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ROUTINE ARTICLE

Economic Impact of Hyperhomocysteinemia in Switzerland

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Summary. **Since more than 20 years elevated homocysteine plasma levels have been associated with an elevated cardiovascular risk. It can be assumed that approx. 5–7% of the Swiss population suffers from hyperhomocysteinemia. These people have an odds ratio of 1.7 (95% confidence interval: 1.5–1.9) to develop a myocardial infarction and an odds ratio of 2.5 (95% confidence interval 2–3) of developing a stroke. These significant cardiovascular endpoints have monetary implications and lead to a loss in life years. The cost consequences and total life years lost were determined with an incidence-based epidemiological model utilizing a Swiss third party payer perspective. We could demonstrate that hyperhomocysteinemia-related sequelae (myocardial infarction and stroke) amount to 41.1–110.2 million CHF. In addition it can be estimated that 6′941–18′478 life years may be lost.**

Comparing these data with the total costs for cardiovascular disease in Switzerland of CHF 987 million, we estimate the share of the economic burden of hyperhomocysteinemia at approximately 10%. Preventive measures could thus yield a positive impact on total health care expenditure in the Swiss healthcare system and warrants further research.

Key Words. **atherosclerosis, cardiovascular risk, costs, cost-effectiveness, homocysteine, hyperhomocysteinemia, myocardial infarction, prevention, stroke, Swiss healthcare system**

Introduction

Because the costs in healthcare have been increasing over proportion in the past decade, economic aspects of a disease are increasingly becoming important. Already since many years it has been shown that the demand for health care services will depend not only what is technically feasible but also how to deal with constrained financial resources. For this reason it is important to allocate health care resources wisely and to invest in areas where the investment yields the greatest benefit in terms of health, life years saved or quality of life. Hence it is important to determine the burden of disease as a first preparatory step. Cardiovascular disease is one of the most frequent causes of death in Switzerland and is also economically relevant due to the possibilities of extensive and costly medical interventions. Even coronary heart disease alone which affects approx. 2% of the Swiss population, led to expenditures of about 2.1 Billion CHF in 1993. Of these approximately 47% were direct costs and 53% were indirect costs [1].

50% of all deaths are caused by atherosclerotic compromised vascular structures [2]. Preventive measures against high blood pressure or high cholesterol levels have been consequently implemented over the last decade. It has been shown that several factors are responsible for the development of arteriosclerosis and its consequences. Albeit intensive research, not all relevant risk factors have been identified as a relevant co-factor in the development of atherosclerotic disease. For many years approximately only 50–60% of all cases of atherosclerosis could be related to a known risk factor [3].

In the last years a new risk factor has increasingly gained significance. Several studies have shown that an elevated homocysteine blood level is associated with an elevated cardiovascular risk. There are only limited empirical estimates of the economic burden of homocysteine as a risk-factor. An early estimate was published by Boushey et al. and suggested this risk factor is responsible for about 10% of all artherosclerotic diseases [4]. These findings however have not yet led to consistent, individual and population-based preventive measures.

In this incidence-based study we investigated the economic significance of cardiovascular risk associated with elevated homocysteine levels from the perspective of the Swiss healthcare system.

Material and Methods

We conducted a cost impact analysis to determine the cost of hyperhomocysteinemia in Switzerland. To achieve this we used a simplified healthcare model

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which was limited to the following constraints:

1. Individuals with hyperhomocysteinemia have an elevated cardiovascular risk.
2. The most relevant cardiovascular endpoints are myocardial infarction and stroke.
3. The time frame analyzed was 1 year
4. Only direct costs for the sequelae *myocardial infarction* respectively *stroke* were considered.

By determining the difference of homocysteine-asscociated risk in patients with and without hyperhomocysteinemia in Switzerland we were able to obtain a rough estimate of the additional number of strokes or myocardial infarctions, including the monetary consequences, or in the case of death, the extent of life years lost.

Epidemiologic evidence

Due to inconsequent standardization of measurement techniques and the non homogenous definition of hyperhomocysteinemia it was difficult to determine the exact prevalence. In most available studies it has been assumed that 5–7% of the population has an elevated level of hyperhomocysteinemia [5]. We asssume this prevalence rate could be applicable for the Swiss situation.

