Determining the cost-effectiveness of preventing cardiovascular disease: Are estimates calculated over the duration of a clinical trial adequate?

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BACKGROUND: Economic analyses of randomized clinical trials often focus only on the results that are observed during the study. However, for many preventive interventions, associated costs and benefits will accrue over a patient's remaining lifetime. To determine the importance of the chosen time horizon, the cost-effectiveness (C/E) of ramipril therapy was calculated and compared in the Heart Outcomes Prevention Evaluation (HOPE), the Microalbuminuria, Cardiovascular, and Renal Outcomes in HOPE (MICRO-HOPE) and the Acute Infarction Ramipril Efficacy (AIRE) study versus the entire life expectancy (L/E) of potential patients. **METHODS:** The Cardiovascular Disease Life Expectancy model, a validated Markov model, was calibrated to accurately forecast the results of each trial. These results were then extrapolated over the remaining L/E of hypothetical patients 55 to 75 years of age. The predicted change in L/E and associated direct health care costs for Canadians were calculated and discounted 3% annually.

RESULTS: In HOPE, the forecasted increased L/E averaged 0.06 years during the five-year study versus 1.3 years over the remaining years of L/E. The associated C/E of ramipril was \$15,000 per year of life saved (YOLS) over the study duration and \$8,500/YOLS over the remaining lifetime. For hypothetical patients, the C/E of ramipril over 4.5 years ranged from \$6,700/YOLS to more than \$58,300/YOLS and was lowest among elderly men. When the remaining L/E was considered, the C/E of ramipril was similar for men and women of all ages, ranging from \$8,100/YOLS to \$10,200/YOLS. The analyses of MICRO-HOPE and AIRE provided similar results.

CONCLUSION: The estimated efficacy and associated C/E of ramipril in HOPE, MICRO-HOPE and the AIRE study is extremely sensitive to the selected time horizon. Economic analyses beyond the duration of randomized clinical trials are required to fully evaluate the potential costs and benefits of long-term preventive therapies.

Key Words: Cardiovascular risk factors; Cholesterol; Cost-effectiveness; Dyslipidemia; Health economics; Health outcomes; Hypertension

There is little debate that preventing the complications of cardiovascular disease is worthwhile. Advancing clinical knowledge supported by the positive results of clinical trials continues to expand the indications for preventive therapy. Unfortunately, the growing number of therapeutic successes comes at a cost that many health care providers can no longer afford. Accordingly, health economic analyses have become an essential component of contemporary health policy.

Cost-effectiveness analyses are now commonplace as health care decision makers attempt to allocate limited resources to those interventions that provide the best value for the money. However, comparisons between studies are often difficult. Common problems include different patient populations in which the underlying risk of

Déterminer le rapport coût-efficacité de prévenir les maladies cardiovasculaires : Les estimations calculées pendant la durée d'un essai clinique sont-elles pertinentes ?

HISTORIQUE : Souvent, les analyses économiques des essais cliniques aléatoires portent seulement sur les résultats observés pendant l'étude. Pourtant, dans bien des interventions préventives, les coûts et les bienfaits connexes augmentent pendant tout le reste de la vie du patient. Pour déterminer l'importance de l'horizon prévisionnel choisi, les auteurs ont calculé le rapport coût-efficacité (RC-E) d'un traitement au ramipril et l'ont comparé à l'étude HOPE sur l'évaluation de la prévention des issues cardiaques, à l'étude MICRO-HOPE sur les issues microalbuminuriques, cardiovasculaires et rénales dans HOPE et à l'étude AIRE sur l'efficacité du ramipril en cas d'infarctus aigu par rapport à toute l'espérance de vie (EV) des patients potentiels.

MÉTHODOLOGIE : Les auteurs ont calibré un modèle d'espérance de vie avec une maladie cardiovasculaire, un modèle Markov validé, afin de prévoir avec précision les résultats de chaque étude. Ils ont ensuite extrapolé ces résultats pendant le reste de l'EV de patients hypothétiques de 55 à 75 ans. Ils ont calculé le changement prévu d'EV et de coûts directs connexes de santé pour les Canadiens et intégré une actualisation annuelle de 3 %.

RÉSULTATS : Dans l'étude HOPE, l'accroissement prévu de l'EV atteignait une moyenne de 0,06 an pendant l'étude de cinq ans, par rapport à 1,3 pendant le reste de l'EV. Le RC-E connexe du ramipril s'élevait à 15 000 \$ par année de vie gagnée (AVG) pendant la durée de l'étude et à 8 500 \$ par AVG pendant le reste de la vie. Chez les patients hypothétiques, le RC-E du ramipril sur 4,5 ans oscillait entre 6 700 \$ par AVG et plus de 58 300 \$ par AVG et était le plus faible chez les hommes âgés. Lorsqu'on tenait compte du reste de l'EV, le RC-E du ramipril était similaire pour les hommes et les femmes de tout âge, variant entre 8 100 \$ par AVG et 10 200 \$ par AVG. Les analyses des études MICRO-HOPE et AIRE ont donné des résultats similaires.

