Cost Implications of the Use of Ramipril in High-Risk Patients Based on the Heart Outcomes Prevention Evaluation (HOPE) Study

Andre Lamy, MD, MHSc; Salim Yusuf, DPhil; Janice Pogue, MSc; Amiram Gafni, PhD; on Behalf of the HOPE Investigators* 

Background—The HOPE study has demonstrated that ramipril is beneficial (ie, prevents cardiovascular death, myocardial infarction, and stroke) for a broad range of patients without evidence of left ventricular dysfunction or heart failure who are at high risk for cardiovascular event. In this study, we report the cost implications, in both the United States and Canada, of the use of ramipril after the HOPE study.

Methods and Results—A third-party perspective was chosen (Medicare for the United States and Ministry of Health for Canada). We calculated the costs of the management strategies of ramipril and placebo. An annual discount rate of 3% was used over the 4.5 years of follow-up. Sensitivity analyses were performed. Costs are reported in United States dollars and in Canadian dollars, respectively. The total costs per patient (including acquisition costs of ramipril) were not different between the groups in both countries (United States, $13 520 versus $13 631; Canada, $8702 versus $8588). From the distribution of cases in the bootstrap analysis, we found that 90% of cases fall either into a cost-neutral or cost-saving situation (64% in United States and 27% in Canada) or into a cost-effectiveness situation with an incremental cost-effectiveness ratio <$10 000 (in respective currency) per primary event saved.

Conclusions—On the basis of these results, we suggest that the use of ramipril is likely to represent an efficient use of resources in both countries. These findings support the use of ramipril in populations included in the HOPE study. 

(Circulation. 2003;107:960-965.)

Key Words: cardiovascular diseases ■ trials ■ cerebrovascular disorders ■ diabetes mellitus ■ cost-benefit analysis

T he role of angiotensin-converting enzyme (ACE) inhibitors1 in high-risk patients without left ventricular dysfunction or heart failure2,3 was evaluated recently in the Heart Outcomes Prevention Evaluation (HOPE) study.4 Ramipril reduced the risk of the primary outcome rate of death from cardiovascular causes, myocardial infarction, and stroke. Additionally, there was a significant reduction in cardiovascular death, myocardial infarction, stroke, and death from any cause. These results have the potential to have a substantial impact on the clinical practice of cardiologists and physicians involved in the treatment of cardiovascular diseases and diabetes. Therefore, it is important to assess the cost consequences of the widespread use of ramipril according to the results of HOPE. In the present article, we report the estimated cost of the management strategy of placebo and ramipril both in United States and in Canada and discuss the overall cost implications of the HOPE findings.

Methods

Clinical Trial

The HOPE study was a large multicenter randomized controlled trial. Patients were recruited from December 1993 to June 1995 at 129 centers in Canada, 27 centers in the United States, 76 centers in Western Europe, and 35 centers in Mexico and South America. Patients who were at least 55 years old were eligible for the study if they had a history of coronary artery disease, stroke, peripheral vascular disease, or diabetes plus at least one other cardiovascular risk factor (hypertension, elevated total cholesterol level, low high-density lipoprotein cholesterol levels, cigarette smoking, or documented microalbuminuria) and who were not known to have a low ejection fraction or heart failure. A total of 9297 patients were randomized to receive ramipril (10 mg daily) or a placebo added to their regular medication for an average period of 4.5 years by the end of the trial in April 1999.

It is important to note that all patients received conventional treatments for their condition, regardless of their group of randomization. These treatments include aspirin, diuretics, antianginal...
therapy, antihypertensive medication, and cholesterol-reducing agents, according to their respective physicians. Therefore, all comparisons are based on ramipril versus placebo in addition to the above therapies. Results are shown in Table 1.

**Cost Analysis**

For the cost analysis, our initial hypothesis was to investigate whether the use of ramipril might be either cost neutral or cost saving. Costs are reported in United States dollars (USD 1999) for the American component and in Canadian dollars (CAN 1999) for the Canadian component of the analysis. An annual discount rate of 3% was used because the study period is 4.5 years.

