A PHARMACOECONOMIC EVALUATION OF THE MYOCARDIAL ISCHEMIA REDUCTION WITH AGGRESSIVE CHOLESTEROL LOWERING (MIRACL) STUDY IN CANADA

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ABSTRACT

Objective
To determine a 16-week total healthcare cost and the cost-effectiveness of short-term, lipid-lowering therapy with atorvastatin 80 mg following acute coronary syndrome (ACS) in Canada.

Methods
The expected costs per patient on atorvastatin 80 mg per day and placebo were compared using clinical outcome data from the MIRACL study and cost data from the Ontario Case Costing Project and the Ontario Schedule of Benefits. The cost per event avoided was also assessed. The clinical outcomes measured included: death, cardiac arrest, non-fatal myocardial infarction (MI), fatal MI, angina pectoris, stroke, congestive heart failure, and surgical or percutaneous coronary revascularizations. All direct medical costs from the perspective of the Canadian health care system were taken into account.

Results
The total expected cost per patient was $2,590 in the placebo group and $2,639 in the atorvastatin group. The incremental cost of atorvastatin treatment ($49.26 per patient) corresponded to a cost of $1,285 per event avoided. The cost savings obtained through the reduction in events offset 86% of the cost of atorvastatin treatment. Budget impact analysis revealed that increased rates of atorvastatin usage following ACS were associated with large numbers of events avoided at a small additional cost when projected to the Canadian population.

Conclusions
In Canada, the clinical benefits of intensive short-term atorvastatin treatment administered within 96 hours after ACS were associated with a favorable cost-effectiveness ratio. The incremental cost of atorvastatin is mostly offset by savings due to the reduction in events in patients treated with atorvastatin.

Key Words*: coronary disease, health economics, Canadian healthcare system*

In Canada, the societal and economic burdens of cardiovascular disease (CVD) are substantial and accounted for $7.3 billion or 17% of all direct costs of illness in 1993. Indirect costs (losses of productivity due to mortality and morbidity) associated with CVD were estimated at $12.3 billion.[1] In addition, CVD accounted for 39% of all deaths in Canada in 1997 and 13% of all hospitalizations in 1993.

Coronary heart disease (CHD) causes the greatest percentage of CVD deaths.[1] One of the primary manifestations of CHD is acute coronary syndrome (ACS), which includes unstable angina and acute myocardial infarction (AMI). Half of all CHD deaths can

be attributed to AMI. Of the 6.5 million physician consultations in Canada for ischemic heart disease, 59% are for myocardial infarction and 41% are for angina.[1]

It is evident that the morbidity and mortality associated with ACS imposes a great financial burden to the Canadian healthcare system. Reducing the incidence of coronary events associated with ACS and the costs of expensive treatments is fundamental to reducing healthcare costs. One means of reducing coronary events and the need for expensive interventions, such as revascularization procedures, is through the effective management of hyperlipidemia. The link between elevated low-density lipoprotein cholesterol (LDL-C) levels and risk of CHD and CHD mortality is well established. [4, 5, 6, 7]

Therefore, the lowering of LDL-C is one of the primary targets for cholesterol-lowering interventions and for managing hyperlipidemia. Key studies have demonstrated that statin therapy serves as an effective means of lowering cholesterol levels and, in turn, reduces the risk of CHD in both primary and secondary prevention.[8, 9,10,11,12]

However, these previous trials have excluded ACS patients. Furthermore, benefits of intensive short-term treatment in ACS patients have not been examined until recently. Early treatment may be important in reducing clinical events since these patients experience the highest rates of mortality and recurrent ischemic events in the early period after ACS. [13, 14, 15]

The Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering (MIRACL) trial was conducted to evaluate the effects of early treatment in patients with ACS using atorvastatin 80 mg on the incidence of early recurrent ischemic events. The MIRACL study was a double blind, randomized, placebo-controlled, multicenter study of 3,086 patients and compared the clinical outcomes of patients with ACS treated with intensive lipid lowering using atorvastatin 80 mg daily or matching placebo.[16]

Treatment was initiated within the first 96 hours following hospitalization for ACS and continued for 16 weeks. The primary combined endpoint of the trial was death, nonfatal acute myocardial infarction, and cardiac arrest with resuscitation or recurrent symptomatic myocardial ishcemia with objective evidence requiring emergency hospitalization.

