related morbidity and mortality is well established.[6-13] Furthermore, the cost-effectiveness of statins for preventing CVD events from a Canadian healthcare perspective is also well documented.[14-26] Nevertheless, there is currently no cost-effectiveness analysis that takes into account relative efficacy and relative pricing amongst different products (be they brand name or generic) from a Canadian perspective. Since generic drug acquisition costs are typically lower than their respective brand name equivalent, generic drugs may be seen as a compelling treatment option for treating an individual patient.[27] However, further assessment is needed to determine whether using generics constitute a more cost-effective treatment option within its respective drug class.

The purpose of this study was to compare the cost-effectiveness amongst the most commonly prescribed statins in Canada (rosuvastatin 10mg to 40mg, atorvastatin 10mg to 80mg, pravastatin 10mg to 40mg, and simvastatin 10mg to 80mg) with respect to lowering LDL-C and to achieving the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) LDL-C goal.[28]

METHODS

Costs

Acquisition costs for brand rosuvastatin, brand atorvastatin, generic pravastatin and generic simvastatin were included. Generic pricing for pravastatin and simvastatin were incorporated in the analysis to better reflect the actual acquisition cost of these drugs in Canada. Costs related to serious adverse events, to physician or nurse visits and to laboratory tests (liver function and lipid) were excluded since it was assumed that they were similar across statins.[29-31] Titration costs (additional physician visit and laboratory tests) were not included.

Efficacy

The statin's efficacy was assessed according to 1) the percent decrease in LDL-C, and 2) the proportion of patients who achieved the NCEP ATP III guideline LDL-C goal according to their individual risk level.[28]

Pharmacoeconomic Analysis

The present pharmacoeconomic analysis is a variant of a previously published and peer-reviewed model developed to assess the cost-effectiveness of various statins within the United States context.[32] The present analysis was conducted from the perspective of health care payers in Canada and used Canadian specific drug acquisition costs as the key economic outcome measure. Instead of using simple sample means, the efficacy for each statin was determined using bootstrap simulation (1,000 resample) on all efficacy data to take into consideration the uncertainty in the sample estimate and to further characterize the sample distribution.[33] The bootstrap technique randomly selects a new sample of the same size (with repeated observation allowed) from the original observed sample; this can be repeated thousands of times, and "bootstrapped" statistics can be estimated. Maximum LDL-C decrease and LDL-C goal attainment were assumed to be achieved within the first 6 weeks of treatment, considering that maximal LDL-C reduction is usually achieved within 4 to 6 weeks for statins.[34-35] For the purpose of this analysis, it was assumed that the efficacy achieved after 6 weeks remained constant over 1 year of continuous treatment.[36-37] This analysis was performed over a 1-year period, so discounting was not applied.

Cost-effectiveness was assessed in terms of cost per unit of clinical efficacy as defined above, as well as in terms of net monetary benefit (NMB). The NMB analysis has been chosen to allow probabilistic comparison of multiple treatment options.[38] NMB may be defined as the monetary value of the clinical effect from a particular treatment minus the cost of that treatment: $NMB = (k) \bullet E - C$, where E is the clinical effect, k is the value associated to the clinical effect (in monetary terms) and C is the cost.

In the NMB analysis, the monetary value of the clinical effect (k-value) is typically determined by the decision maker's willingness-to-pay for each unit of benefit; in this case, for each 1% reduction in LDL-C or for each patient achieving their respective LDL-C goal. Since the "willingness-

to-pay" value is generally unknown and may vary from one decision maker to another,[39] the results were presented for k-values ranging from 0 to infinity. Individual treatment options are considered as cost-effective when the monetary value of the clinical effect exceeds the cost of the treatment (i.e., NMB > 0). To determine the relative cost-effectiveness of the different treatments, the probability of having the highest NMB among comparators was evaluated in the bootstrap simulation.

The NMB results were presented graphically to define a cost-effectiveness acceptability curve, which illustrates the certainty of a statin being cost-effective for different values of k. These curves illustrate the probability, according to the simulation, that each treatment option had the highest NMB among other treatments included in the analysis for each k-value. When the k-value is close to zero, drug acquisition cost dominates the NMB statistics; consequently, the cheapest treatment option is more likely to be the most cost-effective option. As the clinical effect's monetary value increases (increasing k-value), a gain in the clinical effect can compensate substantially higher drug acquisition costs, which translates into superior cost-effectiveness in the NMB statistics. For any k-value, the statin with the highest NMB probability is the most cost-effective option. In the graphical representation of the results, only the individual drugs that were able to achieve a high NMB in the simulation were displayed in the cost-effectiveness acceptability curve.

