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A Clinical Practice Model to Estimate the Cost-Effectiveness of Lipid Lowering Therapy With Statins in Patients at Risk for Coronary Artery Disease

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Epidemiological, clinical, and laboratory studies have clearly established the relationship between elevated concentrations of serum lipids and increased risk for coronary artery disease. Conversely, it has also been demonstrated that lipid-lowering therapy with statins reduces the rate of cardiovascular events. Nevertheless, treatment with statins is costly.

Thus, there has been an increased interest over the last few years in determining the cost-effectiveness of lipid-lowering therapy with statins. In this report we try to present a clinical practice model to estimate the cost-effectiveness of lipid lowering therapy with statins in patients at risk for coronary artery disease. Basically, the result of a cost-effectiveness analysis depends on the stage of the disease, the medication, its dose, as well as the resulting therapeutic effect. The greatest benefit of statin therapy can be expected for the highest absolute risk. It seems likely that a combined use of a risk-population strategy would ascertain the highest cost-effectiveness of lipid-lowering therapy with statins in daily medical practice. But, it would be unacceptable to conclude from improvement of surrogate parameters on clinical events and on cost-effectiveness. Treatment should proceed strictly from the results of the clinical endpoint trials.

According to the results of the clinical endpoint studies, lipid-lowering therapy is essential in secondary prevention. To achieve maximum cost-effectiveness of treatment with statins, a comprehensive therapeutic approach, if necessary including revascularisation procedures is recommended. *J Clin Basic Cardiol 2002; 5: 179–82.*

Key words: coronary artery disease, lipid lowering therapy, statins, cost-effectiveness

Coronary artery disease (CAD) remains the leading cause of death in the Western world. The annual incidence is also considerable. Currently available medical, surgical as well as interventional treatment strategies are increasingly applied in order to stabilise the course of the disease and to improve the patient's quality of life. Nevertheless, all these treatment modalities are costly. Thus, there has been an increased interest over the last few decades in determining the cost-effectiveness of therapeutic interventions in cardiovascular diseases.

Epidemiological, clinical, and laboratory studies have clearly established a strong relationship between elevated lipid levels and risk of CAD [1]. Conversely, it has also been demonstrated, that lipid-lowering therapy, especially those of hydroxy-methyl-glutaryl coenzyme A (HMG-CoA) reductase inhibitors, (statins), considerably reduce the rate of cardiovascular events. Lowering lipids with statins leads to a reduction of LDL cholesterol by 25–35 %. An aggressive approach with an adequate dose makes it possible to lower LDL cholesterol to less than 100 mg/dl without relevant side effects. With the lowering of total cholesterol by 30–50 %, the coronary, cerebrovascular and peripheral ischaemic events can be reduced by more than 30 %.

Basics of Calculating the Cost-Effectiveness of Lowering Cholesterol With Statins

The result of a cost-effectiveness analysis regarding lipid lowering with statins depends on the stage of the disease, the medication, its dose, as well as the resulting therapeutic effect. Thus, it is important to assess the cost-effectiveness of statins separately for the primary and secondary prevention setting of cardiovascular diseases. Due to the fact that several extensive studies exist for CAD, the following analyses of the cost-effectiveness of statins will focus primarily on these circumstances.

Five major prospective, randomised and controlled studies have been published regarding primary and secondary prevention of CAD:

Treatment/Intervention With Statins – Primary Prevention

1. West of Scotland Coronary Prevention Study WOSCOPS [2]
2. Primary Prevention of Acute Coronary Events with Lovastatin AFCAPS/TexCAPS [3]

Treatment/Intervention With Statins – Secondary Prevention

1. The Scandinavian Simvastatin Survival Study – 4S [4]
2. Cholesterol and Recurrent Events Trial – CARE [5]
3. Long-Term Intervention With Pravastatin in Ischemic Disease – LIPID [6]

