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What is the effect of using different cost-effectiveness measures in the economic evaluation of cholesterol-modifying pharmacotherapy?

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Introduction

There is conclusive evidence that the association between cholesterol and coronary heart disease (CHD) is one of cause and effect. [1] Such evidence suggests that modifying cholesterol levels will reduce the incidence of CHD events. For those individuals with elevated cholesterol levels in whom dietary intervention has failed, a variety of drugs are available as the next stage of therapy, and the relatively new generation of HMG-CoA reductase inhibitors (the 'statins') are increasingly becoming the drugs of first choice.

The evidence in favour of programmes aimed at modifying cholesterol levels in order to reduce the burden of CHD is compelling. However, economic criteria represent important constraints to the introduction and magnitude of such programmes, since at a certain point, additional cholesterol reductions become increasingly difficult and expensive to achieve. Therefore, given the growing pressure on scarce health care resources, there is an interest in the application of economic evaluation to cholesterol management in general, and to cholesterol-modifying pharmacotherapy in particular.

Whilst the importance of the economic evaluation of cholesterol-modifying pharmacotherapy is recognised, the ideal form of that evaluation is not so clear cut. A variety of measures may be used to estimate the cost-effectiveness of cholesterol-modifying pharmacotherapy, and each of these has a different informational content to decision-makers, both in terms of their empirical usefulness (the extent to which the information they provide is useful in the real world), and in terms of the relative cost-effectiveness ranking they provide of different cholesterol-modifying agents (the extent to which they show one agent to be more cost-effective than another). In a recent review of the cost-effectiveness literature Morris et al. [2] identified 37 economic evaluations of cholesterol management, 25 of which examined the cost-effectiveness of specific cholesterol-modifying pharmacotherapies. A variety of cost-effectiveness measures were used: cost per 1% reduction in total cholesterol (2 studies); cost per 1% reduction in low-density lipoprotein cholesterol [LDL-C] (6 studies); cost per 1% increase in high-density lipoprotein cholesterol [HDL-C] (1 study); cost per 1% reduction in LDL-C/HDL-C index (1 study); cost per 1mmol/l reduction in LDL-C (1 study); cost per 10% reduction in total cholesterol (1 study); cost per death prevented (1 study); cost per CHD death prevented (1 study); cost per CHD and non-fatal myocardial infarction prevented (1

study); and, cost per life year saved (15 studies). Some studies included more than one type of cost-effectiveness measure. Morris et al. concluded from their review that the statins are generally more cost-effective at modifying cholesterol levels, reducing CHD events and increasing life expectancy than other agents. However, the relative cost-effectiveness of individual agents varied from study to study, making it difficult to identify exactly which one was most cost-effective.

The aim of this paper is to evaluate the effect of using different cost-effectiveness measures in the economic evaluation of cholesterol-modifying pharmacotherapy. Using a Canadian-based economic model we examine the extent to which the relative cost-effectiveness of cholesterol-modifying agents varies depending upon the cost-effectiveness measure used. We also offer some normative judgments regarding the most appropriate cost-effectiveness measure and the usefulness that different measures have to decision-makers.

Choice of cost-effectiveness measure in the economic evaluation of cholesterol-modifying pharmacotherapy

It is helpful to distinguish between different types of cost-effectiveness measure in terms of whether they use intermediate or final outcomes and whether they are 'open-ended' or 'targeting' analyses.

Generally, two types of cost-effectiveness measure have been used in the majority of economic evaluations of cholesterol-modifying pharmacotherapy to date: 'cost per change in cholesterol' and 'incremental cost per life year gained'. Cost per change in cholesterol, the most common form of which is cost per 1% change in LDL-C, uses an intermediate measure of health outcome. Accordingly there are two reasons why this measure or similar is inappropriate for assessing the cost-effectiveness of cholesterol-modifying pharmacotherapy: first, it ignores any additional effects of pharmacotherapy on other types of cholesterol such as HDL-C, the modification of which is likely to have an effect on the health of the patient; second, it assumes a constant rate of marginal return to LDL-C reductions, which is inconsistent with the general finding that CHD risk is an increasing (not constant) function of baseline LDL-C levels.