Sensitivity Analyses

Sensitivity analyses were performed to assess the robustness of the findings. For convenience, the most cost-effective drug, defined as the most cost-effective alternative over the widest k-value range for a clinical effect, was used as the main comparator. Threshold values for the price of alternative statins, to attain a NMB equivalent to the main comparator, were calculated according to $C_j = (k) \bullet E_j - (k) \bullet E_i + C_i$, where C is the drug cost, E is the clinical effect, k is the WTP per unit of clinical effect, i is the main comparator and j is the alternative statin treatment. The difference between the current wholesale acquisition cost of the alternative statin and the threshold value for a clinical effect value (k-value) represents the price decrease required to achieve a NMB equivalent to the main comparator statin. The magnitude of the price decrease may vary according to different k-values. Hence, the sensitivity analyses' results were presented graphically over a wide range of k-values to enable individual decision makers to interpret the sensitivity analysis' results according to different willingness-to-pay values.

Data Source

Acquisition costs (2006) were calculated in Canadian dollars and according to the PPS Pharma Buyers Guide and Brogan iMAM Price Report.[40,41] Clinical efficacy and input patient population data were derived from the STELLAR trial.[42] This was a 6-week, parallel-group, open-label, multicenter study that randomized a total of 2,431 patients to a fixed dose of rosuvastatin (10, 20, or 40mg), atorvastatin (10, 20, 40, or 80mg), pravastatin (10, 20, or 40mg), or simvastatin (10, 20, 40, or 80mg). Fluvastatin, lovastatin and simvastatin 5mg were not included in the STELLAR trial because they are not commonly prescribed. Rosuvastatin 5mg was also not included in the STELLAR trial since it was not marketed at the time of the trial. Enrolled patients were men and nonpregnant women who were ≥ 18 years of age and had hypercholesterolemia (LDL-C concentration ≥ 4.1 mmol/L and <6.5 mmol/L; triglyceride concentration <4.5 mmol/L). The primary end point was the change in plasma LDL-C concentration from baseline to 6 weeks. The proportion of patients who reached NCEP ATP III guideline LDL-C goals was also assessed for each statin dose. The present analysis assumed that LDL-C reduction achieved after 6 weeks of statin treatment would remain the same at one year of continuous treatment.[36,37] To date, the STELLAR trial is the most comprehensive trial that compared the relative effectiveness of the most widely prescribed statin in a single randomized trial.

RESULTS

In terms of milligram-equivalent doses and point estimate mean, rosuvastatin provided the greatest LDL-C reduction and greatest number of patients achieving LDL-C targets. Daily and annual costs and mean data for the two efficacy measurements for all treatment regimens included in the STELLAR trial are compiled in Table 1. The three most cost-effective treatment regimens, for mean costs per 1% decrease in LDL-C and for patients achieving target LDL-C goal, are rosuvastatin 10mg, rosuvastatin 20mg and generic simvastatin 80mg.

TABLE 1 Annual Cost and Clinical Effect for Each Statin Dose

Statin	Wholesale Acquisition Costs (CAD$)	Annual Cost (CAD$)	Mean Percent Decrease in LDL-C	Proportion of Patients Reaching LDL-C Goal	Mean Cost per 1% Decrease in LDL-C (CAD$)	Mean Cost per Patient Reaching LDL-C Goal (CAD$)
Rosuvastatin 10mg	$1.36	$496	-45.87	82.05%	$10.81	$604.51
Rosuvastatin 20mg	$1.70	$621	-52.34	88.75%	$11.86	$699.72
Rosuvastatin 40mg	$1.99	$726	-54.96	89.17%	$13.21	$814.18
Atorvastatin 10mg	$1.66	$606	-36.73	68.99%	$16.50	$878.39
Atorvastatin 20mg	$2.08	$759	-42.57	74.68%	$17.83	$1,016.34
Atorvastatin 40mg	$2.24	$818	-47.79	85.26%	$17.12	$959.42
Atorvastatin 80mg	$2.24	$818	-51.05	82.42%	$16.02	$992.48
Generic Pravastatin 10mg	$0.95	$347	-20.13	31.25%	$14.29	$1,110.40
Generic Pravastatin 20mg	$1.12	$409	-24.29	43.90%	$13.78	$931.66
Generic Pravastatin 40mg	$1.35	$493	-29.68	54.66%	$17.42	$901.94
Generic Simvastatin 10mg	$1.25	$456	-28.3	50.91%	$16.11	$895.70
Generic Simvastatin 20mg	$1.54	$562	-34.98	62.96%	$16.07	$832.63
Generic Simvastatin 40mg	$1.54	$562	-38.81	66.46%	$14.48	$845.62
Generic Simvastatin 80mg	$1.54	$562	-45.78	82.21%	$12.28	$683.62

In the cost-effectiveness acceptability curves (Figure 1 and 2), rosuvastatin 10mg was the most cost-effective statin over a wide range of k-values in terms of a 1% decrease in LDL-C at 1 year ($5.50 to $19) and for patients reaching their LDL-C goal ($300 to $1725). Generic pravastatin 10mg was the most cost-effective treatment option when the value of a 1% decrease in LDL-C is less than $5.50 and the value of patients reaching their LDL-C goal is less than $300.