Secondary outcomes included: the occurrence of each primary endpoint, nonfatal stroke, new or worsening congestive heart failure (CHF) requiring hospitalization, worsening angina requiring rehospitalization but without new objective evidence of ischemia, coronary revascularization by surgical or percutaneous means, time to first occurrence of a primary or secondary endpoint, and percentage changes in blood lipid levels from baseline to end of study.

Results of the MIRACL study demonstrated that intensive lipid lowering with atorvastatin significantly reduced the risk of the primary combined endpoint as well as the risk of stroke and recurrent symptomatic MI with objective evidence requiring emergency hospitalization.[16]

Although the clinical benefits of intensive atorvastatin treatment are evident from the results of the MIRACL trial, the economic impact of reducing the risk of ischemic events in the ACS population remains unknown. The goal of the present pharmacoeconomic analysis was to use the MIRACL clinical results and Canadian reference prices to determine the short-term economic costs and benefits of intensive lipid lowering therapy with atorvastatin in patients with ACS. Additionally we sought to measure the incremental cost-effectiveness of atorvastatin 80 mg daily for a 16-week duration, compared to placebo in the ACS population in Canada.

METHODS

This pharmacoeconomic analysis utilized patient data from the MIRACL trial concerning all inpatient episodes, and the occurrence of primary and secondary endpoints. Canadian medical cost data was used to compare the total direct healthcare costs and incremental cost-effectiveness of a short-term 16-week treatment strategy with

atorvastatin 80 mg daily versus placebo, initiated within 96 hours after hospitalization for unstable angina or non-ST segment elevation MI in Canada.

The analysis was conducted from the perspective of the Canadian healthcare system. Only direct medical care costs were considered in our analysis. Similar methodology has been applied and reported for UK and Sweden-specific analysis of the pharmacoeconomic implications of MIRACL.[17, 18]

TABLE 1 Total Number of Events from MIRACL Trial (as reported in JAMA)

	No. (%) of Patient	
Any **Primary Outcome**	Placebo (n=1548)	Atorvastatin (n= 1538)
Death and/or nonfatal acute MI	169 (10.9)	155(10.1)
Death	68 (4.4)	64 (4.2)
Nonfatal acute MI	113(7.3)	101 (6.6)
Resuscitated cardiac arrest	10 (0.6)	8 (0.5)
Recurrent symptomatic myocardial ischemia with objective evidence and emergency rehospitalization	130(8.4)	95 (6.2)
Any outcome	268 (17.4)	228 (14.8)
Any Secondary Outcome		
Stroke		
Fatal and nonfatal	24(1.6)	12(0.8)
Nonfatal	22(1.4)	9 (0.6)
Coronary revascularization	250 (16.1)	254 (16.5)
Percutaneous coronary intervention	143 (9.2)	150 (9.8)
Surgical	110 (7.1)	106 (6.9)
Worsening angina without new objective evidence of ischemia	106 (6.8)	91 (5.9)
New or worsening congestive heart failure requiring rehospitalization	43 (2.8)	40 (2.6)
Any outcome	344 (22.2)	344 (22.4)
Any primary or secondary outcome	475 (30.7)	450 (29.3)

MI = Myocardial Infarction

Table 1 outlines the total number of events associated with all endpoints in the MIRACL clinical trial as reported in JAMA.[16] Although one may be tempted to utilize these data for the purposes of the present analysis, this would be incorrect because the data on the occurrence of study endpoints does not account for two or more of the same events occurring within individual patients, multiple events occurring within the same hospitalization, or whether the events incurred costs.

These data are therefore incomplete as applied to pharmacoeconomic analysis for which thorough accounting of costs and events is required as opposed to the conventional epidemiological approach for which multiple events in individual patients are not relevant. Because any hospitalization could be associated with one or more primary and/or secondary endpoint, it was necessary to track all of the events that were recorded during each hospital admission. After each hospitalization was analyzed, a frequency distribution was created for the number of hospitalizations associated with each unique combination of events.

