Statins for the Secondary Prevention of Cardiovascular Diseases:

An Analysis of Expected Population Health Gains and Cost-Utility in Austria

Part II of the Project 'Statins: A Comparison Between Predicted and Actual Effects on Population Health in Austria'

Final Report

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List of Abbreviations

CHD	Coronary Heart Disease
CABG	Coronary Artery Bypass Grafting
CVD	Cardio Vascular Disease
DDD	Defined Daily Doses
HTA	Health Technology Assessment
ICUR	Incremental cost-utility ratio
MI	Myocardial Infarction
NNT	Number needed to treat
PCI	Percutaneous Coronary Intervention
QALY	Quality Adjusted Life Years
SA	Stable Angina
USA	Unstable Angina

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Summary

Background:

Cardiovascular diseases (CVD) constitute one of the most significant causes of morbidity and are among the three most frequent causes of death in industrial countries. They comprise coronary heart disease (CHD), cerebrovascular disease and peripheral artery disease (PAD).

high burden of disease from cardiovascular diseases

While death rates from CVD have been decreasing in many European countries including Austria, CVD still account for the largest proportions of hospital stays. The high burden of disease also has economic implications. Health care costs of 1.6 billion Euros, 6 % of the health care budget, were estimated for 2006 for Austria.

decreasing mortality but major costs for treatment

Several risk factors have been identified as causes of CVD, one of them being an elevated 'Low Densitiy Lipoprotein-level' (LDL-level). Among a number of measures to reduce serum cholesterol, pharmacological treatment with 'HMG-CoA Reductase Inhibitors' (statins) has become increasingly dominant since the beginning of the 1990s.

one risk factor: high LDL-level

statins used to reduce LDL

In clinical studies and meta-analyses, statins have shown significant risk reductions with respect to several clinical endpoints such as all-cause mortality, CHD mortality and CHD morbidity and exhibited a high level of safety.

clinical studies demonstrate efficacy of statins

Between 1996 and 2006 the number of prescriptions for statins rose from around half a million to 3.5 million in Austria, corresponding to 0.5 % and 3.1 % of all prescriptions respectively. While the costs per prescription decreased from around 40 Euros to 20 Euros due to the introduction of generics, overall expenditure rose sharply from 15 million Euros in 1996 to 94 million Euros in 2003 and then decreased to 76 million Euros in 2006.

sharply rising numbers of prescription and expenditure in Austria

Research question:

research question:

- How many persons were taking statins between 1996 and 2006 in Austria and what are the expected population health gains from statin treatment in the secondary prevention of CVD for patients with CHD compared to standard advice without statins?
- What is the cost-utility of statin therapy compared to standard advice without statins in the secondary prevention of CVD for patients with CHD from a public payer perspective?

population health gains from treatment in Austria,

cost-utility ratios

Method:

First, model outcomes from a validated and adapted Markov model from the UK that compared statin takers with non-statin takers (based on clinical trial evidence) were related to the actual number of Austrian statin patients from 1996 to 2006. Population effects with regard to non lethal and lethal types of CVD and revascularisation interventions were calculated.

adapted Markov model from UK was used

Second, model outcomes were used to analyse 10-year and life-time cost-utility ratios from a public payer perspective, discounted at 5 %.

One-way sensitivity analyses were conducted to address uncertainty.

uncertainty tested in sensitivity analyses

Results:

Population health gains:

~ 600,000 statin takers between 1996 and 2006

In the base case, it was demonstrated that roughly 36,200 patients started taking statins in 1996. The new cohorts per year were constantly rising and in 2006, about 108,000 new patients were estimated taking the medication. Overall, it was estimated that roughly 600,000 patients were taking statins in the 11-year observation period.

NNT to avoid 1 person going into CVD health state: 21

Of these, around 856 fewer cases of unstable angina, 26,600 fewer MIs and 1,100 fewer strokes occurred, while roughly 6,100 more cases of stable angina were estimated when compared to not taking statins. In other words, 21 persons had to be treated with statins in order to avoid (or postpone) one patient going into a CVD health state.