Even though generic pravastatin 10mg had the lowest potency in reducing LDL-C among drugs included in this analysis, its lower acquisition cost translates into better cost-effectiveness when the clinical effect has little or no monetary value. Rosuvastatin 20mg was the most cost-effective statin when the value for a 1% decrease in LDL-C at 1 year was higher than $19 and when the value of patients reaching their LDL-C goal was higher than $1725. At high k-values, the higher cost of rosuvastatin 20mg was offset by an improvement in percent LDL-C reduction potency. Since either rosuvastatin 10mg or 20mg were closer to the cost-effectiveness probability of 1 for much of the k-value ranges in which clinical effect has a monetary value, this suggests, with a high certainty, that rosuvastatin is cost-effective.

The sensitivity analysis' findings were reported in Figure 3 and 4, using rosuvastatin 10mg as the main comparator. For a particular k-value, the difference between the wholesale acquisition cost (plain line) and the threshold value (dotted line) represent the price decrease required for a particular statin to achieve a NMB equivalent to the main comparator (rosuvastatin 10mg). For example, for a k-value of $15 per 1% decrease in LDL-C, the price of generic simvastatin 40mg would have to decrease by 31% (from $1.54 to $1.07 per day) to have a cost-effectiveness equivalent to rosuvastatin 10mg (Figure 3). From Figure 4, for an arbitrary k-value of $1,000 per patient who reaches their LDL-C goal, the price of generic simvastatin 40mg would have to decrease by 39% to be as cost-effective as rosuvastatin 10mg. In general, the different alternative statins included in the sensitivity analyses necessitated a price decrease to achieve a NMB equivalent to rosuvastatin 10mg. Furthermore, as the WTP for both clinical effect increased, deeper price reduction is required for most of the alternative statins to match the NMB of rosuvastatin 10mg.

FIG. 1 Cost-Effectiveness Acceptability Curves Based on Percent Decrease in LDL-C

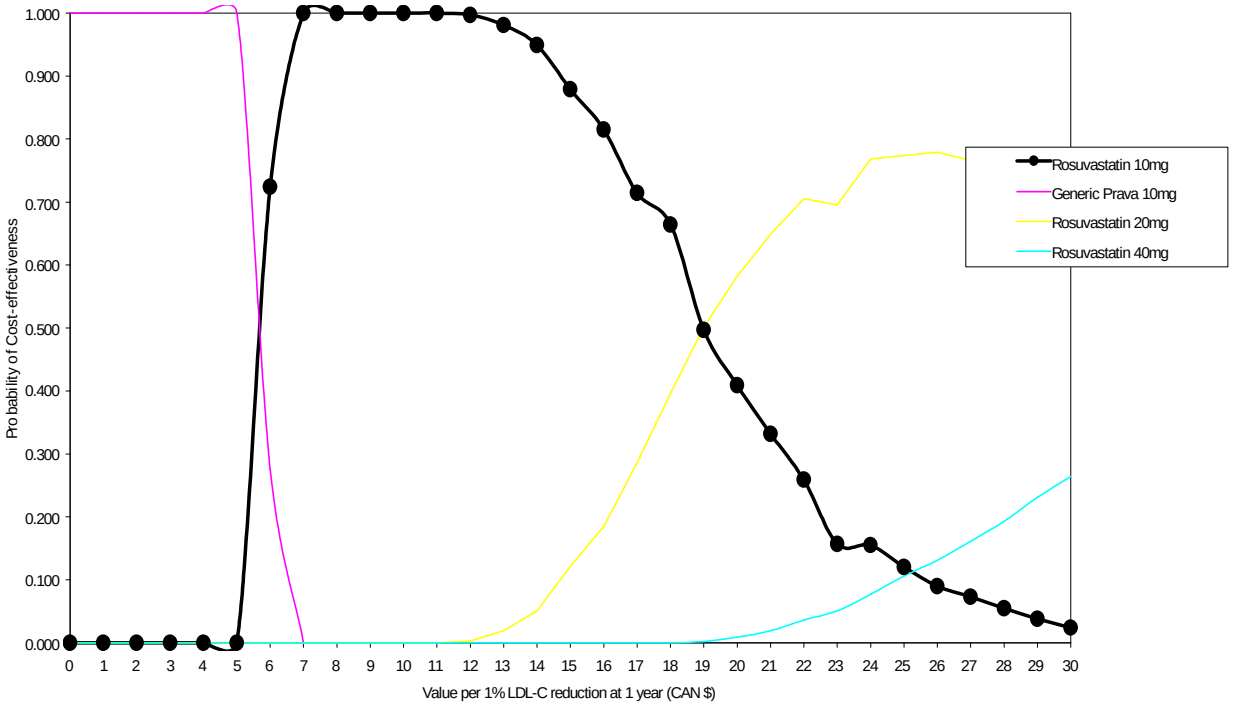


FIG. 2 Cost-Effectiveness Acceptability Curves Based on the Proportion of Patients who Achieved their LDL-C Goal