The use of incremental cost per life year gained avoids these problems, though this cost-effectiveness measure may be of limited use if conducted on an open-ended basis. In the clinical setting, a patient with only moderated elevated cholesterol levels may require only limited reductions in LDL-C. Very expensive agents which are able to produce large reductions in LDL-C may be more cost-effective than cheaper but less effective agents, but may not be worthwhile prescribing if they produce reductions in LDL-C much greater than necessary. Other agents may be less cost-effective, but adequately effective at reducing LDL-C and less costly and therefore more appropriate. Alternatively, cheaper but less effective agents may be more cost-effective than expensive agents able to produce large reductions in LDL-C but may not be worth prescribing if they are unable to produce sufficient LDL-C reductions. Both these scenarios may arise when economic evaluations of cholesterol-modifying pharmacotherapy are conducted on a 'open-ended' basis, where the analysis fails to take into account the magnitude of LDL-C reduction required. Consequently, open-ended economic evaluations of cholesterol-modifying pharmacotherapy are likely to be of only limited use in the real world. What is required is a type of economic evaluation that considers the magnitude of cholesterol modification required in addition to estimating the relative cost-effectiveness of different agents. Such analyses may be thought of as 'targeting analyses'.

To date, a single targeting analysis of cholesterol-modifying pharmacotherapy has been published. Heudebert et al. [3] assessed the costs of various agents in achieving a target LDL-C level of 130mg/dl from baseline levels. However, because cost-effectiveness was couched solely in terms of the least cost agent able to achieve a specific LDL-C reduction this analysis fails to take into account, firstly, the additional effects of pharmacotherapy on other types of cholesterol such as HDL-C, and secondly, additional LDL-C effects over and above those required to reach the target level, both of which are likely to produce beneficial health effects. Both these additional effects (HDL-C modifications, and LDL-C modifications greater than the target level) are important because they will affect CHD risk and life expectancy, but would be neglected in analyses where cost-effectiveness is measured solely in terms of the least cost agent to achieve a target LDL-C reduction.

What is needed is a type of targeting analysis that also includes the wider effects of pharmacotherapy and uses final health outcomes. We therefore estimate the incremental cost per life year gained in reaching a predefined target LDL-C level. A cost-effectiveness measure

of this kind includes the full effects of pharmacotherapy on final health outcomes, will only assess agents capable of achieving the required cholesterol modification, and allows for the fact that in patients with moderately elevated cholesterol levels only limited LDL-C reductions may be required. This represents a new mode of cost-effectiveness measure for the economic evaluation of cholesterol-modifying pharmacotherapy and provides an empirically useful and practical means of assessing the relative cost-effectiveness of different agents.

In the following analysis we estimate the relative cost-effectiveness of cholesterol-modifying pharmacotherapy using different cost-effectiveness measures of the types discussed above. We do this to examine, firstly, how these measures are constructed, and secondly, the extent to which the relative cost-effectiveness of cholesterol-modifying agents may vary depending upon the cost-effectiveness measure used. This is a Canadian-based analysis conducted from the perspective of the Canadian public health care system. Cholesterol-modifying pharmacotherapies available in Canada at the time of analysis are included, namely: atorvastatin 10mg, 20mg, 40mg and 80mg per day; cholestyramine 24g per day; fluvastatin 20mg, 40mg and 80mg per day; lovastatin 20mg, 40mg and 80mg per day; pravastatin 10mg, 20mg, 40mg and 80mg per day; and, simvastatin 10mg, 20mg, and 40mg per day.

Methods

Measuring effectiveness

Effectiveness of cholesterol-modifying pharmacotherapy may be quantified in two stages: the effect of therapy on cholesterol; and, the impact of these changes in cholesterol on lifetime CHD risk and life expectancy.

Drug effects on cholesterol level

The relationship between drug intake and changes in LDL-C and HDL-C was established from a systematic review of the literature. English-language clinical study reports of the efficacy of study drugs were identified by searches of the MEDLINE database and the SOCIAL SCIENCES CITATION INDEX. The reference section of each retrieved study was reviewed to identify further studies. Study inclusion criteria were: (1) double-blind randomised controlled trials; (2) study of hypercholesterolemia in adult subjects without CHD; (3) prior

trial of dietary intervention, as per expert guidelines; and, (4) use of the study drugs as monotherapy. For each drug/dosage combination, average changes in LDL-C and HDL-C were calculated by weighting the changes observed in each trial by the number of patients treated with that dosage strength. Study inclusion criteria and the weighting methodology employed are consistent with previous analyses (see, for example, Martens and Guibert [4] and Schulman et al. [5]).

