Treating Hyperlipidemia for the Primary Prevention of Coronary Disease

Are Higher Dosages of Lovastatin Cost-effective?

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Objective: To compare the average and marginal life-time cost-effectiveness of increasing dosages of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, such as lovastatin, for the primary prevention of coronary heart disease (CHD).

Methods: We estimated the lifelong costs and benefits of the modification of lipid levels achieved with lovastatin based on published studies and a validated CHD prevention computer model. Patients were middle-aged men and women without CHD, with mean total serum cholesterol levels of 6.67, 7.84, and 9.90 mmol/L (258, 303, and 383 mg/dL), and high-density lipoprotein cholesterol levels of 1.19 mmol/L (46 mg/dL), as described in clinical trials. We estimated the cost per year of life saved for dosages of lovastatin ranging from 20 to 80 mg/d that reduced the total cholesterol level between 17% and 34%, and increased high-density lipoprotein cholesterol level between 4% and 13%.

Results: After discounting benefits and costs by 5% annually, the average cost-effectiveness of lovastatin, 20 mg/d, ranged from $11 040 to $52 463 for men and women. The marginal cost-effectiveness of 40 mg/d vs 20 mg/d remained in this range ($25 711 to $60 778) only for persons with baseline total cholesterol levels of 7.84 mmol/L (303 mg/dL) or higher. However, the marginal cost-effectiveness of lovastatin, 80 mg/d vs 40 mg/d, was prohibitively expensive ($99 233 to $716 433 per year of life saved) for men and women, irrespective of the baseline total cholesterol level.

Conclusions: Assuming that $50 000 per year of life saved is an acceptable cost-effectiveness ratio, treatment with lovastatin at a dosage of 20 mg/d is cost-effective for middle-aged men and women with baseline total cholesterol levels of 6.67 mmol/L (258 mg/dL) or higher. At current drug prices, treatment with 40 mg/d is also cost-effective for total cholesterol levels of 7.84 mmol/L (303 mg/dL) or higher. However, treatment with 80 mg/d is not cost-effective for primary prevention of CHD.

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The importance of the total serum cholesterol level as a risk factor for coronary heart disease (CHD) and the potential to reduce risk by lowering the cholesterol level is well documented.1-13 However, screening for hyperlipidemia is a substantial cost burden to society, as is the cost of treatment.14,15 For instance, the cost of treatment with 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors ranges from $420 to $2640 per year.16,17 These drugs are prescribed at a variety of dosage levels ranging from 10 to 80 mg/d. Higher dosages have been shown to enhance the effectiveness of the drugs in modifying blood lipid levels. However, whether the changes associated with increasing dosages are proportional to the relative increase in cost is uncertain.

Cost-effective pharmacological treatment of primary hyperlipidemia should include an evaluation of the risks, benefits, and associated costs of alternative therapies. Yet previous economic evaluations of lipid-lowering drugs have only considered the average cost-effectiveness of specific treatment regimens.18-22 Thus, we compared the average and marginal cost-effectiveness ratios of increasing dosages of HMG-CoA reductase inhibitors at several baseline total cholesterol levels.

RESULTS

Raising the dosage of lovastatin from 20 to 80 mg/d at each baseline total cholesterol level resulted in increasing mean reductions in the total cholesterol level (Table 2). However, lipid-lowering drugs produced a nonlinear lipoprotein response to increasing drug dosages in each study. For example, doubling the drug dosage from 40 to 80 mg/d in the study by Bradford et al9 increased the reduction in
METHODS