In instances where two different study endpoints were recorded during the same hospitalization, these were tracked as a single hospitalization for the purposes of the present analysis. Conversely, if a patient was hospitalized twice for the same event (i.e. worsening angina) the event is counted twice due to the fact that two hospitalizations occurred.

TABLE 2 Event Costs for Outcomes*

Event	Unit Cost
Angina	$3,322.52
Congestive heart failure	$4,301.67
Cardiac arrest	$5,691.08
Stroke	$6,084.79
Nonfatal MI	$5,678.59
Fatal MI	$5,678.59
PTCA	$6,057.66
CABG	$14,017.25
Drug Treatment	
Daily cost of atorvastatin 80 mg	$2.15
Number of days of treatment	97 days
Inpatient	9.75 days
Outpatient	87.25 days
Cost of inpatient atorvastatin treatment	$20.96
Cost of outpatient atorvastatin treatment†	$210.82
Total cost of atorvastatin treatment	$231.78
Additional Monitoring	
Liver function test	$14.70
Follow-up exam	$16.80

*All Unit Costs are in Canadian Dollars
†10% mark-up plus a one-time $4.47 professional fee was added
Source: 1996 Ontario Case Costing Project database, 2000 Ontario Schedule of Benefits. Costs were inflated to 2001 using Statistic Canada Consumer Price Index for Health and Personal Care for Ontario
MI = Myocardial Infarction
PTCA = Percutaneous Transluminal Coronary Angioplasty
CABG = Coronary Artery Bypass Graft

Cost Data

Direct healthcare costs for each outcome were identified and are listed in Table 2. For each clinical event that occurred in the MIRACL trial, a corresponding case-mix group (CMG) coding was identified.

Costs were then obtained from the Ontario Case Costing Project (OCCP) database in Ontario[19], which is considered representative of the Canadian healthcare system as a whole. The costs include all services provided during hospitalization including physician visits, nursing time, pharmacist time, and laboratory tests.

Surgeon and anesthesia fees were added to the surgery endpoints (i.e. CABG and PTCA) using the Ontario Schedule of Benefits.[20] All costs were inflated to reflect 2001 costs using the Consumer Price Index for Health and Personal Care for Ontario of Statistic Canada. To determine the cost of cardiac arrest in Canada ($5,691) the ratio between the cost for fatal MI and cardiac arrest in the US (1.0022) was applied to the Canadian unit cost of fatal MI ($5,678). In the

case where more than one event occurred within a single hospitalization, the recorded event for that patient was the more costly event.

This approach was considered justified in order to avoid the over estimation of cost since the Canadian cost data for hospitalization is derived from case mix groups (CMGs) that include all services provided during the hospitalization for a particular group (i.e. angina). Costing all the events occurring during the same hospitalization will result in counting several times the cost associated with some healthcare units such as cost per hospital bed. This is a conservative assumption since it is likely that more complicated admissions, i.e. those with multiple events, would have a higher cost than single event admissions. In no case was a single admission assigned the cost of multiple events in order to avoid double counting. After each hospital admission was assigned an event, the total number of events were multiplied by its unit cost to derive the total cost of event as outlined in Table 3.

TABLE 3 Cost Assigned for Inpatient Admissions*

		Placebo		Atorvastatin	
Event	**Unit Cost**	**# of Admissions**	**Total Cost of Event**	**# of Admissions**	**Total Cost of Event**
Death†	$0.00	4	$0.00	8	$0.00
Angina	$3,322.52	206	$684,439.12	162	$538,248.24
Congestive Heart Failure	$4,301.67	32	$137,653.44	29	$124,748.43
Stroke	$6,084.79	19	$115,611.01	11	$66,932.69
Myocardial Infarction	$5,678.59	68	$386,144.12	60	$340,715.40
Cardiac Arrest	$5,691.08	3	$17,073.25	3	$17,073.25
Revascularization (PTCA)	$6057.66	149	$902,591.34	156	$944,994.96
Fatal Myocardial Infarction	$5,678.59	32	$181,714.88	25	$141,964.75
CABG	$14,017.25	113	$1,583,949.25	109	$1,527,880.25
Total		626	$4,009,176.41	563	$3,702,557.97

* All Costs are in Canadian Dollars
† These deaths were not related to the study endpoints nor a hospitalization
PTCA = Percutaneous Transluminal Coronary Angioplasty
CABG = Coronary Artery Bypass Graft

Deaths that were not associated with any hospitalizations (22 in the placebo group and 21 in the atorvastatin group) were not included in the cost analysis.