The following medication and respective doses were used in the studies mentioned above:

- 4S: simvastatin 20–40 mg daily
- CARE, LIPID, WOSCOPS: pravastatin 40 mg daily
- AFCAPS/TexCAPS: lovastatin 20–40 mg daily

From a total of five available statins, simvastatin, pravastatin and lovastatin were tested in prospective, randomised and controlled trials with regard to the clinical endpoints of CAD such as death or myocardial infarction (Table 1). The effect of a low fat diet, combined with statin therapy was compared in detail to the outcome of a low fat diet with placebo. All studies demonstrated that the treatment with statins and the resultant lowering of LDL cholesterol significantly reduced the clinical endpoints of CAD

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(Table 2). As differences exist between the individual studies with regard to the recording of the endpoints as well as in the absolute risk, the total therapeutic efficacy differs accordingly.

Evidently, it is the absolute risk which essentially determines the success of the treatment. Thus the cost-effectiveness is calculated in terms of the total success, ie, the absolute risk reduction.

Calculation Models for the Cost-Effectiveness of Statins

Calculations Based on Clinical Study Endpoints

In order to assess the differences between studies with regard to the effect of the treatment, the relative risk was calculated. Thereby from the risk of reaching an endpoint of the placebo group (absolute risk of the placebo = ARP) the risk of the verum group (absolute risk of the verum group = ARV) is subtracted. The absolute risk reduction (ARR) is most important for the assessment of therapy-efficiency in clinical practice, as well as for calculating the cost-effectiveness. Mathematically, it is determined by the difference of both group risks (ARR = ARP – ARV).

The number-needed-to-treat (NNT) is calculated as the reciprocal value of the ARR. NNT indicates how many patients need to be treated for the duration of a study in order to prevent an event (in the case of CAD eg death or myocardial infarction). The AR of the placebo group is used as the reference zero value for the calculation of the NNT at the end of the study, as this value shows the natural progression of the illness without statins. For the purpose of comparison it is recommended to standardise the NNT ie, multiplication with the duration of the study. The approximate number of patients who require treatment for a period of one year in order to prevent one single event is indicated. However, this standardisation requires a constant therapy-effect over the entire duration of the study, which does not apply for lowering lipids with statins. Moreover, it is neglected that only a small proportion of patients has been treated for the entire study period. Thus, there is a tendency to overestimate the term of NNT. In this case the annual NNT is a fictitious value, which allows the comparison of the different lipid-intervention studies of varying duration. The absolute risk of disease and the NNT for these studies are shown in Table 3.

The results clearly demonstrate an advantage of the implementation of statins for lipid lowering. However, the broad application of these substances is only justified once their cost-effectiveness has been established or at least once there is anticipation of their cost-effectiveness.

Various mathematical models have been published in order to substantiate the cost-effectiveness of the individual statins [7, 8]. Nevertheless, the cost of treatment can only entail the actual cost of medication. The greatest benefit of statin therapy can be expected for the highest absolute risk. In comparison to standard treatment, the NNT is relatively small, ie the benefit is accordingly great. For instance, 125 myocardial infarction patients have to be treated for one year with ASS in comparison to 81 patients, who are treated with simvastatin in order to prevent a non-fatal reinfarction. However, the annual treatment costs of a statin-therapy compared with ASS are high and vary considerably. The costs of each statin, based on the current retail prices, are summarised in Table 4. At the time of writing only simvastatin, pravastatin and lovastatin have been adequately tested and proven for prevention of clinical endpoints. As for the other two less expensive drugs, their individual clinical effect still requires further research.

Laboratory tests, specialist appointments etc. are considered standard treatment for CAD or myocardial infarction. Therefore standard costs are assumed regarding the various treatment groups for this aspect. Nevertheless, other direct and indirect costs, which arise during the course of CAD, need to be considered. These are for example, expenses for hospitalisation, revascularisation procedures etc.