CONCLUSION : L'efficacité estimative et le RC-E connexe du ramipril dans les études HOPE, MICRO-HOPE et AIRE sont extrêmement sensibles à l'horizon prévisionnel sélectionné. Les auteurs ont conclu qu'il faut procéder à des analyses économiques qui dépassent la durée des essais cliniques aléatoires pour évaluer pleinement les coûts et bienfaits potentiels de thérapies préventives à long terme.

cardiovascular events can vary widely, inconsistent patient adherence to prescribed therapy and the variable duration of clinical trials. Study duration may be particularly important, given that most preventive therapies are prescribed for a lifetime, while almost all clinical trials are restricted to a time horizon that rarely exceeds five years. Accordingly, the uncertainty surrounding drug efficacy beyond the duration of a specific clinical trial remains a major challenge for health care analysts.

The 33rd Bethesda Conference in 2002 (1), sponsored by the American College of Cardiology, focused on preventive interventions. The working group that reviewed the cost-effectiveness of prevention recognized the importance of the time horizon in economic analyses.

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Among the published studies of hypertension or lipid-lowering therapy that were reviewed, the analyzed time horizon ranged from five years to a lifetime. As a general rule, reported cost-effectiveness ratios tended to be lower over longer periods of therapy. To date, there has not been a systematic evaluation of the importance of the time horizon as a major determinant of both the costs and benefits of treatment.

When focusing on one specific drug, cost-effectiveness estimates can also vary widely, as demonstrated by the range of results published for ramipril (2-10). Ramipril is an angiotensin-converting enzyme inhibitor that has been shown to reduce the risk of fatal and nonfatal cardiovascular events in a number of patient populations. In the Heart Outcomes Prevention Evaluation (HOPE) study (11), ramipril was shown to reduce the rates of death, myocardial infarction and stroke among individuals with cardiovascular disease, or diabetes plus one other cardiovascular risk factor. When data analysis was restricted to those individuals with diabetes (Microalbuminuria, Cardiovascular, and Renal Outcomes [MICRO-HOPE]) (12), treatment reduced the risk of myocardial infarction, stroke, cardiovascular death and total mortality. In the Acute Infarction Ramipril Efficacy (AIRE) study (13), individuals with clinical evidence of heart failure at any time after acute myocardial infarction were also shown to benefit from ramipril, as evidenced by a reduction in cardiovascular events and total mortality. In the first two studies, treatment duration was 4.5 years, while participants in AIRE were followed for approximately 15 months.

To evaluate the importance of the time horizon in economic analyses, the cost-effectiveness of ramipril was compared in these three studies. Initially, the actual study duration was used to estimate the cost-effectiveness of therapy during the clinical trial. A second analysis considered the costs and benefits of lifelong treatment for participants beyond the duration of each trial. A third scenario was also considered, in which it was assumed that treatment continued for the participant's lifetime, but the benefits observed during the trial stopped at the end of the study.

METHODS

The Cardiovascular Disease Life Expectancy model was used to estimate the change in life expectancy and cost-effectiveness associated with ramipril therapy in three published clinical trials, including HOPE, MICRO-HOPE and AIRE (11-13). These three randomized placebo trials lasting 4.5 years, 4.5 years and 15 months, respectively, were associated with a significant reduction in cardiovascular events. The increased life expectancy associated with this reduction in cardiovascular risk was first calculated over the study duration.

A second analysis determined the increased life expectancy associated with risk reduction over the entire life expectancy, assuming that each individual would continue to benefit from long-term ramipril therapy. In this analysis, the treatment benefits observed during the clinical trial were extended over the remaining life expectancy.

A third analysis considered the possibility that long-term ramipril therapy would not be associated with any additional risk reduction beyond that observed in the published clinical trial. Nonetheless, additional benefits would accrue as the larger number of survivors in the active treatment arm experience similar cumulative morbidity and mortality compared with the placebo survivors.

Cardiovascular Disease Life Expectancy Model

The Cardiovascular Disease Life Expectancy Model is a Markov model that estimates the annual probability of fatal and nonfatal cardiovascular disease events based on multivariate logistic regression equations developed on the 15% random sample of the Lipid Research Clinic follow-up cohort (14-16). Independent risk factors include age, sex, blood pressure, total or low-density lipoprotein cholesterol, high-density lipoprotein cholesterol (HDL-C), cigarette smoking, diabetes and diagnosed cardiovascular disease at baseline (14).

In brief, a cohort of patients is entered into the model with specified levels of risk factors. Each year, subjects may die of coronary

artery disease, cerebrovascular disease or other causes. The surviving subjects age one year and re-enter the model for the following year. Mean life expectancy can then be calculated by summing across the total person-years of life experienced by the cohort and dividing by the subjects at risk at entry into the model. The results are expressed in years of life saved (YOLS).