Effect of cholesterol level changes on CHD risk

A computer-generated CHD risk model is used to forecast disease incidence, survival and life expectancy with and without drug therapy. This model utilises risk equations derived from the Framingham Heart Study to forecast one-year CHD incidence given baseline epidemiological data. These CHD risk equations allow measurement of the association between one risk factor such as LDL-C and the incidence of CHD (manifested by myocardial infarction, coronary insufficiency, angina pectoris, sudden death from CHD, and non-sudden death from CHD) while at the same time allowing for some variation in other risk factors. These CHD risk equations, estimated by Martens and Guibert [4] and Martens et al., [6] are used to assess the one-year risk of CHD for individuals currently free of CHD from current age to 75 years.

Life expectancy is calculated by estimating the area under the survival curve from age at initiation of therapy to age 75, where the height of the survival curve at any particular age is the cumulative probability of surviving from the age at initiation of therapy to that age. The cumulative probability of survival is calculated by using age-related CHD incidence and mortality data to assess the one year probability of survival. Probabilities of CHD incidence are first calculated using mean population-based data and then recalculated incorporating appropriate LDL-C and HDL-C changes associated with drug therapy. Epidemiological data for the risk factors used in the CHD risk model were obtained from the Canadian Heart Health Survey. [7]

Measuring costs

Costs are estimated in Canadian dollars (Can$) and calculated in constant 1997-1998 prices. Cost components included in the analyses are: initiation to therapy; drug therapy; monitoring of therapy; and, costs from treatment of CHD events.

Costs to initiate a patient to therapy, including extra clinical visits and appropriate laboratory tests, are $62 for all agents. Annual costs to monitor drug therapy are $62. Average treatment costs for CHD events are estimated to be $17,965 for myocardial infarction, $8,862 for angina pectoris, $8,862 for coronary insufficiency, $539 for sudden death $22,874 for non-sudden death. Costs of initiation to therapy, monitoring therapy, myocardial infarction, angina pectoris, and coronary insufficiency were obtained from updates of comprehensive Canadian-based cost analyses. [4,8-13] For sudden death and non-sudden death there were insufficient Canadian data available and so published US costs were used [14-15] and converted to Canadian dollars. Drug therapy costs are Canadian drug prices taken from the Liste de Medicaments (Quebec). [16]

Measuring cost-effectiveness

Where appropriate, future costs and changes in life expectancy are discounted to present values at an annual rate of 6%. Cost-effectiveness is assessed using a number of measures:

Cost per 1% reduction in LDL-C (intermediate outcome, open-ended analysis)

This is calculated simply as the ratio of the annual drug cost to the change in LDL-C caused by the drug.

Incremental cost per life year gained (final outcome, open-ended analysis)

This is calculated as the ratio of the net change in discounted costs from therapy to the net change in discounted life expectancy, or (D+M-C)/L, where D is the discounted expected lifetime cost of a given regimen of drug therapy, M is the discounted expected lifetime cost of monitoring and treatment of drug-related side-effects, C denotes the discounted expected savings in lifetime CHD treatment costs from a reduced incidence of CHD due to drug therapy, and L is the discounted expected increase in life expectancy resulting from drug therapy.

Least cost agent capable of achieving LDL-C reduction required to meet target level of 160 mg/dl (intermediate outcome, targeting analysis)

Pretreatment LDL-C levels are divided into 5mg/dl bands. The midpoint of each band is calculated and the percentage reduction in LDL-C required to reach the target level from this midpoint is estimated. Results of the systematic review of the LDL-C-lowering effects of pharmacotherapy are then used to calculate, at each pretreatment LDL-C level, those agents capable of achieving the required LDL-C reductions. The least cost agent is then ascertained using drug cost data.