The present cost-calculation merely allows for reports with regard to a conservative standard treatment of CAD

Table 1. The five major randomised, placebo-controlled intervention studies concerning the clinical effect of lipid lowering with statins in patients with CAD

Study	Patients	Statin	Endpoints	Absolute risk
4S	4,444	Simvastatin	Death	High
CARE	4,159	Pravastatin	Death, MI	High
LIPID	9,014	Pravastatin	Death	High
WOSCOPS	6,595	Pravastatin	Death, MI	Low
AFCAPS/TexCAPS	6,605	Lovastatin	MI, UA	Low

MI = myocardial infarction; UA = unstable angina

Table 2. Results of the five major randomised, placebo-controlled intervention studies concerning the clinical effect of lipid lowering with statins in patients with CAD

Study	Statin	LDL-C lowering	Absolute risk	Endpoint reduction
4S	Simvastatin	–35 %	High	–41 %
CARE	Pravastatin	–32 %	Intermediate	–20 %
LIPID	Pravastatin	–25 %	Intermediate	–23 %
WOSCOPS	Pravastatin	–26 %	Intermediate	–27 %
AFCAPS/TexCAPS	Lovastatin	–25 %	Low	–37 %

Table 3. NNT and annual NNT of the five largest lipid-intervention studies

Study	Event	AR-placebo	NNT	NNT/year
4S	Death	8 %	29	155
	MI	23 %	15	81
CARE	Death	6 %	90	450
	MI	13 %	34	167
LIPID	Death	8 %	52	317
	MI	16 %	29	173
WOSCOPS	Death	2 %	164	803
	MI	9 %	41	201
AFCAPS/TexCAPS	Death	Not enough events	–	–
	MI	3 %	87	452

AR-placebo = absolute risk of the placebo group; MI = myocardial infarction

Table 4. Costs of individual statins (Price EUR/pack = retail price)

Statin	Name	Pharmaceutical company	Daily dosage [mg]	€/pack	€/year
Atorvastatin	Sortis	Pfizer	10	36	439
Fluvastatin	Lescol	Novartis	40	25	321
Lovastatin	Mevacor	MSD	20	32	392
Pravastatin	Pravachol	BMS	40	34	828
Simvastatin	Zocord	MSD	20	46	562

without special interventional or surgical procedures. Table 5 lists the total treatment costs of the individual studies extrapolated for costs in Austria and the different risk-groups, for lipid lowering with statins based on the prevention of one myocardial infarction/year. The cost-curve/cost development shown in Table 6 clearly demonstrates the cost-effectiveness (proceeding from the absolute initial risk) of lipid lowering with statins with regard to the endpoint myocardial infarction. This is of great significance for everyday practice. Cost-saving treatment with statins should involve knowledge of the absolute initial risk of each individual patient [1]. Thus it is useful to work out a risk-strategy for prescription procedures. Already a major difference exists in the cost-effectiveness of lipid-lowering statins when adhering to the present cost-benefit calculation – irrespective of whether treating low-risk (primary prevention) or high-risk (secondary prevention) patients. Thus, the medical treatment of patients with hyperlipidaemia also involves Rose's [9] "high-risk-strategy". This means that high-individual-risk patients will be treated very cost-effectively.

However, the health-economical, cost-benefit calculation also needs to consider the influence of the total population, ie, many people with a relatively low risk contribute to more cases in terms of the absolute number of cases as opposed to those patients with a high risk. Lowering the average cholesterol level of the total population over several decades by approximately 10 %, would lead to a 30 % reduction of coronary events. Lifelong statin-treatment exclusively in high-risk patients (with the aim of lowering LDL-cholesterol by 20–25 %), would reduce coronary morbidity and mortality rate of the total population by only 15–20 %. Thus, it seems more likely that the combined use of a risk-population strategy would ascertain the highest cost-effectiveness of lipid lowering with statins in daily medical practice. As the studies have indicated that the clinical effect increases with treatment time, it is also essential to take the therapeutic timeframe into consideration. This is naturally influenced by the age of the patient.

