

## ORIGINAL ARTICLE

# Cost-effectiveness of antihypertensive treatment in patients 80 years of age or older in Switzerland: an analysis of the HYVET study from a Swiss perspective

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This analysis shows the economic benefit of antihypertensive treatment in patients 80 years of age or older from the perspective of the Swiss healthcare system. The cost-effectiveness analysis of antihypertensive treatment in the elderly was carried out applying the results of the Hypertension in the Very Elderly Trial study to the Swiss healthcare system. The analysis shows that hypertension treatment provides, compared with placebo, an additional life expectancy of 0.0457 years per patient, over a follow-up period of 2 years. The medication cost was covered by the reduction of costs related to the treatment of strokes, myocardial infar-

tions and heart failure: the total cost per patient in the active group resulted in a dominant strategy of savings compared with the placebo group. Sensitivity analysis yielded a stable estimate after varying the costs of medication, stroke, myocardial infarction, heart failure and life expectancy, confirming the robustness of these results. Moreover, considering that antihypertensive treatment also positively affects the incidence of dementia, those net benefits might even be underestimated.

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## Introduction

Hypertension is a highly prevalent risk factor for ischaemic heart diseases and stroke worldwide. The increasing longevity and prevalence of contributing factors (for example obesity) strongly affect the morbidity and mortality of cardiovascular events in both developed and developing countries.<sup>1</sup> Therefore, the prevention and management of high blood pressure is a major public health challenge.

In 2004 ischaemic heart diseases caused 40 657 deaths in France, 152 659 in Germany, 38 840 in Spain and 106 142 in the United Kingdom. Stroke-related deaths were 33 487 in France, 68 498 in Germany, 34 250 in Spain and 60 551 in the United Kingdom. In Switzerland, the deaths related to ischaemic heart diseases were about 9200. Half of the deceased men were older than 80 years and half

of the women were older than 87 years. The deaths related to stroke were 4083; more than half of them were 80 years of age or older.<sup>2,3</sup>

Several studies of hypertension have observed the relative risk reduction in total mortality in older and younger adults, indicating an overall significant benefit.<sup>4,5</sup> However, Turnbull *et al.*<sup>6</sup> evidenced the relative paucity of data for patients over 80 years of age, even if this group report more than half of the hypertension-related deaths.

Becket *et al.*<sup>7</sup> investigated in the 'Hypertension in the Very Elderly Trial' (HYVET) the clinical benefit of treating patients with hypertension. In a double-blind, randomized, placebo-controlled, multicenter clinical trial involving 3845 patients 80 years old or older, they evaluated the effect of a stepped care therapy, beginning with 1.5 mg indapamide SR (sustained release) and adding 2–4 mg perindopril, if needed to reach the target blood pressure (BP ≤ 150/80 mm Hg).

The results of the study provided evidence that antihypertensive treatment with indapamide SR, with or without perindopril, in very elderly people is beneficial: active treatment was associated with a 30% reduction in the rate of fatal or nonfatal stroke (95% confidence interval (CI), –1 to 51; *P* = 0.06) and

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a 39% reduction in the rate of death from stroke (95% CI, 1 to 62;  $P=0.05$ ). The rates of death from any cause or from cardiovascular causes were also reduced by 21% (95% CI, 4 to 35;  $P=0.02$ ) and 23% (95% CI, -1 to 40;  $P=0.06$ ), respectively. Finally Becket *et al.* determined a 64% reduction in the rate of heart failure in the active-treatment group. Fewer serious adverse events were reported in the active-treatment group (358 vs 448 in the placebo group;  $P=0.001$ ). Therefore, it is not too late to start antihypertensive treatment in very elderly individuals from a clinical point of view.

In the following study, we estimated the cost-effectiveness of antihypertensive therapy in patients 80 years of age or older from the perspective of the Swiss healthcare system.

## Materials and methods

### Study design

We carried out a retrospective cost-effectiveness analysis of the HYVET study published by Becket *et al.* in May 2008.<sup>7</sup> This double-blind, randomized, placebo-controlled clinical trial was conducted in 13 countries in Western and Eastern Europe, China, Australasia and North Africa, and was used as the basis of efficiency assessment (Table 1).