INTERVENTION GROUP AND PREDICTED MODIFICATION OF LIPID LEVELS

We conducted a MEDLINE search to identify studies that evaluated the dose-response curve of HMG-CoA reductase inhibitors on lipid levels. We included all studies published from January 1986 through December 1995 that were randomized, double-blinded, and placebo controlled. These studies enabled us to compare the marginal efficacy of increasing drug dosages after controlling for the placebo effect of each specific study protocol and for baseline levels of total and high-density lipoprotein (HDL) cholesterol. Three studies using lovastatin were identified. We estimated that treatment with any lipid-lowering drug during the first year would require, on average, 4 visits to the physician ($25.20 per visit), collection of 4 blood specimens for testing ($4.81 per sample), 4 lipid profiles ($175 000) and high-risk persons at a total cholesterol level of 6.67 mmol/L (258 mg/dL). The average cost-effectiveness ratios for low-risk men ranged from $52 463 at a lovastatin dosage of 20 mg/d to $101 567 at a dosage of 80 mg/d. The cost-effectiveness ratios were similar for middle-aged men. However, the marginal cost-effectiveness ratios for increasing the dosage of lovastatin to 40 mg/d (vs 20 mg/d) and 80 mg/d (vs 40 mg/d) were substantially higher for low-risk men ($277 400 and $193 900) and low-risk women ($229 125 and $175 000) (Figure 1). The incremental cost-effectiveness ratios were higher than the average cost-effectiveness ratios because each 2-fold increase in drug dosage was accompanied by at least a 75% increase in price; yet the net benefit in years of life saved was substantially smaller. For high-risk persons (smokers with diastolic blood pressure readings of 100 mm Hg) compared with low-risk persons, the average cost-effectiveness ratios were approximately 50% lower for men and 30% lower for women at each drug dosage. The improved cost-effectiveness is driven by the greater benefits in life expectancy achieved through any improvement in lipid lev-

The hypothetical intervention groups in our cost-effectiveness analyses consisted of men and women whose ages and baseline cholesterol levels were equal to the means for each study. The respective reductions in the total cholesterol level, the low-density lipoprotein cholesterol level, and the total cholesterol–HDL cholesterol ratios and the increase in the HDL cholesterol level reported in these studies are given in Table 2. We contrasted the effects of lovastatin therapy for hypothetical high-risk persons (ie, smokers with a diastolic blood pressure reading of 100 mm Hg) with the effects for hypothetical low-risk persons (ie, nonsmokers with a diastolic blood pressure reading of 80 mm Hg). For these analyses, we assumed a consistent efficacy of lovastatin. Such results have been observed across groups of middle-aged patients, stratified for sex and hypertensive status.

CALCULATION OF COST-EFFECTIVENESS

We calculated the cost-effectiveness of drug therapy from a societal perspective and evaluated the net monetary costs of the drug therapy (in 1992 Canadian dollars) against its net effectiveness, measured in terms of additional years of life expectancy. Our estimates are expected values, reflecting the average experience of all persons with elevated levels of cholesterol, and not just those in whom CHD develops.

We calculated average cost-effectiveness as the ratio of the net change in medical care costs to the net increase in life expectancy as follows:

\[
\frac{C/E}{C/E} = \frac{(CRx - CCHD + CNonCHD)}{LE},
\]

where \(C/E\) is cost-effectiveness, \(CRx\) the expected lifetime cost of a specific regimen of drug therapy, \(CCHD\) the expected savings in lifetime medical care costs because of reducing CHD events, \(CNonCHD\) the expected cost of treating non-CHD diseases during the years of additional life gained by treatment, and \(LE\), the increase in life expectancy that results from adherence to the specified regimen of drug therapy.

The marginal cost-effectiveness of increasing dosages of HMG-CoA reductase inhibitors was derived by determining the ratio of the net difference in lifetime costs to the net difference in life expectancy with each drug regimen vs the next lowest dosage level. The marginal cost for the lowest drug dosage, 20 mg/d, equals the average cost for that dosage. We discounted all future treatment costs and changes in life expectancy at an annual rate of 5%.

LIFETIME COST OF DRUG TREATMENT

The current annual retail costs of lovastatin at 20, 40, and 80 mg/d were $772, $1380, and $2640, respectively. These prices were estimated based on the average retail price for these drugs at 13 Montreal, Quebec–area pharmacies in 1995. These annual costs include a monthly dispensing fee of $7.00 per prescription.