In previously published studies only relative measures of association (relative risks, odds ratios) have been reported. Absolute risk reductions have so far not been determinated for the sequelae of hyperhomocysteinemia. This meant a consequence that the incidence of myocardial infarction and stroke in patients without the risk factor homocystein is not known. Thus population-based incidences had to be used to make appropriate assumptions. This approach, however, is not expected to impact the overall economic results, as we can assume that clinical sequelae of patients with and without hyperhomocysteinemia do not differ.

The incidence of myocardial infarction and stroke were determined by the global health statistics for established market economies [6]. Potential life years lost due to fatal myocardial infarctions and fatal strokes could be estimated on the basis of the age of the cardiovascular events, using data from the global health statistics and using the statistical yearbook of Switzerland [7].

People with hyperhomocysteinemia have an elevated risk of a myocardial infarction and a stroke. The value of the relative risk varies considerably in the prospective case control studies. Stampfer et al. [8]. observed a relative risk of 3.4 (95% confidence interval 1.3–8.8) for myocardial infarction, whereas Folsom and co-workers [9] did not determine any significant difference in relative risks.

A meta analysis form Boushey et al. [4] summarized all studies between 1988 and 1994 on all issues of homocysteinemia. Of all 209 relevant studies, 27 addressed atherosclerosis and homocysteine and 11 studies were addressed folic acid and hyperhomocysteinemia blood levels. These were all considered in a systematic meta-analysis. The determined odds ratios have been to date the most reliable values for the determination of risks and have been used for the present cost impact model. Following odds ratios were used: myocardial infarction; odds ratio = 1.7 (95% CI: 1.5–1.9); stroke; odds ratio = 2.5 (95% CI: 2.0–3.0).

Using these data it is possible to calculate the incidence and mortality rates of myocardial infarction and stroke in people and individuals with hyperhomocysteinemia as follows:

$$I/M_{\text{Hyperhomocysteinemia}} = (100'000 \times \text{A})/(1 + \text{A})$$

$$A = \text{Odds ratio} \times (I/M_{\text{normal hyperhomocysteinemia}}/ \; 100'000 - I/M_{\text{normal hyperhomocysteinemia}})$$

I/M = incidence of *MI* or stroke, resp. mortality rate of *MI* or stroke

For the purpose of the sensitivity analysis, the 95% confidence intervals of the odds ratios were used. Because the prevalence of hyperhomocysteinemia ranged between 5 and 7%, the cost impact analysis was based on these two limits.

We employed two different models:

1. *Model 1* used the lower prevalence limit of 5%,
2. *Model 2* employed a prevalence of 7%. As a reference we also used a model with a potential hyperhomocysteine prevalence of 0%. Furthermore we assumed that these prevalences were independent of age and sex. Using data from the Federal Statistical Office of Switzerland and the prevalence estimates for hyperhomocysteinemia we were able to determine the size of the population at risk for Model 1 and Model 2 (Table 1).

Table 1. *Esimtated number of individuals with hyperhomocysteinemia in Switzerland (in 100'000)*

Age group	CH-Population	People with Hyperhomocysteinemia (Model 1)	People with Hyperhomocysteinemia (Model 2)
Males			
15–44	15.396	0.770	1.078
45–59	9.911	0.346	0.484
60+	5.981	0.299	0.419
Females			
15–44	15.188	0.759	1.063
45–59	6.887	0.344	0.482
60+	8.167	0.408	0.572

Cost data

Cost data for the cardiovascular endpoints myocardial infarction and stroke were derived from previously published evidence [10]. All costs were adjusted to 2004 values using the consumer price index for healthcare in Switzerland.

Four data sources were used: H+ statistics for nationwide hospitalization data, the Swiss drug compendium for legally binding national medication costs as well as diagnosis related groups from the canton of Aarau and Basel. The latter were used because Basel and Aarau have gained early and extensive experience with prospective payments schemes, e.g. diagnosis related groups. Ambulatory cost data were derived from a previously conducted cost structure analysis of myocardial infarctions and strokes [10]. All costing approaches were described in a Swiss economic analysis conducted by our group. For the hyperhomocysteinemia models the cost of a myocardial infarction were estimated at 29′670 CHF and for a stroke 40′942 CHF.