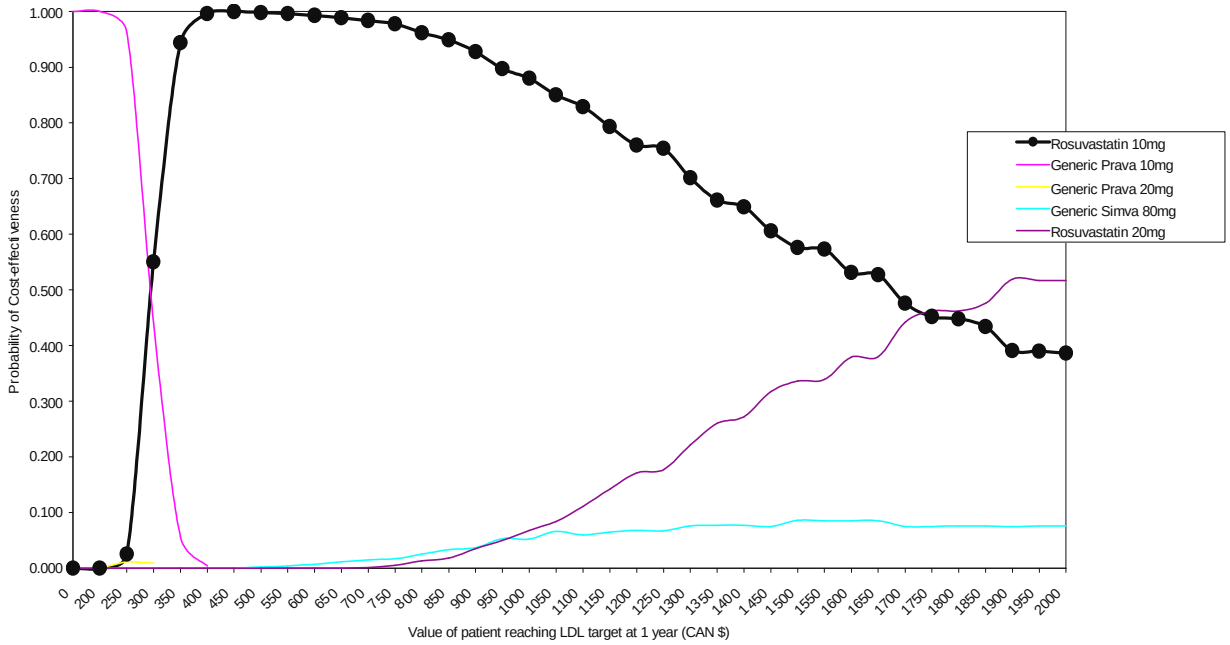
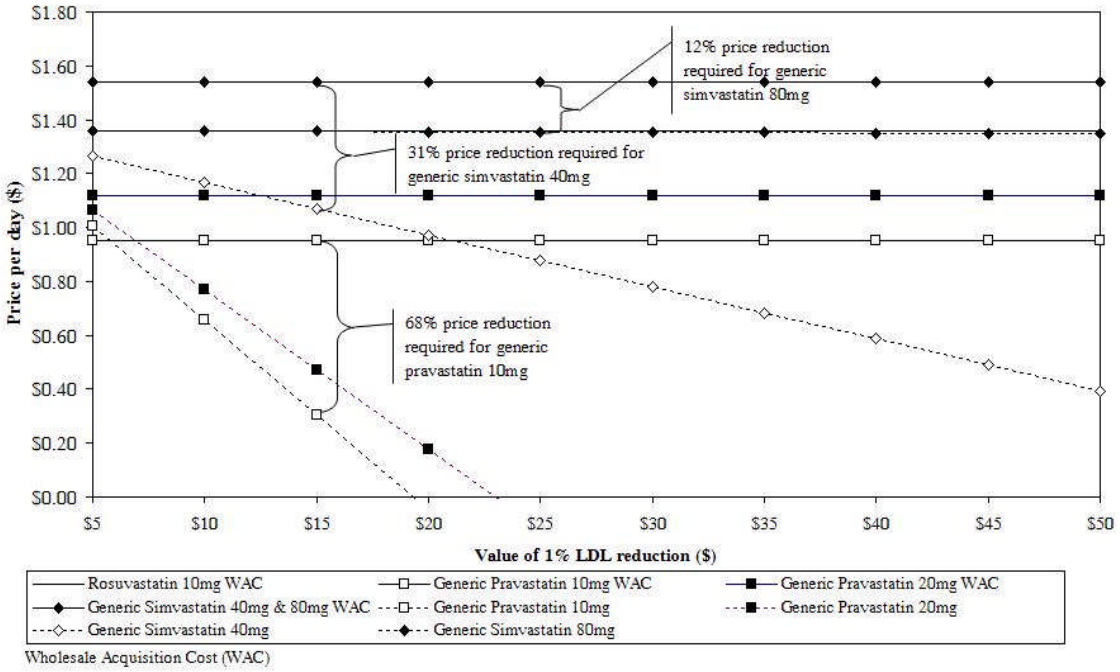
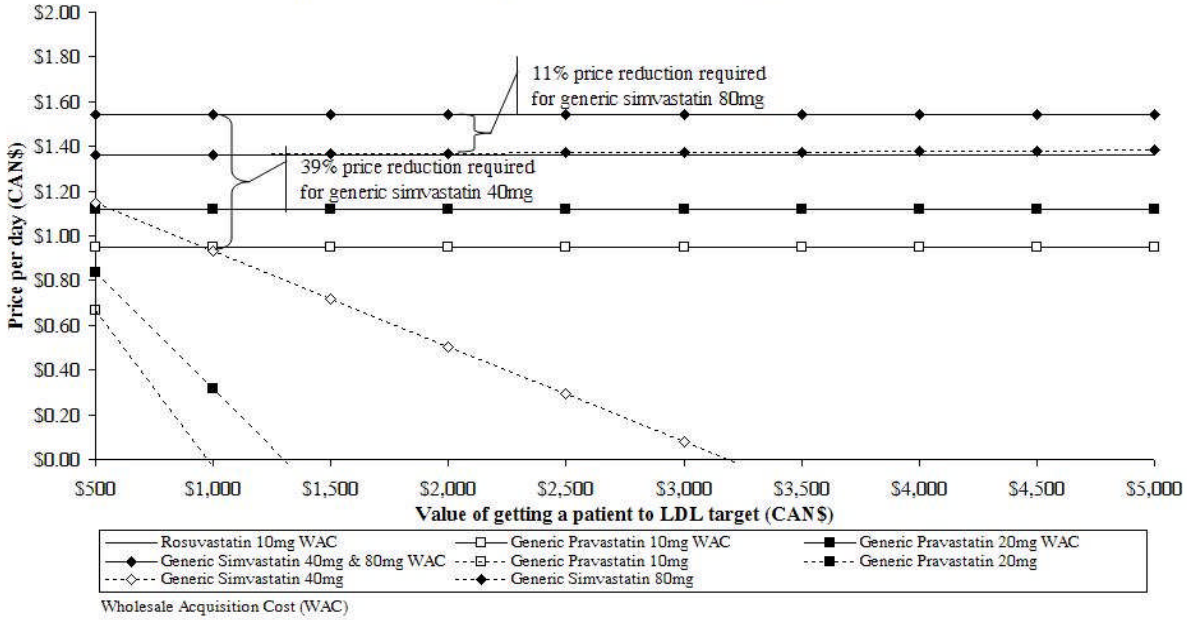