For deaths occurring during a hospitalization, the cost of death was determined according to the reason for the death. For example, the fatal MI CMG cost was applied for "fatal MI". In some cases, no separate CMG existed for a particular type of death, in which case, the CMG for the event causing the death was used. The cost of stroke was incurred for 5 deaths (2 in the placebo group and 3 in the atorvastatin group).

As per the protocol for the clinical trial, there were 9 deaths deemed unrelated to the study in the atorvastatin group and 5 in the placebo group ("non-cardiac" and "unobserved").[16] In both groups, one of the aforementioned deaths was applied to the cost of other events occurring in the admission in which the patient died. In the placebo arm, the applied cost was for CHF, and in the atorvastatin arm, for nonfatal MI.

The total cost of atorvastatin 80 mg treatment was calculated by adding the cost of treatment during the inpatient period and the cost of treatment during the outpatient period. The mean duration of total exposure in the MIRACL clinical trial was 97 days, with an average of 9.75 days of exposure occurring during the inpatient portion of the event and 87.25 days of exposure during the outpatient portion. For the inpatient period the wholesale acquisition cost of atorvastatin 80 mg per day ($2.15) was used.

In the outpatient setting, a 10% mark-up and a one-time $4.47 professional fee ($6.47 dispensing fee minus $2 co-payment in Ontario) were added to the wholesale acquisition cost of atorvastatin 80 mg to calculate the cost of outpatient administration of atorvastatin (Table 2). Because both groups were comparable for usual care, costs of other drug treatments were not considered.

Incremental Cost-Effectiveness Analysis

The incremental cost was based on the total number of events experienced by patients following entry in the study, taking into account the added cost of atorvastatin 80 mg, and calculating the overall difference in cost between the two arms (adjusted for sample size differences).

An incremental cost-effectiveness analysis was performed where the incremental cost associated with atorvastatin treatment was divided by the improvement in health outcomes achieved.[22, 23] The unit of measurement for the improvement in health outcomes associated with intensive atorvastatin therapy was the number of hospitalization events avoided. The total cost per patient was also calculated for both arms.

Sensitivity Analysis

Univariate and multivariate sensitivity analyses were performed to test the robustness of the results to all assumptions.[24] For the univariate analysis, each clinical and economic parameter of the model was varied to determine the stability of the results and to examine if varying an individual parameter within its 95% confidence intervals while holding all other parameters constant could result in the break-even cost, or the point at which the cost of atorvastatin treatment was completely offset by the reduction in healthcare costs associated with treatment.

In the multivariate analyses, where all inputs were changed simultaneously [25], the numbers of event combinations were varied randomly within their 95% confidence interval according to a normal frequency distribution. The cost data used in the model were varied randomly within a range of + 20% from the highest cost and – 20% from the lowest cost according to a uniform frequency distribution.[26, 27, 28, 29]

Scenario testing was also performed to examine the impact of certain additional costs associated with monitoring ($16.80 for one follow-up exam plus $14.70 for one liver function test) and the impact of using a consistent cost for inpatient and outpatient usage of atorvastatin on the cost-effectiveness of atorvastatin treatment in ACS.

TABLE 4 Cost-Effectiveness Results*

	Primary Analysis	
	Placebo	**Atorvastatin**
Total N	1548	1538
Total # of Inpatient Events	626	563
Cost of All Inpatient Events	$4,009,176.41	$3,702,557.97
Cost of Atorvastatin	$0.00	$356,475.72
Total Cost	$4,009,176.41	$4,059,033.69
Cost per Patient	$2,589.91	$2,639.16
Additional Cost/Pt Treated with Atorvastatin		$49.26
Cost Per Event Avoided		$1,284.96