The model has previously been described in detail and has been shown to reasonably estimate events in nine clinical trials (14) of dyslipidemia or hypertension, a published analysis of the diabetic subjects in the Scandinavian Simvastatin Survival Study (4S) (17) and the life expectancy of American adults (18). It has also been used to estimate the cost-effectiveness of different therapies (15,17,19).

Estimating the benefits of ramipril

In each randomized trial, the model was used to estimate the cardiovascular deaths (deaths from coronary and cerebrovascular events) that were observed in the placebo and treatment arms during the course of the study. These estimates were based on the published average level of risk factors observed among participants in each arm of the study (11-13). These factors included age, sex, systolic and diastolic blood pressure, low-density lipoprotein and HDL-C levels, as well as the prevalence of diabetes mellitus, cigarette smoking and previously diagnosed cardiovascular disease.

In HOPE, missing baseline values were imputed using sex-weighted estimates obtained from men and women 55 years of age or older sampled in the 1991 Canadian Heart Health Survey (CHHS) (20), based on the HOPE study's inclusion and exclusion criteria. These selected subjects reported having had a heart attack, a stroke or another heart disease, or had diabetes and at least one cardiovascular risk factor (hypertension, defined as blood pressure higher than 160/90 mmHg or being on treatment for high blood pressure, high total cholesterol level [higher than 5.2 mmol/L], low HDL-C [lower than 0.9 mmol/L] or current cigarette smoking). Microalbuminuria could not be assessed from CHHS data. Subjects with congestive heart failure were not identified in the CHHS and could not be excluded from this cohort.

In MICRO-HOPE, missing baseline values were imputed using sex-weighted estimates obtained from men and women 55 years of age or older recruited in the CHHS, and respecting the study's inclusion and exclusion criteria. These selected subjects had diabetes and at least one cardiovascular disease risk factor (hypertension defined as blood pressure above 160/90 mmHg or being on treatment for high blood pressure, high total cholesterol [higher than 5.2 mmol/L], low HDL-C [lower than 0.9 mmol/L] or current cigarette smoking). Microalbuminuria could not be assessed from CHHS data.

In the AIRE study, missing baseline values were imputed using sex-weighted estimates obtained from men and women 30 years of age or older who were reported as having had a heart attack in the CHHS database.

These preliminary estimates of deaths from cardiovascular events were then compared with the observed results in each trial arm, and the resulting discrepancies were noted. The model was then calibrated so that the observed cardiovascular events in each study could be precisely forecasted. Once model calibration was completed, the life expectancy of participants in the treatment and control arms of each study were calculated to estimate the net increase in life expectancy associated with therapy.

Analyses were first completed over the duration of the study using the average patient profile in each study arm. A second analysis considered the study benefits projected over the remaining life expectancy of study participants. In the present analysis, the reduced mortality rate in the treatment group observed during the trial was assumed to continue with additional therapy, such that the positive effects were projected throughout the remaining lifetime of the patient. Detailed analyses for specific groups of Canadians were then completed using the same risk factor profile observed in each trial, but varying age and sex. At this point, an additional scenario was

considered. In this third analysis, it was assumed that treatment continued for the patient's lifetime, but the benefits observed during the trial stopped at the end of the study. Nevertheless, a differential survival was observed in the treatment and placebo arms as subsequent fatal events climbed in parallel.

All future events were discounted 3% annually, and results were expressed as YOLS.

Cost-effectiveness analysis – costing data included in the model

Cost-effectiveness analyses were completed from the perspective of the health care system using the estimates of increased life expectancy and direct health care costs. Treatment costs included the costs of hospitalization, physician fees, outpatient care and emergency services, when applicable. Hospital costs were estimated using the Canadian Institute for Health Information methodology (21). The average costs of Canadian physician services were based on reimbursement fee schedules from Quebec and Ontario (22,23). Outpatient care costs for survivors of cardiovascular events included separate cost estimates for the first year after the event and the subsequent years. The costs of stroke, in addition to hospital admission and outpatient care costs, included the costs of rehabilitation weighted by the probability of receiving rehabilitation. The same was done for the costs of admission to long-term care facilities. All costs are expressed in 2002 Canadian dollars (\$1 equalled approximately US\$0.80) and were calculated using Canadian health services databases (24-26). Details for estimating all health care costs have previously been reported in detail (15).

In each study, the cost of ramipril was estimated based on Canadian pricing (current at the time of writing) and the dose of study medication prescribed (27). These preliminary cost estimates were then adjusted downward, based on the reported medication nonadherence and withdrawals by study participants. Accordingly, the average estimated daily cost of ramipril was \$1.21 in AIRE, and \$0.88 in HOPE and MICRO-HOPE.

RESULTS

The baseline risk factors of study participants used for the analyses are summarized in Table 1. The observed deaths on which the model was calibrated are also noted. For AIRE, calibration was based only on all-cause mortality because this was the only fatal outcome available. For HOPE and MICRO-HOPE, model calibration was also completed for coronary and cerebrovascular deaths because these were available in the published reports.