NNT to avoid 1 fatal event: 59

Furthermore, it was estimated that in the 600,000 statin takers, 10,300 fatal CVD events (10,200 CHD deaths and 100 cerebrovascular deaths) were avoided or postponed. Put differently, 59 persons had to take statins between 1996 and 2006 in order to avoid or delay one fatal CVD event.

NNT to avoid 1 revascularisation: 86

Finally, the 600,000 statin patients can be weighed against around 7,000 revascularisation interventions avoided meaning 86 patients were treated to avoid one revascularisation intervention.

despite statins 42,000 CVD-cases, 25,400 fatal events and 230,000 revascularisations

It was demonstrated in the model that in spite of statins about 42,000 cases of unstable angina, MI or stroke occurred and 25,400 fatal events (24,000 CHD deaths and 1,400 cerebrovascular deaths) happened. A total of 231,000 revascularisation interventions were carried out in spite of statin treatment.

Costs:

net costs: 33 million € in 1996; 673 million € in 2007; max. 105 million € cost-containment

Total net costs were estimated at 33 million Euros in 1996 and 673 million Euros in 2007. From the latter, 76 million Euros were related to statin treatment only, while further costs to treat CVD were estimated at about 600 million Euros. Potential cost-containment rose from 8 million Euros to 105 million Euros in 2007.

Cost-utility:

cost-utility ratio:

males: 11,400 to 23,200 €/QALY

females: 12,500 to 23,000 €/QALY

Depending on the age-group, discounted incremental costs are between 2,400 and 7,800 Euros for males and between 2,500 and 8,000 Euros for females. Discounted QALYs per person are between 0.21 and 0.37 in males and between 0.20 and 4.19 in females. Incremental cost-utility ratios range from 11,400 to 23,200 Euros per QALY in males and from 12,500 to 23,000 Euros per QALY in females. The ratios decrease with age. In a ten-year time frame, cost-utility ratios rise to more than 60,000 Euros per QALY in younger age groups.

Sensitivity analysis:

results sensitive to statin costs, discount rates, compliance…

Cost-utility results are sensitive to statin costs and discount rates (ratios are lower when lower costs and discount rates are assumed) and to compliance in the younger age groups (higher ratios with lower compliance)

…and to gender/age distribution of statin takers

Cohort sizes and population health gains are sensitive to varying gender and age distributions in statin takers. Choosing a distribution that is close to the socio-demographic characteristics in patients hospitalised for MI, led to increasing cohort sizes (750,000 instead of 600,000 patients in 11 years) and to more health gains, especially with regard to MI and fatal CHD.

Discussion:

in 600,000 statin taker minus 26,600 MIs and minus 10,200 fatal CHD, yet 68,000 cases still occurring

In roughly 600,000 patients who took statins between 1996 and 2007 about 26,600 cases of MI and roughly 10,200 cases of fatal CHDs (mostly MIs) seem to have been avoided or postponed. The effect on (fatal) stroke was low. Moreover, about 7,000 fewer revascularisation interventions have been estimated compared to not taking statins. However, the model demonstrated that about 68,000 CVD cases or fatal events and 230,000 revascularisation interventions still occurred in spite of statin treatment.

number needed to treat consistent with literature

Overall, a considerable number of persons needed to be treated to achieve health gains in one: 21 patients needed to be treated in order to avoid/postpone one patient going into a CVD health state. Furthermore, 59 patients needed to be treated to avoid/postpone one fatal event and 86 patients needed to take statins to avoid one revascularisation intervention. These results are consistent with the literature.

ICUR below 30,000 €/QALY in long-run but interpretation in Austria limited

ICURs are mostly below 30,000 Euros per QALY gained but rise above 60,000 Euros per QALY gained in younger age groups when analysed from a ten-year perspective. Again, results are consistent with the literature; however, in the absence of a willingness-to-pay threshold in Austria, interpretation of the cost-utility results is limited.

several limitations due to data quality

Further limitations exist for the following reasons: First, many parameters in the model are from the UK because they were not available for Austria. Second, Austrian cohort sizes and estimated population health gains are subject to uncertainty. Third, statin prescription data used may include primary prevention cases. Furthermore, the administrative data used for cost-calculation are sub-optimal and cost-calculation did not take into account societal effects from therapy such as the impact on informal care. Moreover, the model outputs are based on the results from clinical statin trials and transfer to routine practice may be limited.