We estimated that treatment with any lipid-lowering drug during the first year would require, on average, 4 visits to the physician ($25.20 per visit), collection of 4 blood specimens for testing ($4.81 per sample), 4 lipid profiles

the mean total cholesterol level from 22% to 29% (Table 2). This relationship was also observed for mean reductions in the low-density lipoprotein cholesterol level, in the total cholesterol–HDL cholesterol ratios, and for increases in the HDL cholesterol level. Accordingly, the cost-effectiveness of lovastatin is potentially sensitive to the drug dosage, because doubling the dosage may double the cost without doubling the potential benefits on the lipid profile response.

AVERAGE AND MARGINAL COST-EFFECTIVENESS RATIOS FOR INCREASING DOSAGES OF LOVASTATIN

Baseline Total Cholesterol Level of 6.67 mmol/L

Results from the study by Bradford et al9 were used to compare the effect of increasing dosages of lovastatin from 0 to 80 mg/d at a mean baseline total cholesterol level of 6.67 mmol/L (258 mg/dL) among patients with moderate primary hyperlipidemia who were 56 years of age. Table 3 gives estimates of the discounted years of life saved and the average cost-effectiveness ratios for low- and high-risk persons at a total cholesterol level of 6.67 mmol/L (258 mg/dL). The average cost-effectiveness ratios for low-risk men ranged from $52 463 at a lovastatin dosage of 20 mg/d to $101 567 at a dosage of 80 mg/d. The cost-effectiveness ratios were similar for middle-aged men. However, the marginal cost-effectiveness ratios for increasing the dosage of lovastatin to 40 mg/d (vs 20 mg/d) and 80 mg/d (vs 40 mg/d) were substantially higher for low-risk men ($277 400 and $193 900) and low-risk women ($229 125 and $175 000) (Figure 1). The incremental cost-effectiveness ratios were higher than the average cost-effectiveness ratios because each 2-fold increase in drug dosage was accompanied by at least a 75% increase in price; yet the net benefit in years of life saved was substantially smaller.

For high-risk persons (smokers with diastolic blood pressure readings of 100 mm Hg) compared with low-risk persons, the average cost-effectiveness ratios were approximately 50% lower for men and 30% lower for women at each drug dosage. The improved cost-effectiveness is driven by the greater benefits in life expectancy achieved through any improvement in lipid lev-

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By using the efficacy results reported by Bradford et al, we estimated the average and marginal cost-effectiveness of lovastatin dosages ranging from 20 to 80 mg/d as high for high-risk men ($117 450) and high-risk women ($160 600). The marginal cost-effectiveness of a lovastatin dosage of 80 mg/d vs a dosage of 40 mg/d was relatively high ($339 500) and approximately 30% lower for high-risk vs low-risk men and approximately 45% lower for high-risk vs low-risk women. Thus, the marginal cost-effectiveness of a lovastatin dosage of 80 mg/d was relatively high ($339 500 for men and $312 883 for women).

Compared with low-risk persons, the discounted life expectancy gains for high-risk persons were 56% higher among men and 22% higher among women. Thus, the average cost-effectiveness of each dosage of lovastatin was approximately 45% lower for high-risk vs low-risk men and approximately 30% lower for high-risk vs low-risk women. The marginal cost-effectiveness of a lovastatin dosage of 40 mg/d vs a dosage of 20 mg/d was also low for high-risk men ($26 053) and low-risk women ($31 314; Figure 1). However, the marginal cost per year of life saved for a lovastatin dosage of 80 mg/d vs 40 mg/d remained high for high-risk men ($178 750) and high-risk women ($234 700; Figure 2).
Base Line Total Cholesterol Level of 9.90 mmol/L

We used the study by Havel et al\textsuperscript{25} to assess the effect of lovastatin on patients with familial heterozygous hyperlipidemia aged 44 years with a baseline total cholesterol level of 9.90 mmol/L (383 mg/dL). Table 3 gives the estimated discounted years of life saved and the average cost-effectiveness ratios. The average cost-effectiveness of each dosage of lovastatin was relatively favorable for low-risk men and women. In addition, the marginal cost-effectiveness of a dosage of 40 mg/d vs a dosage of 20 mg/d was relatively low for low-risk men ($48,938) and increased by 24% for low-risk women ($60,778; Figure 1). However, the marginal cost-effectiveness of a dosage of 80 mg/d vs a dosage of 40 mg/d was substantially higher for the same low-risk patients ($508,425 for men and $716,433 for women).