It was assumed that the effect of antihypertensive treatment on clinical outcomes could be transferred to Switzerland. A summary of the effects on clinical outcomes for the particularly relevant clinical events is shown in Table 2. The detailed HYVET protocol has been published extensively.<sup>8</sup>

### Study end point

The end point of this cost-effectiveness analysis is the incremental cost per life-year gained in Switzerland, expressed in Swiss francs (CHF).

### Determination of costs and effectiveness

**Costs.** To determine the total costs of antihypertensive treatment vs placebo, we included four directly attributable cost groups: (i) the medication costs according to the dosages used in the HYVET study, (ii) the acute costs and 2-year follow-up costs of a myocardial infarction, (iii) the acute costs and 2-year follow-up costs of a stroke and (iv) the costs of heart failure over 2 years. Indirect costs (for example costs related to loss of work) and intangible costs (for example suffering, pain) were not included. We chose the perspective of third-party payers in Switzerland.

The costs of treatment with 1.5 mg indapamide SR (Fludex SR tablet, Servier (Suisse) SA, CHF 0.67 per tablet) and 2–4 mg perindopril (Coversum tablet 4 mg, Servier (Suisse) SA, CHF 1.00 per tablet) were based on pharmacy retail prices in Switzerland, as mainly pharmacies are authorized to sell drugs to ambulatory patients.<sup>9</sup> The mean daily treatment

**Table 1** Design of the HYVET study

Hypothesis	Antihypertensive therapy may reduce the risk of stroke in patients with hypertension who are 80 years of age or older, despite possibly increasing the risk of death
Study design	Randomized, double-blind, placebo-controlled, multicenter trial in 195 centres in 13 countries in Western and Eastern Europe, China, Australasia and North Africa
Inclusion criteria	80 years of age or older Persistent hypertension (sustained systolic pressure of 160 mm Hg)
Exclusion criteria	Contraindication to use the trial medications, accelerated hypertension, secondary hypertension, haemorrhagic stroke in the previous 6 months, heart failure requiring treatment with antihypertensive medication, serum creatinine level $>150$ mmol l <sup>-1</sup> , serum potassium level $<3.5$ mmol l <sup>-1</sup> , gout, clinical dementia, requirement of nursing care
Intervention	2 months placebo run-in phase Active treatment: diuretic indapamide SR (sustained release, 1.5 mg); angiotensin-converting-enzyme inhibitor, perindopril (2 or 4 mg), if needed to reach target blood pressure ( $\leq 150/80$ mm Hg) Placebo
End point	<i>Primary:</i> fatal or nonfatal stroke <i>Secondary:</i> death from any causes
Period of observation	2 years
Patients	3845 patients <i>Active treatment:</i> 1933 patients, average age 83.6 years, 60.7% women, history of cardiovascular disease 11.5%, smokers 6.4%, diabetes 6.8%, mean blood pressure while sitting 173.0/90.8 mm Hg <i>Placebo:</i> 1912 patients, average age 83.5 years, 60.3% women, history of cardiovascular disease 12.0%, smokers 6.6%, diabetes 6.9%, mean blood pressure while sitting 173.0/90.8 mm Hg

Abbreviation: HYVET, Hypertension in the Very Elderly Trial.

costs were calculated on the basis of the reported treatments in the HYVET study: 25.8% of the patient received 1.5 mg indapamide SR alone, 23.9% received 1.5 mg indapamide SR and 2 mg perindopril, and 49.5% received 1.5 mg indapamide SR and 4 mg perindopril. The total drug costs were CHF 420 544 per 1000 patients per year, based on a daily treatment cost of CHF 1.15. The total medication costs were calculated assuming a patient compliance rate of 100% throughout the treatment period. Medication costs were calculated for 100% of the patients, assuming that the acquisition costs also apply to those patients who no longer take the medication, and as  $<12\%$  of patients died during the observation period. A patient co-payment of 10% was deducted from the pharmacy price.