The increased life expectancy associated with therapy over the study duration versus the remaining lifetime is summarized in Table 2. During the 4.5 years of the HOPE study, the observed reduction in total mortality was associated with an increased life expectancy of 0.06 YOLS for men, 0.04 YOLS for women and 0.06 YOLS overall. Given a remaining life expectancy of 14.3 years for men, 17.1 years for women and 15.1 years overall, the benefits of treatment over the remaining lifetime were estimated at 1.3 YOLS for men, 1.4 YOLS for women and 1.3 YOLS overall. Similar results were estimated for MICRO-HOPE, while the benefits forecasted for AIRE were smaller given the shorter remaining life expectancy of individuals with congestive heart failure.

The estimated incremental cost-effectiveness of ramipril versus placebo for each study is presented in Table 3. After discounting future costs and benefits at 3% annually, cost-effectiveness ratios for participants in AIRE over a lifetime of therapy (\$5,000/YOLS) were relatively similar to those estimated over the study duration (\$2,800/YOLS). This is due, in part, to the relatively short remaining life expectancy estimated for these high-risk individuals. On the other hand, longer survival substantially reduced the incremental cost-effectiveness ratios estimated for HOPE and MICRO-HOPE. For instance, the cost-effectiveness of ramipril among women in HOPE was estimated to be \$21,000 during the study versus \$9,700 over their remaining life expectancy.

TABLE 1
Baseline characteristics and outcomes of subjects enrolled in HOPE, MICRO-HOPE and the AIRE study

Characteristic	AIRE (n=1986)	HOPE (n=9297)	MICRO-HOPE (n=3577)
Male sex, n (%)	1461 (73.6)	6739 (72.5)	1322 (37.0)
Age, years	65.0	66.0	65.4
Blood pressure, mmHg			
Systolic	137.8	139±20	142.0
Diastolic	81.1	79±11	79.7
Hypertension, n (%)	554 (27.9)	4355 (46.8)	1996 (55.8)
Pre-existing conditions requiring treatment, n (%)			
Coronary artery disease	N/A	7477 (80.4)	2139 (59.8)
Myocardial infarction	448 (22.6)	4892 (52.6)	N/A
Angina pectoris	708 (35.6)	7529 (81.0)	N/A
Cardiac arrhythmias	122 (6.1)	N/A	N/A
Stroke or TIA	N/A	1013 (10.9)	274 (7.7)
PVD	N/A	4051 (43.6)	672 (18.8)
No history of CVD	0 (0)	807 (8.7)	1119 (31.3)
Diabetes mellitus, n (%)			
Type 2	240 (12.1)	3577 (38.0)	3577 (100)
Smoking	22.6%	1319 (14.2%)	544 (15.2%)
Lipids, mmol/L			
TC	5.62	5.55	5.67
Elevated TC (>5.2 mmol/L)	N/A	6125 (65.9)	2335 (65.3)
LDL-C	3.54	3.49	3.42
HDL-C	1.18	1.18	1.19
Low HDL-C (<0.9 mmol/L)	N/A	1723 (18.5)	N/A
Fatal outcomes, n (%)			
All-cause mortality			
Ramipril	170 (16.9)	482 (10.4)	196 (10.8)
Placebo	222 (22.6)	569 (12.2)	248 (14.0)
CVD deaths			
Ramipril	N/A	269 (5.8)	109 (6.0)
Placebo	N/A	367 (7.9)	171 (9.7)
Non-CVD deaths			
Ramipril	N/A	213 (4.6)	87 (4.8)
Placebo	N/A	202 (4.3)	77 (4.4)

AIRE Acute Infarction Ramipril Efficacy; CVD Cardiovascular disease; HDL-C High-density lipoprotein cholesterol; HOPE Heart Outcomes Prevention Evaluation; LDL-C Low-density lipoprotein cholesterol; MICRO-HOPE Microalbuminuria, Cardiovascular, and Renal Outcomes in HOPE; N/A Not available; PVD Peripheral vascular disease; TC Total cholesterol; TIA Transient ischemic attack

The importance of the time horizon when forecasting the benefits of therapy is particularly apparent when analyses are completed for specific age groups. As summarized in Table 4, a longer time horizon is particularly important among younger individuals, for whom the benefits of therapy can accumulate over the many remaining years of life expectancy. In HOPE, the life expectancy gain for men 55 years of age was 0.03 YOLS throughout the course of the 4.5-year study versus 1.61 YOLS over their entire life expectancy. The longer time horizon was even more important for 55-year-old women, for whom short-term risk was lower than for men, but remaining life expectancy was longer. Accordingly, YOLS over the study was 0.02 years versus 1.58 years over a lifetime. With increasing age, the impact of varying the time horizon diminished, as would be expected. Even if the benefits of therapy were assumed to stop at the end of the clinical trial, the impact on life expectancy was still substantial, as shown in the last two columns of Table 4.