Perspective of the economic analysis

The epidemiological data is specific for Switzerland in so far as the size of the population was related to the overall Swiss population. Incidence, mortality rate, prevalence data and odds ratios were derived from international studies and were considered generalisable. Cost structure data (e.g. ambulatory tariffs and charges for medical services) are highly dependent on the individual country. This cost analysis was performed from the perspective of third party payers. This analysis is also confined to the total cost of therapy and covers only direct costs of medical interventions. Indirect costs were not taken into consideration.

Results

The incremental costs of hyperhomocysteinemia can be determined as a difference of the number of myocardial infarctions and strokes between Model 0 and Model 1 respective Model 2 and the corresponding cost per case. Because Model 1 and Model 2 contain two different distinct scenarios the results will be discussed separately.

Results of model 1

Assuming that nobody in Switzerland suffers from hyperhomocysteinemia, approx. 33′829 myocardial infarctions occur annually. Of these, approx. 12′069 are fatal. Approx. 20′170 cardiovascular strokes occur annually of which 7′680 are fatal. In Model 1 approx. 5% of the population has a significant elevated homocysteine level which leads to an elevated risk of a myocardial infarction of 33–47%. The risk for a cerebral vascular insult in this population increases even 50–66%. Thus it can be estimated in Switzerland approx. 535–960 nonfatal and 299–536 fatal myocardial infarctions occur, as well as 617–1′226 nonfatal and 380–757 fatal myocardial infarctions related to hyperhomocysteinemia. The estimated direct costs resulting from these events lie between 41.1 and 78.7 million CHF. Additionally we estimate that between 6′941–13′198 attributable life years are lost. The results of model one is displayed in Table 2.

Table 2. *Estimated monetary costs of hyperhomocysteinemia (Model 1)*

Total costs for myocardial infarctions	645.6 million CHF
Total costs for myocardial infarctions due to hyperhomocysteinemia	15.9–28.5 million CHF
Percentage	3–4%
Total costs for cerebral vascular insults	370.6 million CHF
Costs for cerebral vascular insults due to hyperhomocysteinemia	25.2–50.2 million CHF
Percentage	7–14%
Attributable cost of hyperhomocysteinemia	41.1–78.7 million CHF

Table 3. *Estimated number of life years lost (Model 1)*

Total number of fatal myocardial infarctions	12′069 years
Total number of fatal cerebral vascular insults	7′680 years
Total	19′749 years
Number of fatal myocardial infarctions due to hyperhomocysteinemia	299–536 years
Number of fatal cerebral vascular insults due to hyperhomocysteinemia	380–757 years
Total	679–1′293 years
Number of life years lost due to hyperhomocysteinemia	6′941–13′198 years

Table (3) displays the calculation of the number of years lost in Model 1.

Results of model 2

Model 2 assumes a prevalence of hyperhomocysteinemia of 7%. From the difference between Model 0 and Model 2 we can calculate the number of fatal and non fatal myocardial infarctions respective cerebral vascular insults due to a hyperhomocysteinemia.

Instead of the annual estimated 535–960 nonfatal and 299–536 fatal myocardial infarctions as well as the 617–1′226 nonfatal and 380–757 fatal cerebral vascular insults we observe significantly increased figures. In Model 2 we can estimated due to hyperhomocysteinemia between 750–1′344 nonfatal and 418–740 fatal myocardial infarctions as well as 863–1′716 nonfatal and 533–1′060 fatal cerebral vascular insults.

Due to these figures we can estimate the direct costs approx. 57.5–110.2 million CHF (as compared to 41.1–78.7 million CHF). In this model we estimate that the number of life years lost would be between

Table 4. *Estimated monetary costs of hyperhomocysteinemia (Model 2)*

Total cost of fatal myocardial infarctions	645.6 million CHF
Cost of fatal myocardial infarctions due to hyperhomocysteinemia	22.2–39.9 million CHF
Percentage	3–6%
Cost of cerebral vascular insults total	370.6 million CHF
Cost of cerebral vascular insults due to hyperhomocysteinemia	35.3–70.3 million CHF
Percentage	10–19%
Total cost	57.5–110.2 million CHF