For this and subsequent analyses we require a target LDL-C level and a pretreatment LDL-C level at which pharmacotherapy should be initiated. Various consensus committees have reviewed recent research developments and furnished guidelines for optimal cholesterol levels in an attempt to reduce the burden of CHD. For example, the National Cholesterol Education Program (NCEP) in the US makes the following recommendations: [17]

"For the patient without CHD or other atherosclerotic disease, the target goals for LDL cholesterol lowering depend on the risk status of the patient and include the following:

- <160 mg/dl if fewer than two other risk factors are present
- < 130 mg/dl if two or more CHD risk factors are present

In primary prevention, most patients who qualify for medical treatment should receive dietary therapy and should increase physical activity. The levels of LDL cholesterol for initiation of dietary therapy are:

- 160 mg/dl in patients who have fewer than two other CHD risk factors
- 130 mg/dl in patients who have two or more CHD risk factors

The LDL cholesterol levels at which drug therapy can be considered *after* an adequate trial of dietary therapy are:

- 190 mg/dl in patients without two other CHD risk factors
- 160 mg/dl in patients with two or more CHD risk factors"

These are broadly consistent with other recommended approaches to treatment (see, for example, British Hyperlipidaemia Association [18]), and are used here for the target LDL-C level and LDL-C level at which drug therapy should be initiated. We therefore assume that drug therapy is initiated for individuals with LDL-C levels in excess of 190mg/dl and that the target LDL-C level is 160mg/dl.

Incremental cost per life year gained of agents able to reach target LDL-C level of 160mg/dl relative to no therapy (final outcome, targeting analysis)

This is calculated in the same way as the open-ended incremental cost per life year gained described above, except cost-effectiveness is considered only among agents that are capable of achieving the reduction in LDL-C required to reach the target level from the pretreatment level.

Incremental cost per life year gained of agents able to reach target LDL-C level of 160mg/dl relative to least cost agent able to reach target (final outcome, targeting analysis)

A variation on the previous measure, this also is calculated in a similar way to the open-ended incremental cost per life year gained described above except cost-effectiveness is considered only among agents that are capable of achieving the reduction in LDL-C required to reach the target level from the pretreatment level, and cost-effectiveness is considered relative to the least cost agent capable of achieving the required LDL-C reduction from the pretreatment LDL-C level.

Results

116 clinical studies met the inclusion criteria for systematic review of drug effect on cholesterol. The weighted average change in LDL-C and HDL-C for each agent is presented in Table 1 along with the annual drug costs. The cost per 1% reduction in LDL-C for each agent is presented in Table 2. Gains in life expectancy, incremental costs and the incremental cost per life year gained relative to no therapy are shown on Table 3 (in this case for 55 year old males with pretreatment LDL-C of 200mg/dl at otherwise average risk). The least cost agents capable of reaching the target LDL-C level of 160mg/dl are presented in Table 4, for pretreatment LDL-C levels of 190-245mg/dl. For example, at pretreatment LDL-C levels of 235-240mg/dl eight agents are capable of producing the 32.6% LDL-C reduction required to reduce LDL-C to the 160mg/dl level recommended by NCEP (fluvastatin 80mg per day, atorvastatin 10mg, 20mg, 40mg and 80mg per day, simvastatin 40mg per day, lovastatin 80mg per day, and pravastatin 80mg per day). Atorvastatin10mg per day is the least cost agent capable of achieving this target reduction.

Incremental cost per life year gained for agents able to reach target LDL-C level of 160mg/dl relative to no therapy are presented in Figure 1 (in this case for 55 year old males at otherwise average risk) by pretreatment LDL-C level. For example, of the eight agents capable of producing the 32.6% reduction required to reduce pretreatment LDL-C levels of 235-240mg/dl to the target level, atorvastatin 20mg per day has the least incremental cost per life year gained relative to no therapy ($40,000).

Incremental costs per life year gained for each agent relative to the least cost agent capable of reaching the target are presented in Figure 2. For example, at pretreatment LDL-C levels of 235-240mg/dl, atorvastatin 10mg per day is the least cost agent capable of achieving the target. Atorvastatin 20mg per day is the most cost-effective of the other agents also able to reach the target level relative to this, with an incremental cost per life year gained of $35,000.

Discussion

In this paper we estimate the relative cost-effectiveness of cholesterol-modifying pharmacotherapy using different types of cost-effectiveness measure. The results of the analysis are summarised in Table 5.