TABLE 2
Estimated years of life saved (YOLS) following ramipril therapy in HOPE, MICRO-HOPE and the AIRE study

Study	Study duration (years)	Remaining life expectancy (years)			Benefits during study (YOLS)			Lifetime benefits (YOLS)		
		Men	Women	All	Men	Women	All	Men	Women	All
HOPE	4.5	14.3	17.1	15.1	0.06	0.04	0.06	1.3	1.4	1.3
MICRO-HOPE	4.5	14.3	17.1	15.3	0.11	0.07	0.10	2.2	2.2	2.2
AIRE	1.25	4.4	6.1	4.9	0.08	0.05	0.07	1.0	1.2	1.1

AIRE Acute Infarction Ramipril Efficacy; HOPE Heart Outcomes Prevention Evaluation; MICRO-HOPE Microalbuminuria, Cardiovascular, and Renal Outcomes in HOPE

TABLE 3
Estimated incremental cost-effectiveness (C/E) of ramipril over placebo (study-specific cohort results*)

	Estimated C/E of ramipril over study duration, \$			Predicted C/E of ramipril over the lifetime of subjects, \$		
	Men	Women	All	Men	Women	All
HOPE	12,800	21,000	15,000	8,100	9,700	8,500
MICRO-HOPE	7,900	13,200	9,900	7,900	9,500	8,500
AIRE	2,300	4,200	2,800	5,100	4,900	5,000

*Costs and benefits were discounted at 3% annually. AIRE Acute Infarction Ramipril Efficacy; HOPE Heart Outcomes Prevention Evaluation; MICRO-HOPE Microalbuminuria, Cardiovascular, and Renal Outcomes in HOPE

TABLE 4
Estimated years of life saved following ramipril therapy

	Age	Study duration only		Lifetime		Modified lifetime*	
		Men	Women	Men	Women	Men	Women
HOPE	55	0.03	0.02	1.61	1.58	0.27	0.18
	65	0.06	0.04	1.34	1.38	0.37	0.28
	75	0.11	0.08	1.08	1.15	0.46	0.41
MICRO-HOPE	55	0.06	0.03	2.73	2.67	0.50	0.34
	65	0.11	0.07	2.18	2.25	0.66	0.51
	75	0.20	0.15	1.65	1.74	0.77	0.69
AIRE	55	0.03	0.02	1.56	1.82	0.45	0.37
	65	0.08	0.05	1.01	1.24	0.51	0.47
	75	0.16	0.12	0.60	0.74	0.47	0.50

All values are presented in years. *Years of life saved over the 'study duration only' period represent the increase in life expectancy associated with treatment benefits observed only during the study. The remaining life expectancy of the participants is not considered. Years of life saved over the 'lifetime' period represent the increase in life expectancy that would be expected if the treatment that continued after the study was terminated, and the benefits observed during the study continued to accrue over the remaining lifetime. Years of life saved over the 'modified lifetime' period represent the increase in life expectancy that would be expected if the treatment that continued after the study was terminated, but treatment benefits came to an immediate halt. The subsequent mortality rates in both study arms would now be identical, but there would be more survivors in the treatment arm immediately following the end of the study, thereby adding to the years of life saved in association with treatment. AIRE Acute Infarction Ramipril Efficacy; HOPE Heart Outcomes Prevention Evaluation; MICRO-HOPE Microalbuminuria, Cardiovascular, and Renal Outcomes in HOPE

The impact of the time horizon on the cost-effectiveness of treatment produced similar results (Table 5). For instance, among 55-year-old men in HOPE, cost-effectiveness of ramipril over the five years of the study was approximately \$30,700/YOLS. Over a lifetime of treatment, this cost-effectiveness ratio drops substantially to approximately \$8,300/YOLS. For similar 55-year-old women with an even greater remaining life expectancy, the time horizon is even more important, with cost-effectiveness ratios dropping from approximately \$58,300/YOLS to approximately \$10,200/YOLS. The one exception

TABLE 5
Incremental cost-effectiveness of ramipril over placebo*

	Age	Study duration only, \$		Lifetime, \$		Modified lifetime†, \$	
		Men	Women	Men	Women	Men	Women
HOPE	55	30,700	58,300	8,300	10,200	17,500	28,500
	65	13,800	23,100	8,100	9,700	11,000	14,700
	75	6,700	8,900	8,200	9,800	8,700	10,200
MICRO-HOPE	55	18,600	37,400	7,600	9,400	11,600	18,400
	65	7,900	13,200	7,900	9,500	8,700	10,700
	75	4,300	5,000	8,500	10,200	8,400	9,800
AIRE	55	6,800	12,400	4,700	4,700	6,900	8,900
	65	2,300	4,200	5,100	4,900	5,700	5,900
	75	500	900	5,800	5,600	5,800	5,400