The costs of an acute myocardial infarction, a stroke and a heart failure (medication costs, interventions, hospitalization, outpatient treatment, rehabilitation) have previously been calculated and published by international expert groups.<sup>10,11</sup> All costs were adjusted to 2007 values, taking into

**Table 2** Comparison of treatment effects of the HYVET study

Group	Active treatment (rate per 1000 per year)	Placebo (rate per 1000 per year)	Unadjusted hazard ratio (95% confidence interval)
<i>Primary endpoint</i>			
Fatal or nonfatal stroke	12.4	17.7	0.70 (0.49–1.01)
Death from stroke	6.5	10.7	0.61 (0.38–0.99)
<i>Secondary endpoint</i>			
Death from any cause	47.2	59.6	0.79 (0.65–0.95)
<i>Fatal or non fatal</i>			
Any myocardial infarction	2.2	3.1	0.72 (0.30–1.70)
Any heart failure	5.3	14.8	0.36 (0.22–0.58)
Any cardiovascular event	33.7	50.6	0.66 (0.53–0.82)

Abbreviation: HYVET, Hypertension in the Very Elderly Trial.

**Table 3** Costs in the treatment and placebo groups per 1000 patients over 2 years

Group	Active treatment (CHF)	Placebo (CHF)	Difference (CHF)
Medication cost	841 087	0	841 087
Cost of stroke	1 459 838	2 083 801	–623 963
Cost of myocardial infarction	83 455	117 595	–34 141
Cost of heart failure	122 817	342 962	–220 145
Total costs per 1000 patients	2 507 197	2 544 359	–37 162
Discounted at 5% per year			–35 392

Abbreviation: CHF, Swiss francs.

account inflation in Switzerland. A myocardial infarction with 2-year follow-up costs CHF 37 934, a stroke with 2-year follow-up accounted for CHF 117 729 and 2 years heart failure costs CHF 23 173.

To determine the treatment costs that could be avoided by hypertension therapy, the avoidable events per 1000 patients over 2 years were taken from the HYVET study and multiplied by the treatment costs of each individual treatment (Table 3). The costs were discounted at 5% per year, which is the standard rate applied to health care investments in Switzerland.<sup>12</sup>

**Effectiveness.** In this analysis, the effectiveness criterion is represented by life-years gained in the active-treatment group compared with the placebo. Estimation of the average life expectancy of very elderly patient with hypertension was based on the declining exponential approximation of life expectancy (DEALE) method.<sup>13,14</sup> The all-cause mortality of the Swiss population was adjusted in terms of age and gender distribution to the HYVET population. In 2006, the average life expectancy of a 65-year-old Swiss person was 83.3 years for men and 86.8 years for women.<sup>15</sup> The remaining life expectancy of persons with a mean age of 83.6 years is therefore 1.93 years. In the HYVET study, the over mortality in the placebo group was 0.0233 years per patient. This figure was used as the disease-specific excess mortality. The combination of the excess mortality

rate and the life expectancy according to the DEALE method, yielded an adjusted life expectancy results of 1.84 years.

**Cost-effectiveness of hypertension treatment.** Costs per life-year saved (YOLS) were deemed to be calculated by dividing the discounted cost difference between active-treatment and placebo group by the number of life-years gained in the active-treatment group.

**Sensitivity analyses.** To test accuracy and sensitivity of the results (that is, the costs per YOLS), a sensitivity analysis was carried out. The YOLS, the hypertension medication costs, and the treatment costs for stroke, myocardial infarction and heart failure were varied by  $\pm 20\%$ . Threshold analyses for the most influencing variables were carried out.

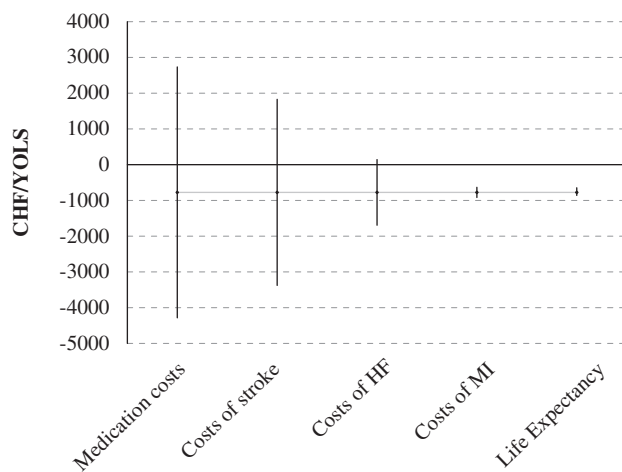
## Results

Table 3 shows the medication and treatment costs per 1000 patients over 2 years in the active-treatment and placebo group. Each patient in the active-treatment group had an additional medication cost of CHF 841 over 2 years (1.15 CHF daily), but also showed a savings potential for the analysed end points: total costs of stroke, myocardial infarction and heart failure were CHF 1666 per patient