The simplest cost-effectiveness measure is cost per 1% change in LDL-C. This leads to the result that fluvastatin 20mg is the most cost-effective pharmacotherapy, because whilst the LDL-C-modifying effect is small (a reduction of 21%), the annual drug cost is low ($274 per annum). The advantage of this cost-effectiveness measure is that its calculation is very straightforward and the data requirements are minimal. However, we would not recommend its use for the following reasons. First, only annual drug costs are considered, and a number of other important costs arising from pharmacotherapy are not included, such as costs saved from averted CHD events. Second, it ignores any additional effects of pharmacotherapy on other types of cholesterol such as HDL-C, the modification of which is likely to have an effect on the health of the patient. Third, it incorrectly assumes a constant (rather an increasing) rate of marginal return to LDL-C reductions.

Incremental cost per life year gained, the most prevalent form of cost-effectiveness measure in previous economic evaluations of cholesterol-modifying pharmacotherapy, avoids these problems. However, both this measure and cost per 1% reduction in LDL-C are 'open-ended' and thus fail to take into account the magnitude of LDL-C reduction required. For example, both these measures recommend that fluvastatin 20mg should be used in preference over other agents, even for individuals with very high pretreatment LDL-C levels (220mg/dl and above). This is even though fluvastatin 20mg reduces LDL-C by only 21%. This recommendation is unlikely to be endorsed by clinicians who will probably not even consider fluvastatin 20mg as a possible therapeutic option for such high risk patients. We would argue then that open-ended cost-effectiveness analyses of this kind may be of little use to health care decision-makers in the real world since they may well recommend inappropriate therapeutic choices. This is unfortunate since the majority of economic evaluations of cholesterol-modifying pharmacotherapy are of this kind.

Estimation of the least cost agent capable of achieving LDL-C reduction required to meet a target LDL-C level is the simplest form of targeting analysis and avoids many of these problems. With this cost-effectiveness measure less effective agents are not recommended for patients with high pretreatment LDL-C levels because they are not even considered in the analysis. This is therefore a more useful and realistic cost-effectiveness measure. However, we would not recommend its because it fails to take into account the full effects of therapy. Since outcomes are considered only in intermediate terms (LDL-C), the recommendations from this cost-effectiveness measure are of limited use if the ultimate goal of cholesterol-modifying pharmacotherapy is the improvement of final outcomes such as life expectancy.

This leads to consideration of the two final cost-effectiveness measures included in this study, which estimate incremental cost per life year gained of agents able to reach a target LDL-C level. These are targeting analyses that also include the wider effects of pharmacotherapy using final health outcomes. We recommend the use of these cost-effectiveness measures for the following reasons. First, they include the full effects of pharmacotherapy on final health outcomes. They include the additional effects of pharmacotherapy on other types of cholesterol such as HDL-C, and they include the additional effects of LDL-C modification over and above those required to reach the target level. Second, only agents capable of achieving a sufficiently large cholesterol modification are ultimately considered in the analysis.

This allows for the fact that in patients with moderately elevated pretreatment LDL-C levels only limited reductions may be required, and that in patients with high pretreatment LDL-C levels substantial reductions are required. This type of analysis is more consistent with what happens in the real world where clinicians take into account the pretreatment cholesterol levels of the patient and the magnitude of cholesterol modification required when prescribing medications.

Incremental cost per life year gained of agents able to reach target LDL-C level relative to no therapy is the simplest form of this type of cost-effectiveness measure. A variation of this is incremental cost per life year gained of agents able to reach target LDL-C level relative to least cost agent able to reach target. This variation is appropriate if we assume that, given scarce health care resources, clinicians currently prescribe the least cost agent capable of achieving the target LDL-C reduction required. Both these cost-effectiveness measures recommend that fluvastatin be used for patients with moderately elevated LDL-C levels and that in patients with higher LDL-C levels, atorvastatin should be preferred.