* All Costs are in Canadian Dollars

TABLE 5 Budget Impact Analysis Results*

Budget Impact Analysis in Canada			
Canadian ACS Inpatient Population	125,450		
Rate of Atorvastatin Use	0%	50%	100%
Cost per Patient	$2,589.91	$2,614.54	$2,639.16
Total Cost All ACS Patients	$324,904,942	$327,994,561	$331,084,179
Number of Events Per Patient	0.404	0.385	0.366
Total Number of Events All ACS Patients	50,731	48,327	45,922
Incremental Cost All ACS Patients	---	$3,089,618	$6,179,236
# Events Avoided All ACS Patients	---	2,404	4,809
# Events Avoided per ACS Patient	---	0.019	0.038
Incremental Cost per ACS Patient	---	$24.63	$49.26
Incremental Cost per Event Avoided		$642.48	$1,284.96

* All Costs are in Canadian Dollars
ACS = Acute Coronary Syndrome

Budget Impact Analysis

A budget impact analysis was performed to determine the impact of the "per patient" results if extrapolated to the Canadian healthcare system.

Several scenarios were examined varying the rates of atorvastatin usage (0%, 50%, and 100%) within the Canadian ACS population. Each scenario estimated the total 16-week cost of recurrent ischemic events for the Canadian ACS population as well as the total number of recurrent ischemic events over a 16-week time period avoided by an increased usage of atorvastatin. The total number of ACS inpatients (N=125,450) in the Canadian population was derived using data from the Canadian Institute for Health Information (CIHI) for the period of April 1, 2000 to March 31.[30]

RESULTS

The total 16-week expected cost was $2,639 per patient in the atorvastatin arm, compared to $2,590 per patient in the placebo arm (Table 4). The incremental cost of intensive atorvastatin treatment ($49.26 per patient) corresponds to a cost of $1,285 per event avoided. The cost of atorvastatin treatment was $232 per patient, 86% of which was offset by the cost savings resulting from the reduction in the number of events in the atorvastatin group compared to the placebo group.

Univariate and multivariate sensitivity analyses were conducted to assess the impact on the results of variations in the input assumptions. The univariate sensitivity analysis demonstrated that the results were sensitive to the rates of CABG, MI and angina and insensitive with respect to all other parameters. The univariate analysis indicated that, while holding all other parameters constant, almost a three fold increase (2.64) in the rate of CABG in both the atorvastatin and placebo arms, resulted in the break-even point, at which the cost of atorvastatin 80 mg treatment was completely offset. For MI and angina, increasing their rates by 2.76 and 1.53, respectively, yielded the break-even cost. In the multivariate analysis, all inputs were varied simultaneously (10,000 iterations) and corresponding results were plotted.

The outcomes of the multivariate analysis indicated that the results are robust against assumptions and that the relative risk of CABG surgery was the parameter that most highly correlated with the economic results. After 10,000 iterations, the mean incremental cost between atorvastatin and placebo was $49.23 with a range from $21.01 to $77.13.

In addition to the sensitivity analyses, two different scenarios were considered. The first scenario assumed that patients on atorvastatin treatment typically require additional monitoring for potential liver toxicity. Therefore, a scenario was created which estimated results when the costs of a liver function test and one physician follow-up visit were included in the treatment cost for patients on atorvastatin. The total expected cost per patient in the atorvastatin group increased to $2,671, and the incremental cost of intensive atorvastatin treatment increased to $81.76 (versus $49.26 for the base case analysis) corresponding to a cost of $2,107 per event avoided.

An additional scenario was analyzed to assess the impact of using a constant cost for atorvastatin for both inpatient and outpatient drug treatment in the analysis. The reference price in this scenario was the inpatient cost of atorvastatin 80 mg ($2.15 versus a daily outpatient cost of $2.42). Under this assumption, the total expected cost per patient in the atorvastatin group decreased to $2,616, resulting in an incremental cost of $26.03 versus placebo. Under this scenario, the cost per event avoided was $679.

Once the sensitivity analysis revealed that the results were robust against all assumptions, a budget impact analysis extrapolated the patient level results of the base case analysis to the population level. The budget impact base case analysis of 0% atorvastatin use resulted in 50,731 subsequent ischemic events occurring each year for all ACS patients at a total estimated cost of $325 million (Table 5).