FIGURE 3: Price decrease required for alternative statins to achieve an NMB equivalent to rosuvastatin 10mg based on percent decrease of LDL-C



Wholesale Acquisition Cost (WAC)

FIGURE 4: Price decrease required for alternative statins to achieve an NMB equivalent to rosuvastatin 10mg based on treating patients to their LDL-C goal



Wholesale Acquisition Cost (WAC)

DISCUSSION

The STELLAR trial findings support that rosuvastatin is more efficacious than milligram-equivalent doses of other statins in lowering LDL-C levels and in enabling patients to achieve NCEP ATP III LDL-C goals.[42] This analysis, which combines the STELLAR clinical trial data and current Canadian acquisition costs, has demonstrated that rosuvastatin can be a cost-effective treatment option, even when generic pricing is taken into consideration.

Previous pharmacoeconomic analyses in Canada have demonstrated that the use of statins, in general, can be cost-effective from a societal perspective for preventing CVD.[14-26] According to recent publications, it has been suggested that the use of generic simvastatin in a non-Canadian healthcare market may contribute to significant decrease in drug expenditure for statins.[43,44] Among generic statins marketed in Canada, only generic pravastatin 10mg was able to achieve a high cost-effectiveness probability. Pravastatin 10mg dominates the NMB analysis at the lowest monetary value range attributed to both clinical effects. At higher monetary values associated with a 1% decrease in LDL-C (over $5.50) or for patients reaching their LDL-C goal (over $300), rosuvastatin 10mg and rosuvastatin 20mg dominate generic pravastatin 10mg, other generic and other branded statins. Thus the present study provides evidence that the empirical use of generic statins does not necessarily translate into a cost-effective treatment option from a Canadian healthcare perspective, conditional upon the monetary value assigned to the incremental clinical effects.