The following criteria can be used for choosing cost-effective lipid lowering treatment with statins in cases of CAD, thereby taking the various limitations with regard to the general recommendation for a treatment-strategy into account.

Low cost-effectiveness
- patient with low absolute risk
- short-term treatment
- older patient

High cost-effectiveness
- patient with high absolute risk
- long-term treatment
- younger patient

Surrogate Marker Based Calculations

Based on the National Cholesterol Education Program's Adult Treatment Panel (NCEP-ATP III) guidelines, the decision to initiate lipid-lowering therapy is guided by the level of LDL cholesterol, the risk factor count, and the presence or absence of documented CAD or other atherosclerotic disease [1]. Most patients fail to achieve and maintain the goals established by the NCEP-panel [10]. According to the NCEP criteria, two recent studies focus on the treatment effect and the cost-effectiveness of lipid lowering with atorvastatin and simvastatin. In a short-term follow-up-study the percentage of patients who met their NCEP goal after 6 weeks of treatment was significantly higher ($p < 0.05$) in the atorvastatin group (86 %) than in the simvastatin group (77 %) [11]. However, in an international study over a 52-week period, there were no significant differences in the percentage of patients achieving an appropriate LDL-C level (atorvastatin 50 %, simvastatin 48 %). In country-wise analyses, therapy with simvastatin was less expensive than therapy with atorvastatin in 8 of 10 countries. In the remaining 2 countries (Germany, Finland), there was no significant difference in costs [12]. As listed in Table 7 comparing the costs of 1 % LDL lowering/year for different statins in Austria, atorvastatin reaches the highest cost-effectiveness for surrogate marker calculations.

Table 5. Yearly treatment-costs of lipid lowering with statins for the prevention of one single myocardial infarction in different studies

Study	Statin	Daily dosage [mg]	LDL-C lowering	NNT/year	€/year
4S	Simvastatin	20	35 %	81	45,550
CARE	Pravastatin	40	32 %	167	138,209
LIPID	Pravastatin	40	25 %	173	143,175
WOSCOPS	Pravastatin	40	26 %	201	166,347
AFCAPS/TexCAPS	Lovastatin	20	25 %	452	177,051

Table 6. Course of treatment-costs of lipid lowering with statins for the prevention of a myocardial infarction in different studies in consideration of the absolute initial risk during primary and secondary prevention of CAD

Study	Statin	Prevention	Risk	NNT/year	€/year	CE
4S	Simvastatin	Secondary	↑	81	45,550	↑
CARE	Pravastatin	Secondary		167	138,209	
LIPID	Pravastatin	Secondary		173	143,175	
WOSCOPS	Pravastatin	Primary		201	166,347	
AFCAPS/TexCAPS	Lovastatin	Primary		452	177,051	

CE = cost-effectiveness

Cost-Effective Lipid-Lowering Therapy With Statins

Despite all the limitations that arise due to the isolated focus on one single risk factor and its treatment, the risk-reduction analysis on lipid lowering with statins shows a cost-effectiveness that covers a broad spectrum of indications. This is naturally more evident in high absolute risk cases ie, the setting of secondary prevention.

An intention to treat involving the combination of both strategies ("high-risk" and "population-strategy") for the prevention of CAD seems advantageous in terms of making the health care system financially possible and probably also cost-effective.