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Table 1. The cost and effectiveness of cholesterol-modifying pharmacotherapy

			Mean change in cholesterol level (%)	
Agent	Daily dose	Cost (Can$) [1]	LDL-C	HDL-C
Atorvastatin	10mg	584	-36	+7
	20mg	730	-42	+14
	40mg	785	-49	+1
	80mg	1,570	-54	+7
Cholestyramine	24g	1,153	-28	+5
Fluvastatin	20mg	274	-21	+4
	40mg	383	-27	+5
	80mg	767	-33	+8
Lovastatin	20mg	631	-25	+8
	40mg	1,164	-31	+9
	80mg	2,263	-40	+12
Pravastatin	10mg	551	-20	+9
	20mg	653	-26	+10
	40mg	785	-27	+6
	80mg	1,570	-38	+5
Simvastatin	10mg	650	-29	+7
	20mg	803	-32	+8
	40mg	986	-37	+11

1 Canadian drug costs for treatment of adults at doses shown for one year

Table 2. The cost per 1% reduction in LDL-C of cholesterol-modifying pharmacotherapy

Agent	Daily dose	Cost (Can$)	Mean % change in LDL-C	Cost per 1% reduction in LDL-C (Can$)
Fluvastatin	20mg	274	-21	13
Fluvastatin	40mg	383	-27	14
Atorvastatin	10mg	584	-36	16
Atorvastatin	40mg	785	-49	16
Atorvastatin	20mg	730	-42	17
Simvastatin	10mg	650	-29	22
Fluvastatin	80mg	767	-33	23
Lovastatin	20mg	631	-25	25
Pravastatin	20mg	653	-26	25
Simvastatin	20mg	803	-32	25
Simvastatin	40mg	986	-37	27
Pravastatin	10mg	551	-20	28
Atorvastatin	80mg	1,570	-54	29
Pravastatin	40mg	785	-27	29
Lovastatin	40mg	1,164	-31	38
Pravastatin	80mg	1,570	-38	41
Cholestyramine	24g	1,153	-28	41
Lovastatin	80mg	2,263	-40	57

Table 3. The incremental cost per life year gained of cholesterol-modifying pharmacotherapy relative to no therapy for 55 year old males with pretreatment LDL-C of 200mg/dL at otherwise average risk

Agent	Daily Dose	Incremental cost (Can$)	Life years gained	Incremental cost per life year gained (Can$)
Fluvastatin	20mg	3,233	0.0882	36,645
Fluvastatin	40mg	4,284	0.1125	38,088
Atorvastatin	20mg	7,648	0.1893	40,407
Atorvastatin	10mg	6,256	0.1502	41,648
Atorvastatin	40mg	8,259	0.1815	45,506
Simvastatin	10mg	7,045	0.1259	55,959
Pravastatin	20mg	7,079	0.1251	56,567
Fluvastatin	80mg	8216	0.1427	57,571
Pravastatin	10mg	6,092	0.1022	59,583
Lovastatin	20mg	6,884	0.1155	59,590
Simvastatin	20mg	8,608	0.1393	61,811
Simvastatin	40mg	10,447	0.1648	63,382
Pravastatin	40mg	8,504	0.1158	73,440
Atorvastatin	80mg	16,451	0.2158	76,225
Lovastatin	40mg	12,417	0.1388	89,437
Cholestyramine	24g	12,379	0.1160	106,749
Pravastatin	80mg	16,660	0.1515	109,995
Lovastatin	80mg	23,906	0.1776	134,600

Table 4. Least cost agent capable of achieving LDL-C reduction required to meet target level of 160 mg/dl, by pretreatment LDL-C level