**Health Care Utilization**

The health care utilization involves documenting the resources that are consumed by patients receiving ramipril or placebo. Total length of stay in hospital and reasons for hospitalizations (primary or secondary diagnosis) were available. Information about the medications taken at home was also collected. Community care and investigations performed out of hospital as an outpatient were not recorded. Given that a substantial proportion of expensive procedures or investigations are performed while patients are hospitalized, it is likely that most of the major components ("big ticket") of health care resource utilization had been collected during the trial. A possible exception would be same-day investigations not requiring revascularization, nuclear testing, or echocardiograms. Crossover of the placebo group when prescription of ACE inhibitors became clinically indicated and compliance of the ramipril group were also collected. The compliance of patients was observed at each visit, and costs of drug were recorded as prescribed rather than consumed. We used the overall percentage of compliance between each specific visit according to the group of randomization. The compliance in the ramipril group was lower than placebo, because ramipril may have troublesome side effects in some patients (eg, cough). We recorded information on all hospitalizations, but noncardiovascular hospitalizations were subsequently removed from the analysis because they were responsible for a small amount of health care expenditure and were equally distributed between the placebo group and the ramipril group.

Our first task was to assign a diagnosis-related group (DRG) code to each diagnosis or procedure according to various clinical scenarios from the variables in the case report forms (primary and secondary diagnosis), such as coronary artery bypass graft surgery, percutaneous transluminal angioplasty, myocardial infarction, unstable angina, congestive heart failure, carotid endarterectomy, peripheral vascular surgery, transient ischemic attack, ventricular arrhythmia, and cardiac arrest (Table 2). We applied American and Canadian unit costs to the resource consumption of all patients (9297) in the study.
Unit Costs

Although the use of health care resources was recorded prospectively at the time of the original study, the associated unit costs were developed at the end of the trial (Table 2). Reliable unit costs for health care services were not readily available from each of the participating centers. For practical reasons, we chose the following approach.

United States

A significant proportion of Americans are insured by private companies, and charges are produced. These charges and hospital bills were not available during the trial. Similarly, costs from Veteran Administration Hospitals were not available. We decided therefore to use the Medicare hospital and professional fees that are readily available. This approach is valid in comparing the relative costs between the active and control groups. For cardiac services in the United States, we have used national averages from the schedule of benefits for the Medicare system (MEDPAR 1999) and the schedule of professional fees.9

There are two exceptions from this Medicare approach. The cost of a stroke in Medicare is relatively low, because costs for rehabilitation facilities and nursing homes are not included in the Medicare reimbursement fee because of different funding schemes. Therefore, use of the Medicare data might substantially underestimate the cost differences because of the reduction in stroke rates with ramipril. For these reasons, we used data from a study by Holloway et al,8 which reported the cost of specific cerebrovascular events at 5 tertiary centers similar to HOPE centers. The distribution of each subtype of stroke (ischemic cerebral infarction, intracerebral hemorrhage, or subarachnoid hemorrhage) was not completely available in the HOPE trial. Therefore, we used a weighted average to determine the unit cost. Also, overt nephropathy and diabetes de novo do not consume hospital resources, because they are the first step in a long pathobiologic process. Nevertheless, outpatient health care resources are consumed but are more difficult to capture. Brown et al8 were able to estimate these costs before cardiovascular and renal complications developed. Medication costs were taken from the Red Book10 (average wholesale price) as drugs consumed at home were able to estimate these costs before cardiovascular and renal complications developed. Medication costs were taken from the Red Book10 (average wholesale price) as drugs consumed at home were consumed but are more difficult to capture. Brown et al8 were able to estimate these costs before cardiovascular and renal complications developed. Medication costs were taken from the Red Book10 (average wholesale price) as drugs consumed at home were recorded systematically over the length of the study. Price of generic drugs was used when generic drugs were available in a specific class of medication.

Canada

For cardiac services in Canada, we relied on a detailed case-costing system (described below) developed at our institution for cardiac surgery and cardiology where all components of health care consumption per patient are meticulously recorded and calculated. We have access, with the support of the administration, to financial statements and computerized financial files. This allowed us to determine with precision, for cardiac diseases, the unit cost per location (a day in the coronary care unit or intensive care unit, step-down unit, and regular ward), pharmacy costs (main pharmacy and ward stock), all blood work, radiology tests, nuclear medicine investigations, and specific therapeutic acts such as coronary artery bypass graft surgery, percutaneous transluminal coronary angioplasty, stents, coronary angiogram, and catheterization.11 Overhead costs were calculated and allocated. Good correlation was obtained with a provincial case-costing project.12 Professional fees (Ontario Fee Schedule) were added. Ontario Drug Benefit program prices were used to establish medication costs. Price of generic drugs was used when generic drugs were available. Our last task was to aggregate these values from our case-costing system into the same DRG codes system.

Statistical Analysis and Sensitivity Analysis

Unit costs were applied to utilization data of individual patient services to arrive at a cost per patient and then averaged within each treatment group (active or placebo). Because cost data are unlikely to be normally distributed, the bootstrap method was used to calculate standard errors and 95% confidence intervals.13 The bias corrected and accelerated method was used for confidence intervals.14 In the HOPE study, the composite outcome was consistently reduced among various subgroups. Cost impact according to these subgroups was also analyzed. Heterogeneity differences in costs by treatment group in various subgroups were tested with an interaction term in an ANOVA. All analyses were completed using SAS 6.12.