*Costs and benefits are discounted 3% annually; †Years of life saved over the 'study duration only' period represent the increase in life expectancy associated with treatment benefits observed only during the study. The remaining life expectancy of the participants is not considered. Years of life saved over the 'lifetime' period represent the increase in life expectancy that would be expected if the treatment that continued after the study was terminated, and the benefits observed during the study continued to accrue over the remaining lifetime. Years of life saved over the 'modified lifetime' period represent the increase in life expectancy that would be expected if the treatment that continued after the study was terminated, but treatment benefits came to an immediate halt. The subsequent mortality rates in both study arms would now be identical, but there would be more survivors in the treatment arm immediately following the end of the study, thereby adding to the years of life saved in association with treatment. AIRE Acute Infarction Ramipril Efficacy; HOPE Heart Outcomes Prevention Evaluation; MICRO-HOPE Microalbuminuria, Cardiovascular, and Renal Outcomes in HOPE

was the AIRE study, in which the cost-effectiveness ratio of \$2,300/YOLS over the short term increased to \$5,100 over the remaining life expectancy. In this study, remaining life expectancy was estimated to be less than five years (Table 2); hence, the additional benefits associated with lifelong therapy were greatly attenuated compared with individuals in HOPE or MICRO-HOPE. This is also apparent in Table 5, which shows that lifetime therapy was associated with a drop in cost-effectiveness ratios for individuals 55 years of age, no change for those 65 years of age and an increase when therapy is started at 75 years of age. If the benefits of therapy were assumed to stop at the end of the clinical trial, cost-effectiveness ratios were still more attractive when the full life expectancy was considered (Table 5, final two columns).

DISCUSSION

The cost-effectiveness analyses presented herein suggest that treatment with ramipril is economically attractive across a wide range of patient scenarios. When the time horizon was restricted to the reported duration of each clinical trial (HOPE, MICRO-HOPE and AIRE) the average estimated cost-effectiveness of ramipril ranged from \$2,800/YOLS in AIRE to \$15,000/YOLS in HOPE (Table 3). Comparing between studies, it is also apparent that lower cost-effectiveness ratios were associated with higher absolute mortality rates. For instance, over 4.5 years of follow-up, the mortality rates in

the placebo group of 12.2% for participants in HOPE and 14% in MICRO-HOPE were associated with cost-effectiveness ratios of \$15,000/YOLS and \$9,900/YOLS, respectively. In the AIRE study, over an average 15 months of follow-up, the total mortality was 23%, which reflects the poor prognosis of individuals with clinically evident congestive heart failure. In this setting, the cost-effectiveness ratio was only \$2,800/YOLS.

However, cardiovascular disease is a chronic condition. With most medications, once treatment is initiated, it is usually continued for the patient's remaining life expectancy. Accordingly, the cost-effectiveness of ramipril projected over the remaining life expectancy of individuals is particularly informative because it captures the long-term costs of therapy, the cost savings associated with delaying or preventing cardiovascular outcomes and the potential benefits associated with increasing life expectancy. With a few exceptions, the estimated cost-effectiveness of ramipril was substantially lower when the remaining life expectancy was considered. In HOPE, the cost-effectiveness ratio of \$15,000/YOLS over the short term dropped to \$8,500/YOLS over a lifetime of treatment. In MICRO-HOPE, the cost-effectiveness ratio of \$9,900/YOLS dropped to \$8,500 under similar circumstances. In both studies, the incremental costs of lifelong therapy were more than offset by the incremental benefits associated with reducing cardiovascular risk over approximately 15 additional years (Table 2). On the other hand, cost-effectiveness ratios do not necessarily increase among groups where the remaining life expectancy is short, as demonstrated in the analysis of the AIRE study.

Examining the results across studies, one notes that if only short-term study duration is considered, one may conclude that ramipril treatment is more cost-effective among the very high-risk individuals enrolled in the AIRE study than among lower-risk individuals in HOPE and MICRO-HOPE. However, when treatment over the remaining lifetime was considered, the cost-effectiveness of treatment differed little between studies, and was estimated to be \$5,000/YOLS, \$8,500/YOLS and \$8,500/YOLS for the AIRE study, MICRO-HOPE and HOPE, respectively.

One of the major assumptions in these analyses was that the short-term benefits observed during a clinical trial continue to accrue over the remaining life expectancy of treated individuals. For instance, a similar result was noted during a two-year follow-up of participants randomly assigned in 4S (28). Once the trial was terminated and cholesterol-lowering therapy was available to participants in both treatment arms, the extended survival curves for total mortality demonstrated that the short-term benefits observed during the clinical trial were maintained after the trial was completed. Given the absence of long-term trial results, are there any data to support this assumption with ramipril? In HOPE, the Kaplan-Meier survival curve summarizing the composite outcome of myocardial infarction, stroke or death from cardiovascular causes demonstrated a ramipril survival curve that continued to deviate further from the placebo curve, with no evidence of a diminished effect of treatment over time (11). The same held true for the survival curves for participants with diabetes reported in MICRO-HOPE (12). The absolute difference in cardiovascular events and all-cause mortality between treatment and placebo groups continued to grow during the clinical trial, without any evidence of attenuation over time.