Pretreatment LDL-C Level (mg/dl)	Reduction In LDL-C Required To Reach Target Of 160 mg/dl (%) [1]	Agents Capable Of Achieving This Reduction (Based On Weighted Mean Reduction)	Least Cost Agent Capable Of Achieving This Reduction
190 up to 195	16.9	Fluvastatin20; Fluvastatin40; Fluvastatin80; Atorvastatin10; Atorvastatin20; Atorvastatin40; Atorvastatin80; Simvastatin10; Simvastatin20; Simvastatin40; Lovastatin20; Lovastatin40; Lovastatin80; Pravastatin10; Pravastatin20; Pravastatin40; Pravastatin80; Cholestyramine24	Fluvastatin20
195 up to 200	19.0	Fluvastatin20; Fluvastatin40; Fluvastatin80; Atorvastatin10; Atorvastatin20; Atorvastatin40; Atorvastatin80; Simvastatin10; Simvastatin20; Simvastatin40; Lovastatin20; Lovastatin40; Lovastatin80; Pravastatin10; Pravastatin20; Pravastatin40; Pravastatin80; Cholestyramine24	Fluvastatin20
200 up to 205	21.0	Fluvastatin20; Fluvastatin40; Fluvastatin80; Atorvastatin10; Atorvastatin20; Atorvastatin40; Atorvastatin80; Simvastatin10; Simvastatin20; Simvastatin40; Lovastatin20; Lovastatin40; Lovastatin80; Pravastatin20; Pravastatin40; Pravastatin80; Cholestyramine24	. Fluvastatin20
205 up to 210	22.9	Fluvastatin40; Fluvastatin80; Atorvastatin10; Atorvastatin20; Atorvastatin40; Atorvastatin80; Simvastatin10; Simvastatin20; Simvastatin40; Lovastatin20; Lovastatin40; Lovastatin80; Pravastatin20; Pravastatin40; Pravastatin80; Cholestyramine24	Fluvastatin40
210 up to 215	24.7	Fluvastatin40; Fluvastatin80; Atorvastatin10; Atorvastatin20; Atorvastatin40; Atorvastatin80; Simvastatin10; Simvastatin20; Simvastatin40; Lovastatin20; Lovastatin40; Lovastatin80; Pravastatin20; Pravastatin40; Pravastatin80; Cholestyramine24	Fluvastatin40

215 up to 220	26.4	Fluvastatin40; Fluvastatin80; Atorvastatin10; Atorvastatin20; Atorvastatin40; Atorvastatin80; Simvastatin10; Simvastatin20; Simvastatin40; Lovastatin40; Lovastatin80; Pravastatin40; Pravastatin80; Cholestyramine24	Fluvastatin40
220 up to 225	28.1	Fluvastatin80; Atorvastatin10; Atorvastatin20; Atorvastatin40; Atorvastatin80; Simvastatin10; Simvastatin20; Simvastatin40; Lovastatin40; Lovastatin80; Pravastatin80	Atorvastatin10
225 up to 230	29.7	Fluvastatin80; Atorvastatin10; Atorvastatin20; Atorvastatin40; Atorvastatin80; Simvastatin20; Simvastatin40; Lovastatin40; Lovastatin80; Pravastatin80	Atorvastatin10
230 up to 235	31.2	Fluvastatin80; Atorvastatin10; Atorvastatin20; Atorvastatin40; Atorvastatin80; Simvastatin20; Simvastatin40; Lovastatin80; Pravastatin80	Atorvastatin10
235 up to 240	32.6	Fluvastatin80; Atorvastatin10; Atorvastatin20; Atorvastatin40; Atorvastatin80; Simvastatin40; Lovastatin80; Pravastatin80	Atorvastatin10
240 up to 245	34.0	Atorvastatin10; Atorvastatin20; Atorvastatin40; Atorvastatin80; Simvastatin40; Lovastatin80; Pravastatin80	Atorvastatin10

1 % reduction from midpoint of range to target of 160mg/dl

Table 5. Most cost-effective cholesterol-modifying pharmacotherapy by cost-effectiveness measure and pretreatment LDL-C level

	Cost-effectiveness measure				
Pretreatment LDL-C Level (mg/dl)	Least cost per 1% reduction in LDL-C	Least incremental cost per life year gained relative to no therapy	Least cost agent capable of achieving LDL-C reduction required to meet target level of 160 mg/dl	Least incremental cost per life year gained of agents able to reach target LDL-C level of 160mg/dl relative to no therapy	Least incremental cost per life year gained of agents able to reach target LDL-C level of 160mg/dl relative to least cost agent able to reach target
190 up to 205	Fluvastatin 20mg	Fluvastatin 20mg	Fluvastatin20	Fluvastatin20	Fluvastatin40
205 up to 220	Fluvastatin 20mg	Fluvastatin 20mg	Fluvastatin40	Fluvastatin40	Atorvastatin20
220 up to 245	Fluvastatin 20mg	Fluvastatin 20mg	Atorvastatin10	Atorvastatin20	Atorvastatin20

