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Cost effectiveness of ramipril in patients at high risk for cardiovascular events: a Swiss perspective

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Summary

Background: Ramipril may prevent cardiovascular death, myocardial infarction and stroke in patients without evidence of left ventricular dysfunction or heart failure who are at high risk for cardiovascular events. In the present study we assessed the cost-effectiveness of ramipril in patients with an increased risk of cardiovascular events from a third party payer's perspective in Switzerland. In addition, the cost-effectiveness of ramipril in the subgroup of diabetic patients was assessed.

Methods: We developed a decision analytic cost-effectiveness model to estimate the incremental costs (in 2001 in Swiss Francs [CHF]), incremental effects (in terms of life-years gained [LYG]) and incremental cost-effectiveness (CHF per LYG) of ramipril versus placebo. Clinical input parameters were derived from the Heart Outcomes Prevention Evaluation (HOPE) study. Cost data were extracted from the literature. Deterministic sensitivity analysis was used to assess the impact of varying the input parameters on the cost effectiveness of the intervention. In addition, first-order Monte Carlo simulation was used to capture patient-to-patient variability, presented as cost-effectiveness acceptability curves.

Results: The incremental cost-effectiveness ratio of ramipril versus placebo was CHF 6,005 per life-year gained in the base case analysis. In diabetic patients the cost-effectiveness ratio was CHF 3,790 per life-year gained. Varying the price of ramipril in a deterministic sensitivity analysis only had a moderate impact on the cost-effectiveness ratio in the overall population (range: CHF 3,652–15,418 per LYG) as well as in diabetic patients (range: CHF 2,370–9,468 per LYG).

Conclusion: Ramipril in patients at high risk for cardiovascular events represents an efficient use of scarce health care resources in Switzerland and is cost-effective under reasonable assumptions. Ramipril is even more cost-effective in the subgroup of diabetic patients.

Key words: cost effectiveness; ramipril; cardiovascular disease

Introduction

Cardiovascular diseases are the leading cause of death in Switzerland and a major public health concern in most industrialized countries [1–3]. In the Heart Outcomes Prevention Evaluation (HOPE) study, ramipril, an ACE-inhibitor, has been shown to reduce the risk of cardiovascular events and improve survival in patients at high risk for cardiovascular events [4, 5]. The HOPE study was a randomised controlled double-blind trial enrolling a total of 9,297 patients without left-ventricular dysfunction and heart failure who were older than 55 years [4]. Patients included in the study had a history of coronary artery disease, stroke, peripheral vascular disease or diabetes and at least one additional risk factor such as hypertension, elevated total cholesterol levels, low high-density lipoprotein cholesterol levels, microalbuminuria or smoking. Patients received either a daily dose of 10 mg ramipril or placebo, in addition to current medication. The planned time-horizon of the study was 5 years but the study was closed after 4.5 years due to the superiority of ramipril over placebo. Ramipril substantially reduced the risk of myocardial infarction, stroke or cardiovascular death (RR: 0.78, 95% CI: 0.70–0.86), which was defined as the primary com-

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posite endpoint in the study [4]. Moreover, ramipril reduced the risk of revascularisation, hospitalisation due to angina pectoris or heart failure and complications in diabetic patients [4–6].

Although the clinical benefit of ramipril has been documented in the HOPE study, the cost effectiveness of ramipril in this patient population from a Swiss perspective still remains to be determined. In times of increasing pressures to contain health care resource consumption, the cost effectiveness of health care technologies needs to be evaluated once the efficacy of the intervention has been demonstrated in randomised controlled trials. A formal cost-effectiveness analysis allows us to address this issue and to assess whether new (and existing) treatment options represent "value for money". In the present study we therefore conducted a cost-effectiveness analysis of ramipril as compared to placebo in patients at increased risk for cardiovascular events from the perspective of third party payers (health insurers) in Switzerland.