Despite the fact that all major trials on lipid lowering with statins for the treatment of CAD were able to show a statistically significant risk reduction, considerable differences exist with regard to the extent and period of time. The unquestioning trust in the class-effect of statins is problematic. For instance, according to Thomas & Mann (1998), the change from simvastatin with a medium daily dose of 21.8 mg to a cheaper alternative of fluvastatin with 36.8 mg, has lead to a significant increase in cardiovascular events within six months [13]. If one were to adhere to the regulations of evidence-based medicine, it would not be justified to extrapolate the results based on the research of one drug to a similar one

Table 7. Costs of % LDL-lowering/year for different statins (KKP – Austria)

Statin	Name	Pharma-ceutical Company	Daily dosage [mg]	LDL↓ %	1 % LDL↓ (€)
Atorvastatin	Sortis	Pfizer	10	39	0.87
Fluvastatin	Lescol	Novartis	40	23	1.06
Lovastatin	Mevacor	MSD	20	29	1.10
Pravastatin	Pravachol	BMS	40	24	1.37
Simvastatin	Zocord	MSD	20	35	1.30

or to an entire substance class. Moreover, it would be equally unacceptable to conclude from improvement of surrogate parameters on clinical events and on cost-effectiveness. Under these circumstances, treatment should proceed strictly from the results of the published studies.

Despite all the evidence that lipid lowering with statins under clearly defined conditions is cost-effective, this therapy, similar to revascularisation procedures in patients with CAD, would involve large expenses, which would remarkably strain the health-care budget. According to estimates from the USA, the treatment of a non-fatal myocardial infarction for one year amounts to € 14,682 (converted from US$) [14]. The prevention of a myocardial infarction by lipid lowering with statins would cost, according to the proposed calculation model, € 45,550, ie, approximately three times as much. Nevertheless, the prevention of one myocardial infarction is most probably more cost-effective than the expenditure for all the health-related and social consequences that result from one infarction, especially within the first year.

The recently published AVERT-study addresses the issue of the cost-effectiveness of the drug-induced lipid reduction as opposed to revascularisation procedures in order to prevent ischaemic events as an endpoint of CAD [15]. Again the question arises, whether the prevention of an ischaemic event would be more cost-effective than its treatment. The former is more likely viable in the case of a stable CAD than in acute myocardial infarction. According to the AVERT report, treating a patient with atorvastatin (80 mg/day) for 18 months would cost € 4,605. A PTCA, depending on the number of stents used, in Austria costs approximately € 3,000 to € 5,000. The fact remains that the therapeutic long-term effect of either treatment modality cannot be predicted with certainty for each individual case. Due to the present situation, in terms of classifying the patients concerned as high-risk, it is therefore necessary to combine both treatment strategies.

A major limitation with regard to the practical application of the results from AVERT lies in the fact that two treatment methods were compared that do not necessarily share the same goal. The main focus of the PTCA still remains the more symptomatic treatment of a stable angina pectoris, whereas the aim of lowering lipids eg with statins is a reduction in the number of future coronary events ie, the PTCA influences the symptoms and the lipid treatment preferentially affects the prognosis of CAD. Also this perspective allows a synergistic effect of both treatment strategies.

Measures that promote a healthy lifestyle for the general population, especially for the high-risk groups, are economical and an integral part of the comprehensive treatment of CAD [16]. However, it remains undisputed that a change in lifestyle alone cannot replace the therapeutic benefit of statins. Simply for economical reasons, the change to a healthy diet combined with regular exercise, should, at least during primary prevention, comprise the first step towards an effective lipid lowering [17]. According to the results of the studies mentioned above, lipid-lowering therapy is essential in secondary prevention. To achieve maximum cost-effectiveness of lipid lowering with statins, a comprehensive therapeutic approach, if necessary including revascularisation procedures is recommended for treatment strategies of CAD.

As outlined above, our analyses focused on costs per prevented case of myocardial infarction. Clearly, the benefit of statin treatment expands to other endpoints, eg reductions of PTCA, CABG, cases of congestive heart failure or new onset of angina. Every additional benefit – on top of prevention of myocardial infarction – adds to stabilise the general course of the atherosclerotic disease without increasing costs. Thus, in summary, our calculations tend to underestimate benefits and overestimate costs of lipid lowering therapy with statins.

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