Figure 1. Incremental cost per life year gained of agents able to reach target LDL-C level of 160mg/dl relative no therapy, by pretreatment LDL-C level for 55 year old males at otherwise average risk

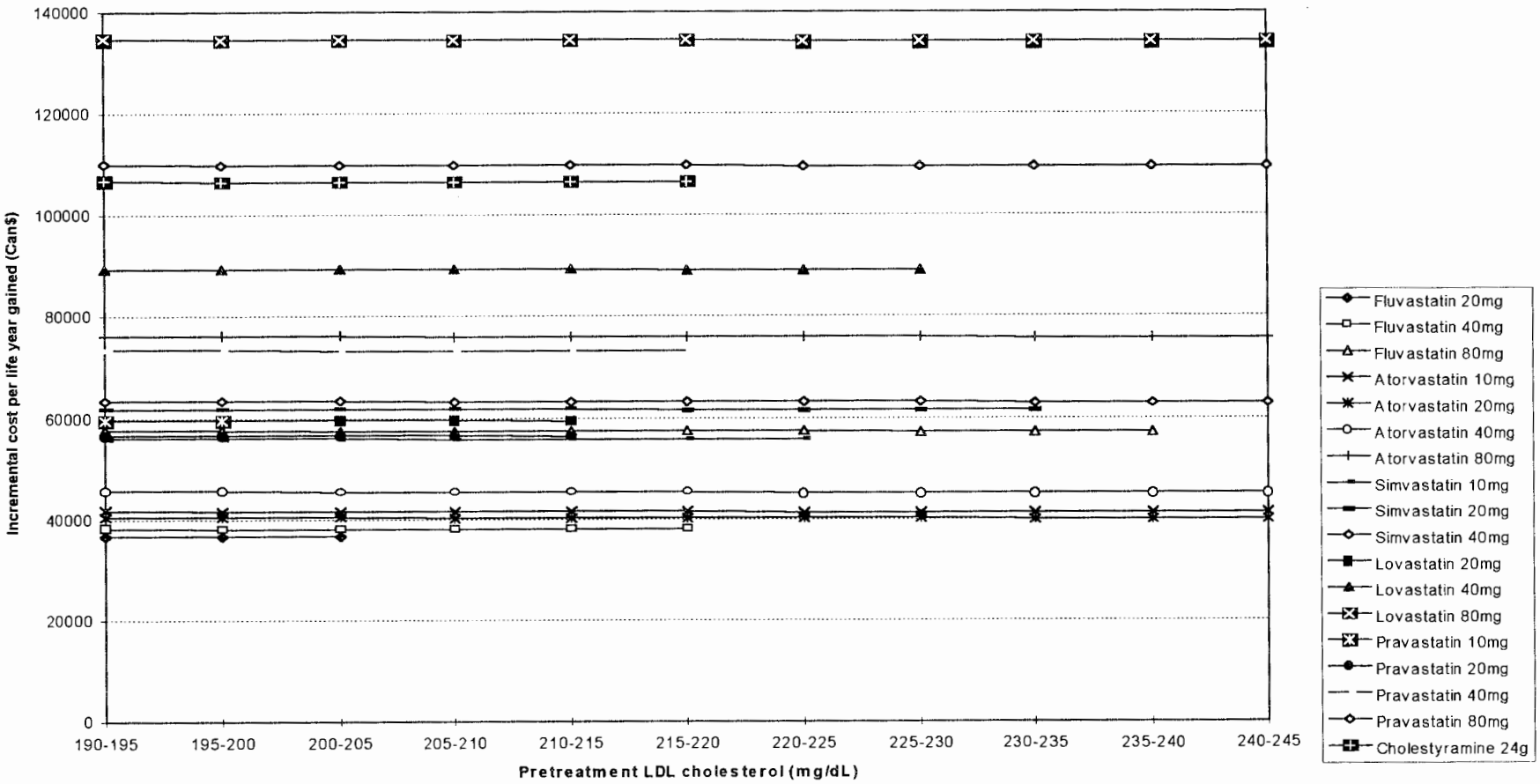

Figure 2. Incremental cost per life year gained of agents able to reach target LDL-C level of 160mg/dl relative to least cost agent able to reach target, by pretreatment LDL-C level for 55 year old males at otherwise average risk