**Table 4** Expected additional life expectancy due to hypertension treatment

<i>Average age of patients at baseline in the HYVET study</i>	
Active-treatment group	83.6 years
Placebo group	83.5 years
<i>Normal life expectancy of a 65-year-old Swiss person</i>	
Men	83.3 years
Women	86.8 years
<i>Life expectancy study population (60% women)</i>	
Mortality rate per patient year	1.93 years
Expected fatal cases in placebo group	0.0233
Disease-specific mortality rate per year	59.6 per 1000 patients per year
	0.0233
<i>Adjusted mortality</i>	
Adjusted average mortality (DEALE)	0.0239
Remaining life expectancy (DEALE)	1.841 years
<i>Expected fatal events in 2 years</i>	
Active-treatment group	94.4 per 1000 patients
Placebo group	119.2 per 1000 patients
Cases prevented	24.8 per 1000 patients
<i>Years of life saved (YOLS) per 1000 patients (prevented cases per 1000 patients per remaining life expectancy)</i>	
	$24.8 \times 1.841 = 45.66$ years
<i>Incremental life expectancy of hypertension treatment in comparison to placebo</i>	
	0.0457 years per patient

Abbreviations: DEALE, declining exponential approximation of life expectancy; HYVET, Hypertension in the Very Elderly Trial.



**Figure 1** Sensitivity analysis. CHF, Swiss francs; YOLS, years of life saved; HF, heart failure; MI, myocardial infarction.

over 2 years. Total costs of treatment in a placebo patient were CHF 2544. Thus, the total cost difference in favour of treatment group is nominal CHF 37 per patient per 2 year (discounted: CHF 35).

The effectiveness calculation yielded an additional life expectancy of 0.0457 years in the active-treatment group compared with the placebo group over a period of 2 years (Table 4).

This analysis resulted in a net cost savings, and hence a ratio of costs per YOLS is not required.

The sensitivity analysis (Figure 1) shows that the factors that mostly contribute to the costs variability are medication, stroke and heart failure costs. In case of a 20% increase of drug costs, the treatment would result in a cost-effectiveness of CHF 2734 per YOLS. In contrast, a 20% decrease results in a net benefit of CHF 4284. To reach the threshold for

stroke and heart failure, it would be necessary to reduce their cost of 6.0% and 16.9%, respectively. That means the stroke and heart failure cost over a period of 2 years should be reduced by CHF 7012 and CHF 3912, respectively. A hypothetical increase of 20% of the stroke costs results in a cost saving of CHF 3378 (a dominant strategy). On the other side, a 20% reduction results in a cost-effectiveness of CHF 1828 per YOLS.

## Discussion

The HYVET study was stopped prematurely, after 140 strokes for ethical reason; the active-treatment group already showed evidence of a reduction in the rate of the primary and secondary end points. Despite this anticipated stop, the economic assessment of antihypertensive treatment in patients 80 years of age or older has shown that the administration of the diuretic indapamide SR and, if necessary, of the angiotensin-converting-enzyme inhibitor, perindopril, is cost-effective. The benefits are primarily attributed to the prevention of stroke and heart failure.

The incremental life expectancy of 0.0457 years (about 16–17 days) looks relatively small. However, as emphasized by Wright *et al.*<sup>16</sup>, the gain in life expectancy should be compared with gains from other interventions aimed at the same target population.

Unfortunately, strict comparison with other studies is difficult, as cost-effectiveness analyses of hypertension treatment usually include younger patients, or are based on country-specific situations. For example, the cost-effectiveness analyses of losartan (an angiotensin type 1 receptor blocker) in

patient with hypertension and left ventricular hypertrophy based on the results of the LIFE study,<sup>17</sup> reported an incremental life expectancy of 0.0495 years (about 18 days) and a potential cost-savings of CHF 24 in Switzerland, and a cost-effectiveness of 864 € (1380 CHF), 4188 € (6689 CHF), 3195 € (5103 CHF) and 1337 Can \$ (1347 CHF) per life-year saved in the Netherlands, Sweden, UK and Canada, respectively.<sup>18–22</sup> However, the average age in the LIFE study was 66.9 years, with all patients between 55 and 80 years of age.