Rosuvastatin 10mg is the only starting dose among statins that had a high probability of cost-effectiveness in the NMB analysis.[45] Amongst starting doses, it is more efficacious in terms of percent LDL-C reduction and number of patients achieving LDL-C target. When the relationship between drug acquisition cost and efficacy is taken into consideration it is the most cost-effective option. The results from the sensitivity analyses suggest that rosuvastatin 10mg's superior cost-effectiveness is robust to substantial price decrease of alternative statins. As for the k-value for either clinical efficacy parameter increases, a greater price reduction would be required for most of the alternative statins to be as cost-effective as rosuvastatin 10mg.

The present study has a number of potential limitations. First, this study used efficacy data directly from a randomized clinical trial. Although findings from the "real-world" setting have indicated reduced statin effectiveness in the usual care setting outside of clinical trials, rosuvastatin's superiority over other statins in reducing LDL-C levels and in allowing patients to achieve cholesterol targets has been maintained in "real-world" observational studies.[46] Second, the effectiveness of the various treatment options was assessed according to a surrogate endpoint (1% LDL-C reduction) rather than hard endpoint events (such as death and cardiovascular events). However, the use of 1% LDL-C reduction to determine cost-effectiveness is relevant since there is a proportional decrease in the incidence of deaths and cardiovascular events associated to the reduction of LDL-C levels.[13] Third, the present analysis assumed that LDL-C reduction after 6 weeks of statin treatment would remain constant after one year of continuous treatment. There is currently evidence that supports that tachyphylaxis does not occur at 1 year of statin treatment.[36,37] However, further studies are required to address whether tachyphylaxis occurs over a more extended period of statin use.

Fourth, treatment monitoring and adverse event rates were not integrated within the present analysis since it was assumed that they are all consistent across statins. There is actually no evidence that suggests that these aspects are different between the statins.[29-31,34,35] Treatment adherence and persistence were also not included in the model since it is unknown if they vary across statins.

Fifth, titration was not incorporated into the analysis since it is a fixed-dose model. Although titration is associated with increased cost, it would not likely change the overall ranking of the most cost-effective alternatives in the NMB analysis since only rosuvastatin 20mg requires titration among these drugs. This would slightly shift its cost-acceptability curve toward a higher k-value. However, rosuvastatin 20mg's superior clinical effect would likely offset the incremental titration cost in the highest k-value spectrum.

Other features associated to individual drug such as HDL elevation potency, pleiotropic

properties (e.g. effect on atherosclerosis plaques), drug interaction profile, drug convenience packaging or compliance programs may also affect willingness to pay and cost-effectiveness ratio depending on the monetary value associated to them.[42,47,48] These features were not integrated in the analysis, but they may be of value in the treatment decision making process. More specifically, individual drug HDL elevation potency may have a significant impact on the NMB analysis result if HDL elevation is considered as a valuable clinical effect. Since recent evidence suggests that HDL is an independent risk factor for cardiovascular event in patients currently taking lipid treatment,[49,50] further assessment may be required to take into account HDL elevation profile in assessing relative cost-effectiveness of statins.

In conclusion, a pharmacoeconomic model has been adapted to assess the relative cost-effectiveness of the most prescribed statins in Canada. The findings from this study demonstrate that prescribing generic statins may not necessarily translate into the most cost-effective treatment option for Canadian patients with dyslipidemia.

Acknowledgements

The authors would like to acknowledge Tony Kim, the industrial pharmacy residency preceptor. This manuscript was supported by AstraZeneca Inc, Canada. Yvan BL Tran was the industrial pharmacy resident affiliated to the Leslie Dan Faculty of Pharmacy, University of Toronto. However, the results and conclusions are those of the authors and no official endorsement by the University of Toronto was intended or should be inferred.