Table 5. *Number of life years lost (Model 2)*

Total number of fatal myocardial infarctions	12′069 years
Total number of fatal cerebral vascular insults	7′680 years
Sum	19′749 years
Number of fatal myocardial infarctions due to hyperhomocysteinemia	418–750 years
Number of cerebral vascular insults due to hyperhomocysteinemia	533–1′060 years
Sum	951–1′810 years
Number of life years lost due to hyperhomocysteinemia	9′716–18′478 years

9′716–18′478 (as compared to 6′941–13′198 in Model 1). The results of Model 2 are displayed in Table 4. Table 5 displays the calculation of the number of years lost in Model 2

These two models demonstrate that the direct costs due to hyperhomocysteinemia lie between 41.1 and 110.2 million CHF. In general this would mean that in Switzerland approx. 4–10% of the direct costs of all myocardial infarctions and cerebral vascular insults can be attributed to the risk factor homocysteine. With respect to mortality the results are similar. Between 3% and 9% of all deaths due to myocardial infarctions and cerebral vascular insults are in direct relationship to hyperhomocysteinemia. Depending on the baseline risk the resulting number of life years lost lie between 6′941–18′478 life years lost.

Discussion

Due to the assumptions used in determining the prevalence of hyperhomocysteinemia and the relative risks of the cardiovascular endpoint, these results yield considerable dispersion. Using the lower limits of the confidence interval of the odds ratio and the lower incidence rates the total costs amount to 41.1 million CHF. In relationship to the 987 million CHF which are spent annually to treat cardiovascular diseases [1] this amount does not seem to be of great relevance. However assuming a prevalence of 7% and an odds ratio of 1.9 for myocardial infarctions as well as an odds ratio of 3.0 for cerebral vascular insults hyperhomocysteinemia for these two endpoints represents a cost proportion of 10% of total cost. These are certainly more cost relevant.

A similar situation is observed with respect to life years lost. Our budget impact analysis is very sensitive with respect to the variability of prevalence and odds ratio.

Our results contrast and supplement the findings from Tice et al. [13] performed in the United States. They performed a cost-effectiveness analysis using the Coronary Heart Disease Policy Model, a validated, state-transition model of CHD events in adults aged 35 through 84 years. They concluded that folic acid and cyanocobalamin supplementation may be cost-effective among many population subgroups and could have a major epidemiologic benefit for primary and secondary prevention of CHD if ongoing clinical trials confirm that homocysteine-lowering therapy decreases CHD event rates.

The initially posted question on the cost relevance of hyperhomocysteinemia in Switzerland is thus only clarified from a limited perspective. However these data give a first impression on the range of costs which are related to the consequences of hyperhomocysteinemia. These can be used as a basis for further research in the area of individual and population based preventive strategies.

Our model has several limitations: The incidence of myocardial infarction in cerebral vascular insults in patients without hyperhomocysteinemia is not known. For these reasons we had to use secondary published, aggregated data. Thus the incremental cost of hyperhomocysteinemia might lead to a slight overestimation of the true cost.

The prevalence of hyperhomocysteinemia is insofar questionable as there are not yet consistent and precise definitions. In most studies there is not a solid upper limit. Usually authors tend to use the upper 95% confidence interval limit as a reference value for hyperhomocysteinemia.

Another limitation is that our model did not include data from two clinical trials which were published subsequent to our model development [11,12]. The two controlled total homocysteine (tHcy)-lowering treatment studies have been conducted in the United States and Canada among patients with coronary artery disease who have been chronically exposed to a background of folic acid-fortified cereal grain flour since 1999. These trials were however small and the effect sizes were well in the realm of the values used in our models.

Lastly, in our model, we only analyzed two cardiovascular endpoints: myocardial infarction and cerebral

vascular insults. Although these are the most frequent cardiovascular sequelae they do not represent the totality of hyperhomocysteinemia in used costs. Unfortunately, we did not have health economic data on congestive heart failure, which represents another clinically relevant endpoint. Thus in the present study we give an underestimate of the true costs. In the future, however, a more complete burden of disease study is warranted, which should include a wider range of clinical and economic sequelae, perhaps even indirect costs.

Financing and Conflicts of Interest

This project was performed without external funding. No conflicts are declared.

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