A sensitivity analysis was performed to assess various estimates of some unit costs, such as new diagnosis of diabetes, overt nephropathy, and stroke. Variations of their unit cost were potentially more significant because they were extracted from various publications. The sensitivity analysis was performed using a lower or higher estimate (±25%). Various combinations of different unit costs for new diagnosis of diabetes, overt nephropathy, and stroke were tested separately, per group, and by scenarios more likely to demonstrate a significant difference.

Results

Hospitalization and Procedure Costs

The costs for hospitalizations and for the development of various conditions were significantly reduced in the ramipril group. These costs were $2987 per patient for the ramipril group and $3601 per patient for the placebo group in the United States and $2430 per patient for the ramipril group and $2994 per patient for the placebo group in Canada. The costs for coronary artery revascularization procedures, carotid endarterectomy, and peripheral revascularization were $3990 per patient for the ramipril group and $4740 per patient for the placebo group in the United States and $1970 per patient for the ramipril group and $2323 per patient for the placebo group in Canada.

Drug Costs

A slight decrease in use of β-blockers, calcium-channel blockers, and antiplatelet agents in the ramipril group was also seen (NS), but the cost of nonstudy medication was substantial in both groups. These costs were $5063 per patient for the ramipril group and $5186 per patient for the placebo group in the United States and $3119 per patient for the ramipril group and $3188 per patient for the placebo group in Canada. The acquisition cost of ramipril is $34.50 USD per month in United States or $28.50 CAN per month in Canada. The total acquisition costs for ramipril were significantly increased in the ramipril group. These costs were $1480 per patient for the ramipril group and $104 per patient for the placebo group in the United States and $1183 per patient for the ramipril group and $83 per patient for the placebo group in Canada.

Overall Costs

When costs of hospitalizations, procedures, study drugs, and medications are added together, there is little difference between ramipril and placebo. Table 3 provides the total costs at $13 520 per patient for the ramipril group and $13 631 per patient for the placebo group in the United States, with a reduction of $111 per patient with ramipril. The total costs are $8702 per patient for the ramipril group and $8588 per patient for the placebo group in Canada, with an increase of $114 per patient with ramipril. An annual discounting rate of 3% was applied because the mean follow-up of the study is 4.5 years. The total discounted cost is $12 463 per patient for the ramipril group and $12 567 per patient for the placebo group in the United States, with a reduction of $105 per patient with
ramipril. The total discounted cost is $8019 per patient for the ramipril group and $7915 per patient for the placebo group in Canada, with an increase of $103 per patient with ramipril.

**Statistical Analysis and Sensitivity Analysis**

The distribution of cases in the bootstrap analysis with a 95% confidence interval is displayed graphically in a cost-effectiveness plane (Figures 1 and 2). As can be seen from these figures, it is possible (less in United States, more in Canada) that there may be added costs because of the introduction of ramipril. Specifically, we notice that in 36% of cases in the United States and 73% of cases in Canada, the total costs are likely to increase because of the use of ramipril. In half of these cases, the increase in costs will be $200 (in respective currency) or less per case. Because of these cases where total costs are likely to increase, we calculated the incremental cost-effectiveness ratios (ICERs).

We use the absolute risk reduction for primary event saved (cardiovascular death, myocardial infarction, or stroke) of 3.8% as the incremental effect. In United States, we found that most cases (64%) will be cost neutral or cost saving. In all cases, 94% will be either cost neutral or cost saving or with a cost-effectiveness situation with an ICER < $10,000 per primary event saved. In Canada, the proportion of cases that are cost neutral or cost saving is lower (27%). For all cases, 91% will be