Methods

The model

We used a decision analytic model to estimate the cost-effectiveness of ramipril in Switzerland. Clinical input parameters were derived from the HOPE study and cost data were extracted from the literature [4–14]. The decision tree used for our economic evaluation is shown in figure 1. In the HOPE study, patients were either randomised to ramipril 10 mg daily or to the placebo group [4]. The incremental effects of ramipril in our model were expressed as life-years gained. Incremental cost calculations were based on the difference in event rates for the different outcomes in the two treatment arms as shown in figure 1. Each outcome (i.e. myocardial infarction, revascularisation, stroke, cardiac arrest, heart failure, deteriorating angina pectoris, diabetic complications, new onset diabetes) induces the consumption of health care resources and therefore has a cost associated with it.

Effects

Effects were expressed as life-years gained (LYG). LYG were based on the difference between the areas under the survival curves of the ramipril versus placebo group in the HOPE study (LYG_1 = life-years gained during the follow-up period of the trial) and by means of the DEALE (declining exponential approximation of life expectancy) method (LYG_2 = life-years gained beyond the follow-up period of the trial) [15, 16].

The number of prevented deaths from all causes was used to calculate life-years gained (LYG), as quantified by the following formulas:

$$LYG = LYG_1 + LYG_2$$
$$LYG_1 = \Delta S \cdot t \cdot 0.5$$
$$LYG_2 = \left[\frac{1}{\frac{1}{LEN} - \frac{\ln(1 - pD_p)}{t}} - t \right] \Delta S$$

ΔS denotes the survival-rate difference between the ramipril and placebo group at the end of the HOPE study. t is the observation period in the HOPE study (4.5 years). LEN, which is the life expectancy of a normal population of the same age and gender as the patients included in the HOPE study (mean age 66 years, 73.3% men and 26.7% women), is 15.86 years. ln denotes the natural logarithm and $(1–pD_p)$ the proportion of patients alive in the placebo group at the end of the HOPE study.

Costs

Cost of medication. The cost of medication was estimated at CHF 1.59 per day using the 100-tablet pack and CHF 2.80 per day using the 20-tablet pack. For the base-case analysis the estimate of CHF 1.83 per day was used, assuming that the 100-tablet pack was used in 80% of patients and the 20-tablet pack in 20% of patients. These costs were based on the prices for Triatec® (Ramipril), effective on May 1st 2003, as published by the Swiss Federal Office for Social Insurance [17], after deduction of the Swiss cost-stability contribution of 3.2% [18, 19]. According to the ramipril use in the HOPE study (334 days in the first year, 287, 266 and 243 days in the