REFERENCES

1. Statistics Canada. Cause of death - Chapter IX: Diseases of the circulatory system. (May 2, 2006) (http://www.statcan.ca/english/freepub/84-208-XIE/2005002/tables/ch9.pdf (August 10, 2005).
2. Choi BK, Pak AW. A method for comparing and combining cost-of-illness studies: an example from cardiovascular disease. Chronic Dis Can 2002 Spring;23(2):47-57.
3. Heart and Stroke Foundation of Canada. The Growing Burden of Heart Disease and Stroke in Canada 2003. Ottawa: Heart and Stroke Foundation of Canada, 2003.
4. Genest J, Frohlich J, Fodor G, McPherson R; Working Group on Hypercholesterolemia and Other Dyslipidemias. Recommendations for the management of dyslipidemia and the prevention of cardiovascular disease: summary of the 2003 update. CMAJ 2003 Oct 28;169(9):921-4.
5. Grundy SM. United States Cholesterol Guidelines 2001: expanded scope of intensive low-density lipoprotein-lowering therapy. Am J Cardiol 2001 Oct 11;88(7B):23J-27J.
6. The Scandinavian Simvastatin Survival Study Group. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). Lancet 1994;344:1383–9.
7. Shepherd J, Cobbe SM, Ford I, et al. for the West of Scotland Coronary Prevention Study Group. Prevention of coronary heart disease in men with hypercholesterolemia. N Engl J Med 1995;333:1301–7.
8. Sacks FM, Pfeffer MA, Moye LA, et al. for the Cholesterol and Recurrent Events Trial Investigators. The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. N Engl J Med 1996;335:1001–9.
9. The Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study Group. Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. N Engl J Med 1998;339:1349–57.
10. Downs JR, Clearfield M, Weis S, et al. for the AFCAPS/TexCAPS Research Group. Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels: results of AFCAPS/TexCAPS. JAMA 1998;279:1615–22.
11. Heart Protection Study Collaborative Group. MRC/BHF heart protection study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomized placebo-controlled trial. Lancet 2002;360:7–22.
12. Serruys PW, de Feyter P, Macaya C, et al. Fluvastatin for prevention of cardiac events following successful first percutaneous coronary intervention. JAMA 2002;287:3215–22.
13. Baigent C, Keech A, Kearney PM, et al; Cholesterol Treatment Trialists' (CTT) Collaborators. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomized trials of statins. Lancet 2005 Oct 8;366(9493):1267-78.

14. Pilote L, Ho V, Lavoie F, Coupal L, Zowall H, Grover SA. Cost-effectiveness of lipid-lowering treatment according to lipid level. Can J Cardiol 2005 Jun;21(8):681-7.
15. Grover SA, Ho V, Lavoie F, Coupal L, Zowall H, Pilote L. The importance of indirect costs in primary cardiovascular disease prevention: can we save lives and money with statins? Arch Intern Med 2003 Feb 10;163(3):333-9.
16. Spaans JN, Coyle D, Fodor G, et al. Application of the 1998 Canadian cholesterol guidelines to a military population: health benefits and cost effectiveness of improved cholesterol management. Can J Cardiol 2003 Jun;19(7):790-6.
17. Russell MW, Huse DM, Miller JD, Kraemer DF, Hartz SC. Cost effectiveness of HMG-CoA reductase inhibition in Canada. Can J Clin Pharmacol 2001 Spring;8(1):9-16.
18. Perreault S, Levinton C, Le Lorier J. Efficacy and cost of HMG-CoA reductase inhibitors in the treatment of patients with primary hyperlipidemia. Can J Clin Pharmacol 2000 Autumn;7(3):144-54.
19. Grover SA, Coupal L, Paquet S, Zowall H. Cost-effectiveness of 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors in the secondary prevention of cardiovascular disease: forecasting the incremental benefits of preventing coronary and cerebrovascular events. Arch Intern Med 1999 Mar 22;159(6):593-600.
20. Perreault S, Hamilton VH, Lavoie F, Grover S. Treating hyperlipidemia for the primary prevention of coronary disease. Are higher dosages of lovastatin cost-effective? Arch Intern Med 1998 Feb 23;158(4):375-81.
21. Otten N. A Canadian perspective. Value Health 1998 Nov;1(4):218-23.
22. MacNeil P. Economic aspects of hypercholesterolemia treatment with HMG-CoA reductase inhibitors: a review of recent developments. Can J Cardiol 1998 Apr;14 Suppl A:14A-16A.
23. Riviere M, Wang S, Leclerc C, Fitzsimon C, Tretiak R. Cost-effectiveness of simvastatin in the secondary prevention of coronary artery disease in Canada. CMAJ 1997 Apr 1;156(7):991-7.
24. Perreault S, Hamilton VH, Lavoie F, Grover S. A head-to-head comparison of the cost effectiveness of HMG-CoA reductase inhibitors and fibrates in different types of primary hyperlipidemia. Cardiovasc Drugs Ther 1997 Jan;10(6):787-94.
25. Hamilton VH, Racicot FE, Zowall H, Coupal L, Grover SA. The cost-effectiveness of HMG-CoA reductase inhibitors to prevent coronary heart disease. Estimating the benefits of increasing HDL-C. JAMA 1995 Apr 5;273(13):1032-8.
26. Martens LL, Guibert R. Cost-effectiveness analysis of lipid-modifying therapy in Canada: comparison of HMG-CoA reductase inhibitors in the primary prevention of coronary heart disease. Clin Ther 1994 Nov-Dec;16(6):1052-62; discussion 1036.
27. Adis Editors. Generics take off in France, 2006. PharmacoEconomics and Outcomes News;506. p.1.
28. NCEP Expert Panel. Third Report of National Cholesterol Education Program (NCER) Expert Panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel III). Final Report. Circulation 2002;106:3143-3421.
29. Guyton JR. Benefit versus risk in statin treatment. Am J Cardiol 2006 Apr 17;97(8A):95C-97C.
30. Goettsch WG, Heintjes EM, Kastelein JJ, Rabelink TJ, Johansson S, Herings RM. Results from a rosuvastatin historical cohort study in more than 45,000 Dutch statin users, a PHARMO study. Pharmacoepidemiol Drug Saf 2006 Jul;15(7):435-43.
31. McAfee A, Ming E, Seeger J, et al. The comparative safety of rosuvastatin: a retrospective matched cohort study in over 48,000 initiators of statin therapy. Pharmacoepidemiol Drug Saf 2006 Jul;15(7):444-53.
32. 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 Jun 1;95(11):1314-9.
33. Briggs AH, Gray AM. Handling uncertainty when performing economic evaluation of healthcare interventions. Health Technol Assess 1999;3(2):1-134.
34. Brown WV, Bays HE, Hassman DR, et al. 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 Dec;144(6):1036-43.
35. Olsson AG, Istad H, Luurila O, et al. Rosuvastatin Investigators Group. Effects of rosuvastatin and atorvastatin compared over 52 weeks of treatment in patients with hypercholesterolemia. Am Heart J 2002 Dec;144(6):1044-51.
36. Dart A, Jerums G, Nicholson G, et al. A multicenter, double-blind, one-year study comparing safety and efficacy of atorvastatin