Although the AIRE study was terminated after an average follow-up of approximately 15 months, subsequent long-term follow-up for an additional three years was reported in the AIRE extension study (13,29). While ramipril was associated with an absolute reduction in total mortality of 5.7% during the active clinical trial, this difference increased to an absolute mortality reduction of 11.4% over the additional three years of follow-up. Moreover, the RR reduction of 27% observed during the randomized clinical trial increased to 36% during the additional three years of follow-up, despite the fact that all trial medication had been terminated and individuals were treated at the discretion of the physicians.

The observation that cost-effectiveness ratios associated with effective treatment tend to decline as the time horizon increases is not

unique to the Markov model used in these analyses. Malik et al (5) estimated the cost-effectiveness of ramipril in HOPE over five years and over 20 years. Cost effectiveness was £36,600, £13,600 and £4,000 per life year gained at five years and £5,300, £1,900 and £100 per life year gained at 20 years in low-, medium- and high-risk groups, respectively. Backhouse et al (30) estimated the cost-effectiveness of the HOPE results in the United Kingdom over both the study duration and the estimated remaining life expectancy (30). The authors also concluded that the cost-effectiveness ratio of £5,544 per year of life gained during the study would decline with increasing therapy beyond the clinical trial. A similar conclusion was also reached by Schädlich et al (31) when estimating the cost-effectiveness of ramipril in Germany using the results of HOPE and MICRO-HOPE. Finally, Hart et al (32) analyzed the cost-effectiveness of the HOPE study among patients in Spain and noted that in sensitivity analyses, the cost-effectiveness of treatment was more sensitive to post-trial life expectancy than any other variable.

CONCLUSION

These analyses demonstrate that the cost-effectiveness of ramipril appears to be economically attractive among individuals at high risk of future cardiovascular events. When the analyses focus only on the duration of the clinical trial, high absolute mortality rates are associated with lower cost-effectiveness ratios, suggesting that ramipril was most cost-effective among individuals with congestive heart failure who were enrolled in AIRE. On the other hand, when the remaining life expectancy of the patient was considered, ramipril appeared to be equally cost-effective among lower-risk individuals enrolled in HOPE and MICRO-HOPE. If health economic analyses are used to help health care decision makers to identify cost-effective treatments and the most appropriate indications for therapy, these results suggest that restricting analyses to the short term of the clinical trial is suboptimal. Because treatment is designed to be prescribed for a lifetime, over which time some degree of therapeutic benefit is likely to be maintained, it is appropriate to also estimate the cost-effectiveness of treatment over the short and long term.

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REFERENCES

1. Fletcher GF, Balady GJ, Vogel RA. Preventive cardiology: How can we do better? Presented at the 33rd Bethesda Conference, Bethesda, Maryland, December 18, 2001. *J Am Coll Cardiol* 2002;40:579-651.
2. Lamy A, Yusuf S, Pogue J, Gafni A; Heart Outcomes Prevention Evaluation Investigators. Cost implications of the use of ramipril in high-risk patients based on the Heart Outcomes Prevention Evaluation (HOPE) study. *Circulation* 2003;107:960-5.
3. Carroll CA, Coen MM, Rymer MM. Assessment of the effect of ramipril therapy on direct health care costs for first and recurrent strokes in high-risk cardiovascular patients using data from the Heart Outcomes Prevention Evaluation (HOPE) study. *Clin Ther* 2003;25:1248-61.