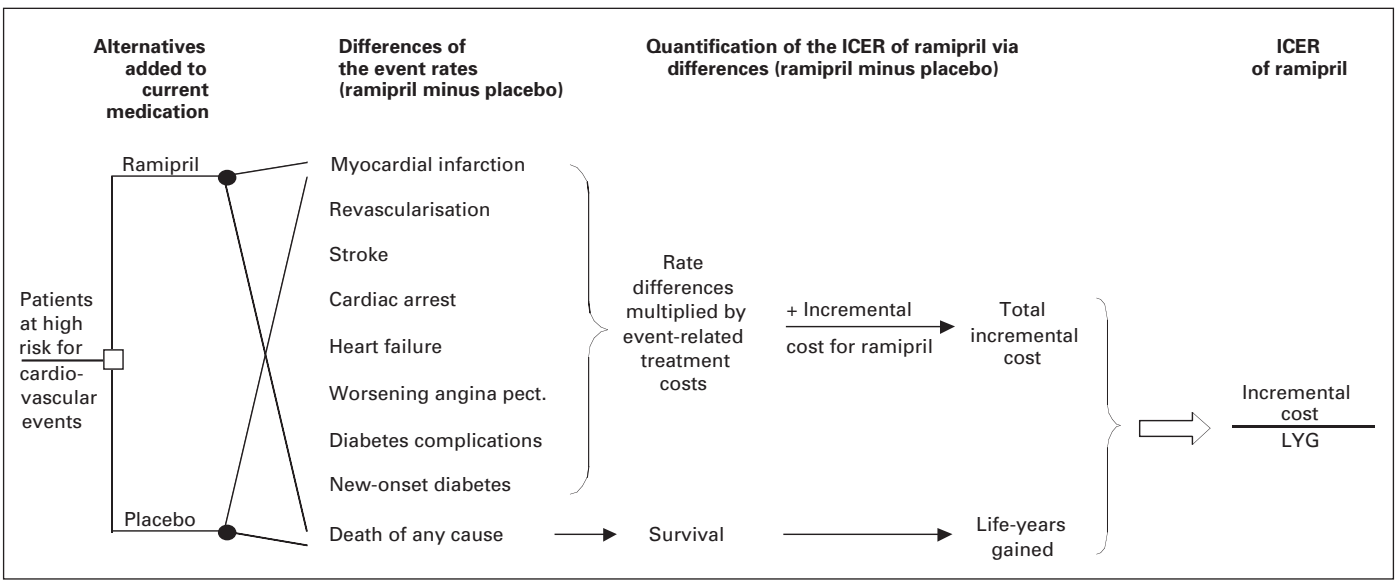

Figure 1
Decision tree of the cost-effectiveness model.

Table 1
Cost to Swiss health insurers for treating target events.

Target event	Costs (CHF)	Range (min to max) (CHF)	References
Per case:			
Myocardial infarction (inpatient)	11,427	7,533 to 16,563	[9, 21–23, 39]
Bypass surgery (inpatient)	13,803	10,600 to 18,408	[9, 21–23, 39]
PTCA (inpatient)	4,880	3,307 to 7,963	[22, 23, 39]
Other revascularization	6,866	4,514 to 13,277	[8–10, 21–23, 39]
Stroke (inpatient)	29,884	22,483 to 36,836	[9, 21–23, 39]
Cardiac arrest (inpatient)	13,105	6,217 to 19,934	[9, 21–23, 39]
Heart failure (inpatient)	18,489	15,734 to 21,936	[9, 21–23, 39]
Unstable angina pectoris (inpatient)	7,153	4,080 to 11,655	[9, 21–23, 39]
Increased outpatient costs after inpatient treatment or intervention	2,358	1,908 to 2,809	[12]
Per patient and year:			
Diabetes complications (in- and outpatient)	2,380	1,966 to 2,793	[13]
Newly diagnosed diabetes (in- and outpatient)	2,380	1,966 to 2,793	[13]

CHF denotes Swiss Francs

subsequent years and 116 days in the last 6 months of the study), costs for ramipril were estimated at CHF 2.28 per day per patient during the study period (CHF 2.10 discounted at 5% p.a.) using the larger pack [4]. The corresponding figures for the smaller pack are CHF 3.49 (undiscounted) and CHF 3.22 (discounted).

Treatment costs (table 1). For myocardial infarction, stroke, cardiac arrest and angina pectoris, costs and the respective ranges were based on length of stay (LOS) in hospitals during the year 1998 [20], and daily treatment costs in hospitals during the years 2001 [21, 22] and 2002 [9] in Switzerland. In case of a revascularization, LOS for femoropopliteal bypass, endarterectomy, vascular revision and leg amputation was extrapolated from the years 1994 and 1998 [8, 10, 20] to the year 1999 on the basis of the generally observed shortening of LOS by 19.6% between 1994 and 1999 [20]. Inpatient days were valued using cost estimates for an inpatient day in 2001 or 2002 [9, 22, 23]. Cost estimates for bypass surgery and percutaneous transluminal coronary angioplasty (PTCA) were calculated similarly. Estimates for increased outpatient costs over a period of six months after hospital discharge were based on a published study on the treatment costs of ischaemic heart disease and stroke in 1990 [12]. This procedure implied an actualisation of costs, i.e., all costs were expressed in 2001 Swiss Francs (CHF) using the consumer price index for health care. Finally, yearly treatment costs for diabetic patients experiencing microvascular complications and for newly diagnosed diabetes, respectively, were based on a published study on the costs of type-2 diabetes treatment in Switzerland [13].

Cost effectiveness

The incremental cost-effectiveness ratio was calculated as incremental costs divided by incremental effects. As the time horizon of the study was 4.5 years (more than one year), costs and effects were discounted using an annual discount rate of 5%. However, undiscounted costs and effects were also calculated.