### Table 3. Average Costs Per Patient in United States and Canada (With 95% CI)

<table>
<thead>
<tr>
<th>Category of Cost</th>
<th>Ramipril, USD</th>
<th>Placebo, USD</th>
<th>Difference</th>
<th>Ramipril, CAN</th>
<th>Placebo, CAN</th>
<th>Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospitalizations</td>
<td>2987 (2798 to 3207)</td>
<td>3601 (3388 to 3829)</td>
<td>-614 (-912 to -316)</td>
<td>2430 (2267 to 2602)</td>
<td>2994 (2814 to 3180)</td>
<td>-564 (-810 to -318)</td>
</tr>
<tr>
<td>Procedures</td>
<td>3990 (3690 to 4310)</td>
<td>4740 (4407 to 5072)</td>
<td>-750 (-1200 to -300)</td>
<td>1970 (1818 to 2125)</td>
<td>2323 (2160 to 2487)</td>
<td>-353 (-575 to -131)</td>
</tr>
<tr>
<td>Medications</td>
<td>5063 (4965 to 5166)</td>
<td>5186 (5083 to 5290)</td>
<td>-123 (-268 to 22)</td>
<td>3119 (3060 to 3184)</td>
<td>3188 (3127 to 3253)</td>
<td>-69 (-157 to 21)</td>
</tr>
<tr>
<td>Study drug</td>
<td>1480 (1461 to 1498)</td>
<td>104 (94 to 112)</td>
<td>1376 (1355 to 1396)</td>
<td>1183 (1167 to 1197)</td>
<td>83 (76 to 90)</td>
<td>+1100 (1083 to 1115)</td>
</tr>
<tr>
<td>Total cost</td>
<td>13 520 (13 104 to 13 954)</td>
<td>13 631 (13 169 to 14 090)</td>
<td>-111 (-734 to 512)</td>
<td>8702 (8446 to 8967)</td>
<td>8588 (8306 to 8869)</td>
<td>+114 (-269 to 497)</td>
</tr>
</tbody>
</table>

![Figure 1](http://circ.ahajournals.org/)

Figure 1. Bootstrap results displayed in a cost-effectiveness plane (United States).

![Figure 2](http://circ.ahajournals.org/)

Figure 2. Bootstrap results displayed in a cost-effectiveness plane (Canada).
either cost neutral or cost saving or with a cost-effectiveness situation with an ICER < $10,000 per primary event saved.

Unit cost for new diagnosis of diabetes, overt nephropathy, and stroke were selected for the sensitivity analysis because variations were potentially more significant than other variables. A sensitivity analysis was performed using a lower or higher estimate (± 25%). Various combinations of different unit costs were tested, such as separately one by one, all 3 together, and in mixed combinations. The overall result was not modified, because no significant differences were detected for the United States and Canada.

Subgroups Results
Total costs for each subgroup were analyzed with an interaction test. In both countries, the difference within each subgroup was not significant except for the age group (Table 4). In patients 65 years of age or older, ramipril use seemed to significantly reduce costs, whereas among patients younger than 65 years of age, it modestly increased costs ($P=0.008 for interaction in United States and $P=0.006 in Canada). A bootstrap analysis to compare the ramipril group with the placebo group in both age groups and countries did not alter these differences. The interaction is likely because of the higher absolute benefit among the elderly caused by a higher event rate in the older age group. In both countries, 99% of cases in patients 65 years of age or older fall into a cost-saving or cost-neutral situation (93% in United States and 78% in Canada) or into a cost-effectiveness situation with an ICER < $10,000 (in respective currency) per primary event saved.

Discussion
In this study, we started with the hypothesis that ramipril would be cost saving or cost neutral because we believed that savings from reduced events would be enough to compensate for the added costs of ramipril. However, we found that the 95% confidence interval for the difference in costs per patient in the United States ranged from $−734 to $+512 and in Canada from $−269 to $+497. Although there was no obvious difference in the overall mean costs between ramipril and placebo, we are not able to declare ramipril to be cost neutral, given that we did not determine an equivalence margin in advance to define what we mean by cost neutrality. However, the additional analysis performed (ie, calculating the probability of cost-saving or cost-neutral cases from the distribution of cases in the bootstrap) enables us to provide useful information to decision makers. We find that overall, in both countries, >90% of cases fall either into a cost-neutral or cost-saving situation (64% in United States and 27% in Canada) or into a cost-effectiveness situation with an ICER < $10,000 (in respective currency) per primary event saved.

This cost analysis was conducted after the randomized trial had been completed. Thus, a limited amount of variables were available to enable us to measure detailed health care utilization. Although the length of stay in hospital was collected, the location of each day in hospital was not specified. However, the use of health care resources was recorded prospectively at the time of the original study, and the utilization of an event-driven system (such as DRGs) alleviates these limitations. Our unit costs are probably conservative, because community care and investigations without hospitalization were not collected in either country. In particular, the unit cost for stroke used is conservative, because long-term expenses beyond the acute treatment of stroke were not available. Collection of these resources would have been in favor of the ramipril group, because the proportion of disabling strokes was significantly lower in the ramipril group. New diabetes and overt nephropathy are two areas where costs may have been overestimated, but we believe our results are robust, as demonstrated by the sensitivity analysis testing various estimates. Also, at the end of the trial (4.5 years), in view of clinical events still diverging