Compared with low-risk persons, the discounted gains in life expectancy owing to therapy for high-risk men and high-risk women were, on average, 72% and 32% greater, respectively. Thus, the average cost-effectiveness ratios for each dosage of lovastatin were also low and favorable for high-risk men and high-risk women. Moreover, the marginal cost-effectiveness of a dosage of 40 mg/d vs a dosage of 20 mg/d was relatively low for high-risk men and high-risk women ($25,711 and $43,461, respectively; Figure 1). However, the marginal cost-effectiveness of a dosage of lovastatin of 80 mg/d vs a dosage of 40 mg/d remained prohibitively high for high-risk men and high-risk women ($181,400 and $494,125, respectively; Figure 2).

Primary prevention with the HMG-CoA reductase inhibitor lovastatin at a dosage of 20 mg/d has been found to be cost-effective for high-risk men,\textsuperscript{21,22} older high-risk women, and middle-aged low-risk men.\textsuperscript{22} However, less attention has been focused on more aggressive treatment strategies, which clinicians may prescribe for patients in whom target lipid levels are not achieved with low-dosage therapy. Yet the eventual choice of dosage has important implications for the cost-effectiveness of any screening program for the primary prevention of CHD.\textsuperscript{16,39,40}

Using the cost per year of life saved of renal dialysis as an example of a commonly accepted cost-effective treatment\textsuperscript{41,42} (approximately $50,000 in current dollars), we can evaluate the cost-effectiveness of treatment with increasing dosages of HMG-CoA reductase inhibitors for various patient groups. The average cost-effectiveness of a lovastatin dosage of 20 mg/d was favorable for all high-risk and low-risk men and women,
regardless of the baseline total cholesterol level and type of primary hyperlipidemia ($11,040-$52,463). However, the marginal cost-effectiveness of a lovastatin dosage of 40 mg/d (vs 20 mg/d) was relatively favorable only for persons with baseline total cholesterol levels of 7.84 mmol/L (303 mg/dL) or higher ($25,711-$60,778).

Although treatment with a lovastatin dosage of 80 mg/d was estimated to yield the greatest increase in discounted years of life saved, the benefit was not commensurate with the associated cost increase. The marginal cost-effectiveness of a dosage of 80 mg/d (vs 40 mg/d) was prohibitively expensive for low- and high-risk men and low- and high-risk women irrespective of the baseline total cholesterol level ($99,233-$716,433). Treatment with 80 mg/d is not cost-effective for the prevention of primary CHD.

Our results also indicate that for high- and low-risk men and high- and low-risk women, the average cost-effectiveness ratios are:

Table 3. Estimates of Years of Life Saved and Average Cost-effectiveness Ratios for Increasing Dosages of Lovastatin*

<table>
<thead>
<tr>
<th>Dosage of Lovastatin, mg/d</th>
<th>Years of Life Saved</th>
<th>Average Cost-effectiveness Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>20 mg</td>
<td>40 mg</td>
</tr>
<tr>
<td>Bradford et al,* 6.67 mmol/L (258 mg/dL)†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low risk</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>0.24</td>
<td>0.27</td>
</tr>
<tr>
<td>Women</td>
<td>0.27</td>
<td>0.31</td>
</tr>
<tr>
<td>High risk</td>
<td>0.37</td>
<td>0.43</td>
</tr>
<tr>
<td>Men</td>
<td>0.34</td>
<td>0.39</td>
</tr>
<tr>
<td>Women</td>
<td>0.41</td>
<td>0.69</td>
</tr>
</tbody>
</table>