Our cost-effectiveness study includes a base-case analysis supplemented with different methods of sensitivity analysis [24]. In the base-case analysis, exclusively average values of the model input parameters were used. We assessed the impact of varying the price of ramipril on the cost-effectiveness of the intervention in a deterministic one-way sensitivity analysis. In addition, we performed a worst/best-case scenario analysis combining all model input parameters that would jointly favour or disfavour the intervention to assess the robustness of our model results. Finally, a first-order Monte Carlo simulation was performed to assess the variance of the cost-effectiveness ratio given the baseline values [25].

Results

Effectiveness of ramipril

Table 2 shows the number of target events prevented by administering ramipril over a period of 4.5 years in a hypothetical cohort of 100 patients. These target events are valued using the cost estimates in table 1.

Average for LYG

In a hypothetical cohort of 100 patients (here chosen for standardisation purposes), ΔS had a mean value of 1.85 (based on the number of prevented deaths from all causes; see table 2) and S_P had a mean value of 87.77. The formulae above yield an undiscounted total of 15.98 LYG and a discounted total (at 5% per year) of 11.88 LYG.

Worst case for LYG

Based on the lower limit of 0.57 of the 95% confidence interval (CI) of ΔS (number of prevented deaths from all causes; see table 2) and on the lower limit of 86.83 of the 95% CI of S_P, there was a total of 4.67 LYG (undiscounted) and 3.50 LYG (discounted at 5% per year) in the worst case.

Best case for LYG

Based on the upper limit of 3.14 of the 95% CI of ΔS (number of prevented deaths from all causes; see table 2) and on the upper limit of 88.71 of the 95% CI of S_P, there was a total of 27.56 LYG (undiscounted) and 20.42 LYG (discounted at 5% per year) in the best case.

Table 2
Clinical effectiveness of ramipril: Number of prevented events in a hypothetical cohort of 100 patients according to the HOPE study.

Event	Number of prevented events (95% CI)*		References
Economic parameters			
Myocardial infarction	2.37	(1.10 to 3.65)	[4]
Cardiological revascularization	2.58	(1.15 to 4.01)	[4, 5]
Other revascularization	–0.24	(–0.90 to 0.42)	[4, 5]
Stroke	1.50	(0.69 to 2.31)	[4]
Cardiac arrest	0.47	(0.06 to 0.88)	[4]
Hospitalization owing to heart failure	0.40	(–0.32 to 1.12)	[4]
Hospitalization owing to unstable angina pectoris	0.22	(–1.10 to 1.54)	[4]
Microvascular diabetes complication **	2.74	(0.73 to 4.76)	[4]
Newly diagnosed diabetes***	1.78	(0.71 to 2.85)	[4]
Effictiveness parameter			
Death from all causes	1.85	(0.57 to 3.14)	[4]

* The 95% confidence interval (CI) is based on a binomial distribution of the event frequency among the 4,645 patients in the ramipril group and the 4,652 patients in the placebo group (negative values signify greater frequency in the ramipril group).
** The denominator in the ramipril group consists of 1,910 patients (1,808 with diabetes at the beginning of the study and 102 with newly diagnosed diabetes during the course of the study). The denominator in the placebo group consists of 1,924 patients (1,769 with diabetes at the beginning of the study and 155 with newly diagnosed diabetes during the course of the study).
*** The denominator in the ramipril group consists of 2,837 patients without diabetes at the beginning of the study. The denominator in the placebo group consists of 2,883 patients without diabetes at the beginning of the study.

Table 3
Base-case results (per 100 patients) – Incremental costs, incremental effects and incremental cost-effectiveness ratio of ramipril compared to placebo.

Parameters	Total Population of HOPE Study		Diabetics in the HOPE study	
	Non-discounted values	Discounted values (5% per annum)	Non-discounted values	Discounted values (5% per annum)
Additional costs for ramipril, 10 mg daily	CHF 228,265	CHF 210,586	CHF 228,265	CHF 210,586
Cost difference in treatment of the target events*	–CHF 153,101	–CHF 139,235	–CHF 149,092	–CHF 135,936
Total additional costs	CHF 75,164	CHF 71,351	CHF 79,173	CHF 74,650
Life-years gained (LYG)	15.97	11.88	26.27	19.69
Incremental cost-effectiveness ratio	CHF 4,704/LYG	CHF 6,005/LYG	CHF 3,014/LYG	CHF 3,790/LYG

* Negative figures denote savings

Base-case analysis

In the base-case analysis, only average values of the cost and effectiveness parameters were used. Table 3 shows the base-case results of the cost-effectiveness analysis. The discounted and undiscounted incremental cost-effectiveness ratios of ramipril compared to placebo were CHF 4,704 per LYG and CHF 6,005 per LYG, respectively. Since the costs for treatment are incurred earlier and the life-years gained experienced later in time, discounting leads to a higher cost-effectiveness ratio.