### TABLE 4. Average Cost Per Patient According to Various Subgroups in United States and Canada

<table>
<thead>
<tr>
<th>Category of Patients</th>
<th>Ramipril, USD</th>
<th>Placebo, USD</th>
<th>Difference (95% CI)</th>
<th>Ramipril, CAN</th>
<th>Placebo, CAN</th>
<th>Difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Diabetes</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>13 865</td>
<td>13 945</td>
<td>−261 (−1277 to 756)</td>
<td>8912</td>
<td>8873</td>
<td>39 (−599 to 677)</td>
</tr>
<tr>
<td>No</td>
<td>13 414</td>
<td>13 438</td>
<td>−24 (−820 to 773)</td>
<td>8568</td>
<td>8412</td>
<td>156 (−318 to 629)</td>
</tr>
<tr>
<td><strong>Age, y</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥65</td>
<td>13 184</td>
<td>13 836</td>
<td>−652 (−1487 to 182)</td>
<td>8643</td>
<td>8872</td>
<td>−229 (−753 to 295)</td>
</tr>
<tr>
<td>&lt;65</td>
<td>13 943</td>
<td>13 385</td>
<td>558 (−397 to 1514)</td>
<td>8775</td>
<td>8246</td>
<td>529 (−33 to 1091)</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>14 019</td>
<td>14 074</td>
<td>−55 (−828 to 718)</td>
<td>8991</td>
<td>8834</td>
<td>157 (−309 to 623)</td>
</tr>
<tr>
<td>Female</td>
<td>12 204</td>
<td>12 357</td>
<td>−153 (−1207 to 902)</td>
<td>7940</td>
<td>7881</td>
<td>−59 (−585 to 704)</td>
</tr>
<tr>
<td><strong>Hypertension</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>13 989</td>
<td>14 268</td>
<td>−279 (−1210 to 653)</td>
<td>9097</td>
<td>9143</td>
<td>−46 (−617 to 525)</td>
</tr>
<tr>
<td>No</td>
<td>13 093</td>
<td>13 087</td>
<td>6 (−848 to 859)</td>
<td>8342</td>
<td>8114</td>
<td>228 (−289 to 746)</td>
</tr>
<tr>
<td><strong>Cardiovascular</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>14 399</td>
<td>14 413</td>
<td>−24 (−718 to 669)</td>
<td>9207</td>
<td>9041</td>
<td>166 (−251 to 585)</td>
</tr>
<tr>
<td>No</td>
<td>7802</td>
<td>7443</td>
<td>359 (−721 to 1439)</td>
<td>5376</td>
<td>5002</td>
<td>374 (−362 to 1109)</td>
</tr>
</tbody>
</table>

*P=0.008 for homogeneity test among age subgroups.
†P=0.006 for homogeneity test among age subgroups.
(annual hazard rate) at that time, it is likely that a cost-saving situation may have been reached if the follow-up period of the trial had been longer.

A third-party-payer perspective as an integrated public health care system where all direct costs are recorded (Medicare in the United States and Ministry of Health in Canada) was chosen for the cost analysis. Although it is suggested that a societal perspective be considered, it is recognized that the use of other perspectives is acceptable and might be more appropriate in some cases.15,16 Our study considers costs from the perspective of health care system because of the limitations of data available to us. Cost items that are missing include out of hospital patients costs as well as nonmedical costs such as loss of productivity and the time provided by family and friends caring for patients. There is no good reason to believe that these costs are likely to be higher for the ramipril arm compared with the control arm. On the contrary, these costs are likely to be lower because of the reduction in major cardiovascular events, diabetes, and worsening angina. Hence, it seems that our analysis can be seen as a reasonable proxy for societal perspective or perhaps an overestimation of the true societal cost of ramipril.

In the United States and Canada, the use of ramipril based on the approach of the HOPE trial is a good strategy because it improves clinical outcomes, such as cardiovascular death, myocardial infarction, and stroke and >90% of cases fall into a cost-saving or cost-neutral situation (64% in United States and 27% in Canada) or into a cost-effectiveness situation with an ICER <$10 000 (in respective currency) per primary event saved. On the basis of the results, we suggest that the use of ramipril is likely to represent an efficient use of resources in both countries.

Acknowledgment

This analysis was supported financially by Aventis Pharma and King Pharmaceuticals. They have not been involved in the design, conduct, interpretation, analysis, or writing of this study.

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_Circulation_. 2003;107:960-965; originally published online February 3, 2003;
doi: 10.1161/01.CIR.0000050600.49419.25
_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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