Bradford et al,* 7.84 mmol/L (303 mg/dL)†

| Low risk                  |         |         |         | 44,807  | 45,687  | 73,938  |
| Men                       | 0.28    | 0.47    | 0.52    |         |         |         |
| Women                     | 0.34    | 0.56    | 0.62    |         |         |         |
| High risk                 | 0.44    | 0.74    | 0.82    | 24,391  | 25,065  | 40,059  |
| Men                       | 0.41    | 0.69    | 0.76    | 29,215  | 30,067  | 48,914  |
| Women                     | 0.58    | 0.76    | 0.79    | 27,653  | 35,499  | 61,357  |

Havel et al,* 9.90 mmol/L (383 mg/dL)†

| Low risk                  |         |         |         | 21,461  | 27,872  | 48,321  |
| Men                       | 0.69    | 0.90    | 0.94    |         |         |         |
| Women                     | 0.58    | 0.76    | 0.79    |         |         |         |
| High risk                 | 1.18    | 1.54    | 1.64    | 11,040  | 14,469  | 24,648  |
| Men                       | 0.77    | 1.00    | 1.04    | 18,666  | 24,369  | 42,437  |
| Women                     | 1.00    | 1.25    | 1.30    | 22,250  | 29,067  | 57,914  |

*Years of life saved and all costs and benefits in the cost-effectiveness ratios are discounted at an annual rate of 5%. Low risk indicates nonsmokers with a diastolic blood pressure reading of 80 mm Hg (ie, no risk factors other than elevated lipid levels); high risk, smokers with a diastolic blood pressure reading of 100 mm Hg. The dollars are Canadian, but increments in the United States are comparable (see the "Comment" section in the text).

†Average baseline total cholesterol level.
effectiveness ratios are lower for persons with higher baseline total cholesterol levels. This effect is due to the generally greater effectiveness of these drugs in reducing total cholesterol levels among patients with higher baseline values.

Many of our estimated cost-effectiveness ratios for women are less than 10% higher than those estimated for men receiving similar treatment. In the absence of coronary risk factors other than a high cholesterol level, women aged 55 years and older face lower coronary risk than do their male counterparts, which should reduce the relative benefit of lipid intervention. However, these women also have a longer life expectancy than men with similar risk profiles. The benefits of intervention, therefore, accrue over a longer time for women, so that the relative cost-effectiveness of treatment for men and women becomes more similar. These estimates are consistent with those obtained in previous studies of low-risk patients aged 55 years and older.

The annual costs of lovastatin used to derive these cost-effectiveness estimates (ie, $772 for 20 mg/d, $1380 for 40 mg/d, and $2640 for 80 mg/d) were based on Canadian prices. However, the reported 1996 average wholesale price for lovastatin at varying doses in the United States implies an average cost of $759 for 20 mg/d, $1369 for 40 mg/d, and $2738 for 80 mg/d. Thus, the comparable increments in cost for increasing doses of lovastatin in Canada and the United States imply that the conclusions derived from this analysis apply to both countries.

The specific prices of various doses of any lipid-lowering agent will affect the marginal cost-effectiveness of more aggressive treatment strategies. Additional studies of other lipid-lowering agents must be undertaken to determine the incremental cost of higher dosages of these drugs compared with their incremental benefits.

Our cost-effectiveness estimates are based on the assumption that lipid-lowering drugs work exclusively through their effect on lowering the level of low-density lipoprotein cholesterol or total cholesterol and raising the level of HDL cholesterol. If future clinical trials identify an important role of triglycerides or nonlipid risk factors, such as blood coagulability, in predicting CHD risk, then our estimates will need to be revised.

It is also possible that one or more adverse effects might result from all methods of reducing the cholesterol level. Adverse effects and the potential net benefits of treatment may depend on the specific therapy used and the treatment duration, implied by the results of randomized controlled trials, meta-analyses, and international cohort studies. Until further information is available, appropriate pharmacological treatment of primary hyperlipidemia should first include an evaluation of the risks, benefits, and associated costs of alternative therapies.

As the costs of health care continue to rise, we must reconsider services that offer no additional healthy outcomes for substantial increases in costs. All health care services should be reevaluated for the societal goal of achieving the greatest benefits for the most people, thus maximizing the utility of medical care.


43. PDR Generics. 2nd ed. Montvale, NJ: Medical Economics; 1996.