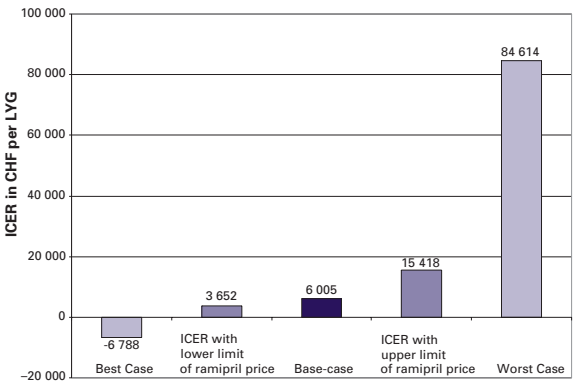

Figure 2
One way sensitivity analysis of the price of ramipril and best-case/worst-case scenario analysis in the HOPE population (discounted with 5% per year). ICER: Incremental cost-effectiveness ratio.

Sensitivity analysis

The results of the deterministic univariate sensitivity analysis on the cost of ramipril are shown in figure 2. When the lower limit for the price of ramipril is used, the cost-effectiveness ratio is CHF 3,652 per LYG whereas the corresponding figure is CHF 15,418 per LYG when the upper limit for the price of ramipril is used.

The results of the worst/best-case scenario analysis are also shown in figure 2. The worst case is determined by the combination of the upper limit for ramipril costs and the lower limits of all remaining parameters (see table 2). Therefore, the highest additional ramipril costs were combined with the lowest savings and lowest number of life-years gained (worst case for LYG). Similarly, the best case is determined by the combination of the lower limit for ramipril costs and the upper limits for all remaining variables (see table 2). Therefore, the lowest additional ramipril costs were combined with the highest savings and highest number of life-years gained (best case for LYG). A negative cost-effectiveness ratio indicates cost-savings as well as gains in life-years (dominant strategy). Finally, the results of the first-order Monte Carlo simulation (based on 10,000 iterations) are pre-

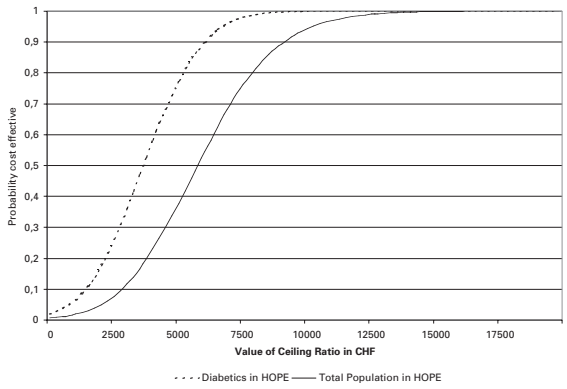

Figure 3
Cost-effectiveness acceptability curves for the total population and for the diabetic subgroup in the HOPE study.

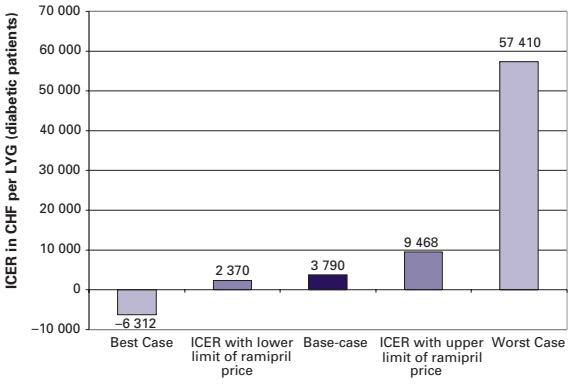

Figure 4
One way sensitivity analysis of the price of ramipril and best-case/worst-case scenario analysis in the diabetic patient subgroup (discounted with 5% per year). ICER: Incremental cost-effectiveness ratio.

sented as cost-effectiveness acceptability curves in figure 3 [26]. This cost-effectiveness acceptability curve estimates the probability that the intervention is cost-effective (given the baseline model parameters), i.e., the joint probability that the intervention is both cost-saving and leads to gains in life-years or that the intervention has an incremental cost-effectiveness ratio, which is below the threshold (ceiling) cost-effectiveness ratio used as a cut-off point for resource allocation.