versus simvastatin in patients with hypercholesterolemia. Am J Cardiol 1997 Jul 1;80(1):39-44.
37. Davidson M, Ma P, Stein EA, et al. Comparison of effects on low-density lipoprotein cholesterol and high-density lipoprotein cholesterol with rosuvastatin versus atorvastatin in patients with type IIa or IIb hypercholesterolemia. Am J Cardiol 2002 Feb 1;89(3):268-75.
38. Stinnett AA, Mullahy J. Net health benefits: a new framework for the analysis of uncertainty in cost-effectiveness analysis. Med Decis Making 1998 Apr-Jun;18(2 Suppl):S68-80.
39. Weinstein MC. From cost-effectiveness ratios to resource allocation: where to draw the line? In: Sloan FA, ed. Valuing Health Care: Costs, Benefits, and Effectiveness of Pharmaceuticals and Other Medical Technologies. New York: Cambridge University Press, 1995:77-96.
40. PPS Pharma. PPS Pharma Buyers Guide. Moncton: Total Pricing System Inc., January 2006.
41. Brogan. Brogan iMAM. (June 1, 2006) http://www.broganinc.com/ (June 1, 2006).
42. Jones PH, Davidson MH, Stein EA, et al. STELLAR Study Group. Comparison of the efficacy and safety of rosuvastatin versus atorvastatin, simvastatin, and pravastatin across doses (STELLAR* Trial). Am J Cardiol 2003 Jul 15;92(2):152-60.
43. Anonymous. A switch in time saves more than nine. Two popular statins, Pravachol and Zocor, go generic this summer, paving the way for significant savings. Harv Heart Lett 2006 May;16(9):1-2.
44. Moon JC, Bogle RG. Switching statins. BMJ 2006 Jun 10;332(7554):1344-5.
45. Canadian Pharmacists Association: Compendium of Pharmaceuticals and Specialties. Ottawa: Canadian Pharmacists Association, 2006.
46. Bullano MF, Wertz DA, Yang GW, et al. Effect of rosuvastatin compared with other statins on lipid levels and national cholesterol education program goal attainment for low-density lipoprotein cholesterol in a usual care setting. Pharmacotherapy 2006 Apr;26(4):469-78.
47. Nissen SE, Nicholls SJ, Sipahi I, et al. ASTEROID Investigators. Effect of very high-intensity statin therapy on regression of coronary atherosclerosis: the ASTEROID trial. JAMA 2006 Apr 5;295(13):1556-65.
48. Bottorff MB. Statin safety and drug interactions: clinical implications. Am J Cardiol 2006 Apr 17;97(8A):27C-31C.
49. Koro CE, Bowlin SJ, Stump TE, Sprecher DL, Tierney WM. The independent correlation between high-density lipoprotein cholesterol and subsequent major adverse coronary events. Am Heart J 2006 Mar;151(3):755.e1-e6.
50. Wei L, Murphy MJ, MacDonald TM. Impact on cardiovascular events of increasing high density lipoprotein cholesterol with and without lipid lowering drugs. Heart 2006 Jun;92(6):746-51.