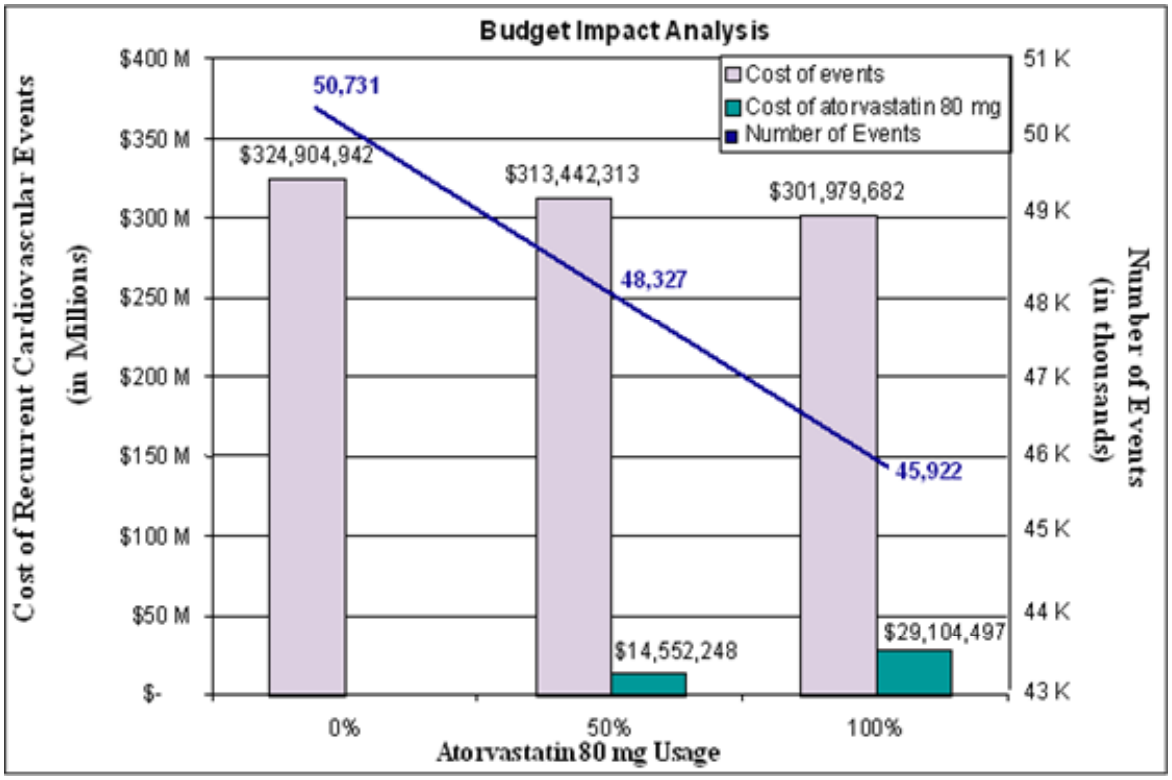
In a scenario where 50% of patients were assumed to be using atorvastatin, the total cost for all ACS patients increased by $3 million ($328 million) while the number of recurrent cardiovascular events decreased by 2,404 (recurrent cardiovascular events was 48,327).

This cost increased to $331 million in a scenario in which atorvastatin was used in 100% of patients hospitalized for ACS ($6 million more than in the 0% atorvastatin use scenario); however, the number of events dropped to 45,922 (4,809 less recurrent cardiovascular events relative to the 0% atorvastatin use scenario).

Figure 1 depicts the direct inverse linear relationship between atorvastatin use and number of events following hospitalizations and the positive relationship between atorvastatin use and the total cost of cardiovascular events.

According to Figure 1, it is evident that increased atorvastatin 80 mg usage is associated with a large number of events avoided and at a small additional cost when projected to the Canadian ACS population. In fact, for an increase of 1.9% in total costs, we estimated a decrease of 9.5% in recurrent cardiovascular events when comparing the scenario in which no use of atorvastatin 80 mg takes place to the scenario in which atorvastatin was used in 100% of ACS patients.

FIGURE 1 Budget Impact Graph (Based on 125,450 ACS hospitalizations in Canada)*



*All costs are in Canadian Dollars

DISCUSSION

The MIRACL trial demonstrated the clinical benefits of intensive treatment with atorvastatin, initiated within days after hospitalization for ACS. Early treatment with atorvastatin 80 mg significantly reduced the incidence of recurrent ischemic events over a 16-week time period.