Subgroup analysis in diabetic patients

We performed a separate subgroup-analysis for diabetic patients because of their higher risk of experiencing cardiovascular events than non-diabetics [4–7]. In a hypothetical cohort of 100 diabetic patients considerably more deaths from all causes were prevented than in the entire population. Therefore, more life-years were gained in this patient subgroup by administering ramipril. The mean value of LYG in this patient population was 19.69 years, the worst case 5.96 LYG, and the best case 34.17 LYG (in a hypothetical cohort of 100 patients, using a time horizon of 4.5 years and a discount rate of 5%). Table 3 shows the base case results of the analysis. The discounted cost-effectiveness ratio was CHF 3,790 per LYG whereas the undiscounted figure was CHF 3,014 per LYG. Figure 4 shows the results of the deterministic univariate sensitivity analysis on the costs of ramipril in addition to the worst/best case scenario analysis. Finally, the cost-effectiveness acceptability curve for diabetic patients is shown in figure 3.

Discussion

In the present study we have shown that ramipril represents considerable value for money in the Swiss setting. Under reasonable assumptions, the cost effectiveness of ramipril in patients at high risk for cardiovascular events was CHF 6,005 per LYG. In the diabetic patient subgroup, ramipril was even more cost-effective with a cost-effectiveness ratio of CHF 3,790 per LYG. Our results are comparable to those of other countries [27–32]. An economic evaluation of the HOPE study has been published from the perspectives of the National Health Service in the United Kingdom and the German Statutory Health Insurance [33, 34]. In the base case, these evaluations resulted in an amount of € 4,074 and € 4,406 per life-year gained, respectively. In another UK study from the perspective of health care providers, the cost effectiveness of ramipril for the treatment of cardiovascular risk reduction was £ 13,600 per LYG and £ 1,900 per LYG when a 5 year and a 20 year time horizon was used, respectively [32]. This suggests that ramipril is even more cost-effective when a life long treatment of patients is considered. In a Swedish study, the cost effectiveness of ramipril was € 5,300 per LYG when direct medical costs were considered [30]. In a Spanish cost-effectiveness analysis from the perspective of third party payers, which was also based on the HOPE study, the incremental cost-effectiveness ratio for ramipril was € 10,329 per LYG [29]. Finally, ramipril in high-risk patients based on the HOPE study has been shown to be cost-saving or cost-neutral or have a cost-effectiveness ratio below $10,000 per primary event prevented when a third party payer perspective in the US or Canada was taken [27, 28]. The cost-effectiveness ratios listed above are all within the range of currently funded health care programmes in the respective countries and may therefore be considered cost-effective.

Our analysis was also conducted from the perspective of third party payers (health insurers) in Switzerland as these are largely responsible for paying the additional costs of ramipril. Therefore, the analysis was limited to categories of costs that are borne by these health insurers. Due to the perspective and time horizon chosen, other direct costs such as rehabilitation treatment and long-term care were excluded from the analysis, as were productivity costs. Productivity costs would have been included in a societal perspective of the analysis where all costs and benefits are considered irrespective to which they accrue [35].

The design of the HOPE study implies a high

external validity as ramipril was administered in addition to current medication in patients at high risk for cardiovascular events [4]. It is therefore well suited to model the cost-effectiveness of ramipril in daily practice. On the other hand, patients were recruited into the HOPE from 1993 to 1995 and disease conditions were treated according to the standards at that time [4]. However, according to current standards antihypertensive drugs, antithrombotic agents and lipid lowering agents should have been used more frequently in these patients [37]. This would have led to a reduction of the baseline risk in this population and the absolute risk reduction and hence the cost-effectiveness of ramipril would have been less prominent. According to a recent national survey on the prescription of cardiovascular drugs among outpatients with coronary artery disease in Switzerland, evidence based drug prescription has improved [37]. In patients with a history of myocardial infarction or coronary revascularisation, 84% were administered antiplatelet agents, 82% were administered lipid lowering drugs and 71% were administered beta-blockers [37]. In the HOPE study these pharmaceuticals were used less frequently [4].