4. Carroll CA, Coen MM, Piepho RW. Economic impact of ramipril on hospitalization of high-risk cardiovascular patients. *Ann Pharmacother* 2003;37:327-31.
5. Malik IS, Bhatia VK, Kooner JS. Cost effectiveness of ramipril treatment for cardiovascular risk reduction. *Heart* 2001;85:539-43.
6. Beard SM, Gaffney L, Backhouse ME. An economic evaluation of ramipril in the treatment of patients at high risk for cardiovascular events due to diabetes mellitus. *J Med Econ* 2001;4:199-205.
7. Björholt I, Andersson FL, Kahan T, Ostergren J. The cost-effectiveness of ramipril in the treatment of patients at high risk of cardiovascular events: A Swedish sub-study to the HOPE study. *J Intern Med* 2002;251:508-17.
8. Erhardt L, Ball S, Andersson F, Bergentoft P, Martinez C. Cost effectiveness in the treatment of heart failure with ramipril. A Swedish substudy of the AIRE study. *Acute Infarction Ramipril Efficacy. Pharmacoeconomics* 1997;12:256-66. (Erratum in 1997;12:706).
9. Hart WM, Rubio-Terres C, Pajuelo F, González Juanatey JR. Cost-effectiveness of the treatment of heart failure with ramipril: A Spanish analysis of the AIRE study. *Eur J Heart Fail* 2002;4:553-8.
10. Schädlich PK, Huppertz E, Brecht JG. Cost-effectiveness analysis of ramipril in heart failure after myocardial infarction. Economic evaluation of the Acute Infarction Ramipril Efficacy (AIRE) study for Germany from the perspective of Statutory Health Insurance. *Pharmacoeconomics* 1998;14:653-69.
11. Yusuf S, Sleight P, Pogue J, Bosch J, Davies R, Dagenais G. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. The Heart Outcomes Prevention Evaluation Study Investigators. *N Engl J Med* 2000;342:145-53. (Errata in 2000;342:1376, 2000;342:748).
12. Effects of ramipril on cardiovascular and microvascular outcomes in people with diabetes mellitus: Results of the HOPE study and MICRO-HOPE substudy. Heart Outcomes Prevention Evaluation Study Investigators. *Lancet* 2000;355:253-9. (Erratum in 2000;356:860).
13. Effect of ramipril on mortality and morbidity of survivors of acute myocardial infarction with clinical evidence of heart failure. The Acute Infarction Ramipril Efficacy (AIRE) Study Investigators. *Lancet* 1993;342:821-8.
14. Grover SA, Paquet S, Levinton C, Coupal L, Zowall H. Estimating the benefits of modifying risk factors of cardiovascular disease: A comparison of primary vs secondary prevention. *Arch Intern Med* 1998;158:655-62. (Erratum in 1998;158:1228).
15. Grover SA, Coupal L, Paquet S, Zowall H. Cost-effectiveness of 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors in the secondary prevention of cardiovascular disease: Forecasting the incremental benefits of preventing coronary and cerebrovascular events. *Arch Intern Med* 1999;159:593-600.
16. Heiss G, Tamir I, Davis CE, et al. Lipoprotein-cholesterol distributions in selected North American populations: The lipid research clinics program prevalence study. *Circulation* 1980;61:302-15.
17. Grover SA, Coupal L, Zowall H, Dorais M. Cost-effectiveness of treating hyperlipidemia in the presence of diabetes: Who should be treated? *Circulation* 2000;102:722-7.
18. Grover SA, Coupal L, Gilmore N, Mukherjee J. Impact of dyslipidemia associated with Highly Active Antiretroviral Therapy (HAART) on cardiovascular risk and life expectancy. *Am J Cardiol* 2005;95:586-91.
19. Grover SA, Coupal L, Zowall H, Alexander CM, Weiss TW, Gomes DR. How cost-effective is the treatment of dyslipidemia in patients with diabetes but without cardiovascular disease? *Diabetes Care* 2001;24:45-50.
20. MacLean DR, Petrasovits A, Nargundkar M, et al. Canadian heart health surveys: A profile of cardiovascular risk. Survey methods and data analysis. Canadian Heart Health Surveys Research Group. *CMAJ* 1992;146:1969-74.
21. Resource Intensity Weights. Summary of Methodology, 1996/97. Canadian Institute for Health Information, 1996.
22. Régie de l'assurance maladie du Québec. Manuel des Médecins Spécialistes RAMQ. Québec: Régie de l'assurance maladie du Québec, 1996.
23. Ontario Ministry of Health. Schedule of benefits: Physician services, 1992. Toronto: Ontario Ministry of Health, 1992.
24. Statistics Canada. CANSIM Matrix 9440, Series L. Ottawa, 2002.
25. Statistics Canada. CANSIM Matrix P100200. Ottawa, 2002.
26. Statistics Canada. CANSIM Matrix L95705. Ottawa, 2002.
27. IMS Canada. Canadian Compuscript, November 2000. Point-Claire: IMS Canada, 2000.
28. Pedersen TR, Wilhelmsen L, Faergeman O, et al. Follow-up study of patients randomized in the Scandinavian simvastatin survival study (4S) of cholesterol lowering. *Am J Cardiol* 2000;86:257-62.
29. Hall AS, Murray GD, Ball SG. Follow-up study of patients randomly allocated ramipril or placebo for heart failure after acute myocardial infarction: AIRE Extension (AIREX) Study. *Acute Infarction Ramipril Efficacy. Lancet* 1997;349:1493-7.
30. Backhouse ME, Richter A, Gaffney L. Economic evaluation of ramipril in the treatment of patients at high risk for cardiovascular events. *J Med Econ* 2005;3:97-109.
31. Schädlich PK, Brecht JG, Rangoonwala B, Huppertz E. Cost effectiveness of ramipril in patients at high risk for cardiovascular events: Economic evaluation of the HOPE (Heart Outcomes Prevention Evaluation) study for Germany from the Statutory Health Insurance perspective. *Pharmacoeconomics* 2004;22:955-73.
32. Hart WM, Rubio-Terres C, Margalet Fernández I, González Juanatey JR. [Cost-effectiveness analysis of Ramipril treatment of patients at high-risk of cardiovascular events in Spain.] *An Med Interna* 2002;19:515-20.