This pharmacoeconomic analysis demonstrated that this type of intensive, short-term treatment strategy was cost-effective, with an attractive incremental cost-effective ratio of $1,285 to prevent one fatal or non-fatal cardiovascular related hospitalization. The incremental cost of atorvastatin treatment ($231.78 per patient) was offset by the cost savings obtained through the reduction in the number of cardiovascular events in the atorvastatin group compared to the placebo group, resulting in a net incremental cost of $49.26 per patient treated with atorvastatin.

Our economic method for this study may be considered conservative because the analysis does not include higher costs for multiple event admissions, and also does not include complications beyond the initial hospital stay nor any events avoided after the 4-month study period. The potential costs or benefits of treatment were not modeled beyond the time period of the trial and long-term costs, such as rehabilitation after stroke, were not considered. In fact, no outpatient costs after discharge (e.g. specialist visits, exercise tests, ultrasounds, etc.) that is typically required after non-fatal MI and strokes were considered because these data were not collected prospectively.

These assumptions translate into an under-estimation of the benefits of atorvastatin 80 mg because our calculations included the inpatient and outpatient costs of atorvastatin over the period of analysis while at the same time the calculations considered only the inpatient cost for the events analyzed in this trial.

As well, the results should not be extrapolated to long-term (greater than 16 weeks) treatment with atorvastatin. The clinical and economic analysis of MIRACL is also limited to the specific dose of atorvastatin 80 mg daily for 16 weeks and the results do not apply to patients referred for early invasive management of ACS.

Indirect costs such as time missed from work, productivity loss were also not considered, which results in an underestimation of the benefits of atorvastatin 80 mg given within a few days after an ACS episode. A recent Canadian study showed the importance of accounting for indirect costs associated with CVD in economic evaluations.[31]

This study found that the annual employment income lost due to CVD was highest for those aged 40-49 and ranged from $4,894 to $16,667 for men, and from $4,381 to $6,933 for women. Additionally, this study found that productivity losses for women were $2,257 among those 40-49 years old and at $3,083 among those aged 50-59. The corresponding values for men were $1,018 and $896, respectively. This study demonstrated that when indirect costs are taken into consideration in the analysis, lifelong therapy with atorvastatin 10mg is estimated to save lives and also money in primary CVD prevention.

The consideration of indirect costs in cardiovascular economic evaluations is especially relevant since indirect costs associated with cardiovascular disease (i.e., value of lost productivity and the loss of future earnings due to premature death) were calculated at $12.3 billion in 1993 representing 62% of the total CVD cost in Canada.[1]

The occurrence of hospitalizations for this analysis used data from all participating countries and reported only pre-determined clinical endpoints as set forth in the international protocol. While the data is not specific to Canada, the protocol of the MIRACL trial required that a committee review each event to determine if the event should be considered an endpoint. Because the clinical effects of atorvastatin treatment did not differ among geographical regions in MIRACL the use of international data for individual country analysis is justified.

Furthermore, the trial was not powered to analyze patient level data broken down by

country; the sample size for Canadian patients would be insufficient to analyze separately. Only hospitalizations related to the endpoints of the clinical trial were considered in the analysis. Hospitalizations due to unrelated adverse events were not included. However, the incidence of hospitalizations due to adverse events in the MIRACL trial was extremely low (3 hepatitis cases in the atorvastatin group) and the inclusion of these costs in the analysis would have had no significant effect on the primary results.

The cost of patients lost to follow-up was also not included in this economic analysis. It is well established that loss to follow-up is a common cause of missing data in clinical trials. The percentage lost to follow up in the MIRACL study was relatively small at 0.7% and the impact of adding the costs of these 11 patients would be negligible.

As in the UK, [32] the clinical benefits of intensive short-term treatment administered within a few days after ACS is associated with a favorable cost-effectiveness in Canada (i.e., incremental cost: $49.26 per patient). Eighty six percent of atorvastatin treatment cost is offset by cost savings due to the reduction in the number of events in the atorvastatin group compared to the placebo. Moreover, the potential clinical benefits realized by avoiding cardiovascular events through intensive atorvastatin treatment in the short-term may continue long after the occurrence of ACS and could translate into potentially significant long-term cost savings.

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