Our cost-effectiveness model has several limitations. Firstly, incremental effects were expressed as life-years gained and not quality-adjusted life-years gained. If length of life were adjusted for quality of life, the incremental effectiveness would have even been larger. This would have also captured prevented disease conditions that would not necessarily lead to death (at least within the follow-up period of the HOPE trial). That is, our study actually underestimates the cost effectiveness of ramipril in patients at high risk for cardiovascular events. Secondly, we did not explicitly model the side effects of ramipril such as coughing, angio-oedema and renal failure. These side effects would have been best modelled in terms of a reduction in quality of life. However, utilities were not assessed in the HOPE trial and our study might therefore be seen as an approximation of the true cost effectiveness of ramipril in the absence of any evidence of the impact of these side effects on the patient's quality of life. Thirdly, cost data were extracted from the literature and imputed into the model. Although clinical data may be comparable across countries, cost data usually are not, because of differences in medical practice, epidemiology and costing procedures. An economic evaluation therefore needs to be conducted for each country separately. Thus, a modelling approach can be seen as a method to adjust the cost estimates for local conditions in Switzerland [38].

Although the time-horizon of the cost-effectiveness analysis was restricted to 4.5 years, we have included the life-years gained in the ramipril group after 4.5 years of follow-up using the DEALE method, assuming the same mortality rate in both treatment arms. This approach is analogous to the method applied by Backhouse et al. [33] and has been chosen to capture the benefit resulting from the additional survivors accruing after 4.5 years of follow-up in the treatment arm. One objection to this approach may be that the costs in these additional years of life gained are not included in the analysis. We have therefore also performed the analysis restricting the life-years gained to the follow-up period of 4.5 years only. The discounted incremental cost-effectiveness ratios in the general HOPE population and the diabetic subgroup were CHF 20,474 and 12,580 per life-year gained, respectively. If the upper and lower limits for the ramipril price were used in these analyses, the respective incremental cost-effectiveness ratios were CHF 11,816–49,880 per life-year gained (general HOPE population) and CHF 7,418–29,264 per life-year gained (diabetic subpopulation), respectively. According to current standards, these cost-effectiveness ratios may be considered acceptable.

In conclusion, ramipril for the treatment of patients at high risk for cardiovascular events represents an efficient use of scarce health care resources in Switzerland and is cost-effective under reasonable assumptions. Ramipril is even more cost-effective in the subgroup of diabetic patients.

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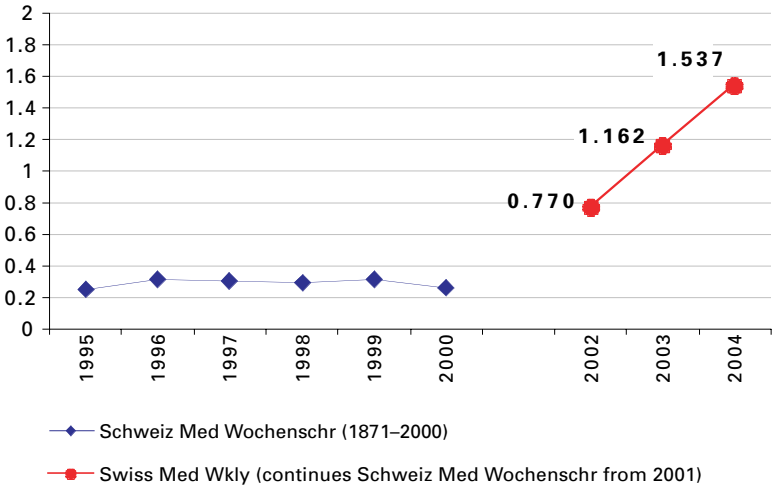

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