In another study, Tsevat *et al.*<sup>23</sup> have estimated that 35 years old men with hypertension would gain 1.1–5.3 years (13–64 months) by reducing their diastolic blood pressure to 88 mmHg. For 35 years old women the incremental life expectancy would be 0.9–5.7 years (11–68 months).

In a more recent analysis, Gandjour *et al.*<sup>24</sup> have estimated that antihypertensive treatment of 60–69 years old individuals would result in 0.2–0.6 life-years (2–7 months) gained for men and 0.1–0.6 life-years (1–7 months) for women.

It should be mentioned that the HYVET study also included an assessment of cognitive function, as earlier observational studies have shown a positive association between hypertension and incidence of dementia.<sup>25–32</sup> In this substudy,<sup>33</sup> Peters *et al.* reported a trend for a positive influence of the active treatment on the incidence of cognitive function and dementia (with a hazard ratio of 0.86, 95% CI 0.67–1.09). As the study was stopped prematurely and because the follow-up period was short, this finding was not significant. Nevertheless, Peters *et al.* combined their results with other placebo-controlled trial of antihypertensive treatment in a meta-analysis, in which they could observe a significant risk reduction in treated patients (hazard ratio 0.87, 95% CI 0.76–1.00,  $P=0.045$ ).

In this cost-effectiveness analysis, we decided not to include the effects of antihypertensive treatment on dementia incidence, as they were not significant in the HYVET *per se*. However, it is necessary to mention that the monetary and psychological costs of caring for people with dementia are very high.<sup>34,35</sup> Thus, the net savings of antihypertensive treatment in this population might be even more favourable and might be underestimated in this analysis, respectively.

In this analysis, we also excluded the costs of adverse events, which were significantly lower in the active-treatment group of the HYVET study ( $P=0.001$ ). However, it should be considered that such costs would speak even more in favour for active treatment.

A limitation of the HYVET study, and consequently of this cost-effectiveness analysis, is the absence of data related to diabetes and renal failure. These diseases strongly influence the quality of life of the affected persons,<sup>36</sup> are highly prevalent in the elderly and are quite expensive, as reported, for

example, by Mullins *et al.* in their comparison of hypertension-related costs from multinational clinical studies.<sup>37,38</sup>

Another limitation of this analysis is that the HYVET study implicitly assumed a homogeneous population across the countries participating in the study. But the study was conducted in 13 countries that partially strongly differ between each other in demographics characteristics (for example age distribution, ethnic composition, life style and so on), health care system, risk factors prevalence, and quality of diagnoses, treatment and monitoring. The results of the HYVET study were transferred into a Swiss context, using country-specific demographic rates and health care costs, but it was not possible to adjust the analysis for all differences between the Swiss and the original study population. In addition, it should not be forgotten that the HYVET study population is only partly representative for a total collective of hypertensive patients, as there were well-defined exclusion criteria. An additional limitation is that the HYVET study did not include data on the quality of life of the patients and on respective rehabilitation measures.

A last limitation of this analysis is the assumption of a 100% compliance of drug treatment.

The demography of our society is changing as fast as never before. In the last few decades the mean life expectancy has strongly grown up. The actual standards of study design, which seems to preferably include patient below 80 years of age, are becoming obsolete. New and more studies are needed to analyse the cost-effectiveness of medication in very elderly people.

In conclusion, the antihypertensive treatment of very elderly persons, on the basis of the HYVET study and performed from a Swiss perspective, reduced the stroke and heart failure incidence, increasing the life expectancy by 0.0457 years per patient and resulting to be net cost-saving, that is, reflecting a dominant strategy.

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#### What is known about the topic

- Hypertension is a highly prevalent risk factor for ischaemic heart diseases and stroke worldwide, and the increasing longevity and prevalence of contributing factors (for example obesity) strongly affect the morbidity and mortality of cardiovascular events. The prevention and management of high blood pressure is a major public health challenge.
- Antihypertensive treatment reduces the relative risk of total mortality indicating an overall significant benefit.
- The actual standards of study design seem to preferably include patient below 80 years of age.

#### What this study adds

- Antihypertensive treatment shows benefits also in very elderly persons (80 years of age or older).
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## Conflict of interest

The authors declare no conflict of interest.

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