Conclusion:

health gains in MI and CHD mortality are likely but…

Results suggest that prescribing statins to about 600,000 to 750,000 patients in the period between 1996 and 2006 should have resulted in observable population health gains (especially with respect to MI and CHD death), compared to the alternative of not taking the medication.

…many (fatal) CVD cases still occur

Nevertheless, the 45,000 avoided or postponed CVD cases, fatal events or revascularisation interventions need to be balanced against 300,000 CVD cases, fatal events or interventions that still occurred.

cohort size and health gains are subject to uncertainty

Both, the size of the statin cohort and the health gains are subject to some uncertainty and therefore should be interpreted as rough estimates rather than precise figures.

ICUR mostly below 30,000 €/QALY, interpretation requires public debate

Cost-utility ratios were mostly below 30,000 Euros per QALY gained which has been rated as favourable in other countries. Whether the expected health gains are sufficient after weighing benefits and costs is a matter of political and public debate.

further research: primary prevention, sub-group analysis, verification of expected health gains

Further research is required which should address primary prevention and sub-group analysis. Moreover, verification is needed on whether expected health gains are observable in Austrian cardiovascular disease epidemiology.

1 Introduction

cardiovascular disease (CVD): high prevalence, high mortality rates

Cardiovascular diseases (CVD) are among the most prevalent diseases in industrial countries. They result in high morbidity and mortality rates. A high blood cholesterol level is regarded as one of several significant risk factors of CVD. Several primary and secondary prevention strategies have been developed which focus on reducing serum cholesterol. They are dominated by pharmacological interventions. The most widely used products are statins (cholesterol lowering drugs). They were introduced in the beginnings of the 1990s and have since dominated the market of cholesterol lowering drugs.

dominant prevention strategy: statins

literature: statins are efficacious and cost-effective

The use of statins has not only been proven to be efficacious in clinical studies but they have also been described as being cost-effective in economic evaluations. The reason for the latter is primarily that clinical studies showed reductions in hospital interventions. Thus some of the additional costs of statin therapy can apparently be offset by savings in hospital costs. Since their introduction use of and expenditure for statins have risen dramatically. Already in 2000, expenditure for statins in EU-15 countries and Norway was equal to 4 billion Euros and rose to over 20 billion Euros between 2000 and 2004 [1].

rising prescriptions and expenditure

open questions:

differences between statin benefits in trial results and "real life",

population health impact,

country-specific cost-effectiveness

From a Health Technology Assessment (HTA) perspective the constant increase in the use of statins should be viewed with a critical eye and the benefits need to be assessed. Even though efficacy has been proven in clinical studies, several questions remain unanswered. First of all, clinical studies only cover a selected study population and show efficacy under ideal conditions. However, they do not show the effectiveness of therapy under 'real-life' conditions and they say little about the overall population health impact of statins. Secondly, available economic evaluations are primarily based on effect sizes of statins from clinical studies and may over- or underestimate the cost-effectiveness results in real life [2]. Finally, country specific factors may make it difficult to transfer results of studies to one's own country and may thus require a separate analysis.

mathematical model to predict health gains and costs for Austria

For addressing these issues for Austria, a mathematical model will be used in order to predict costs, outcomes and the cost-effectiveness of statin therapy for the secondary prevention of CVD within the context of an Austrian health care system. The model outputs will be used to estimate population health gains and costs for the period since statins have been introduced into the Austrian market up to 2006.

structure of report

The report is divided into several chapters. Chapter 2 specifies the research question. Chapter 3 describes the public health background of CVD, the medical background of statins and the economic background in terms of international economic evaluation studies on statins. Furthermore, the development of statin use in Austria will be described. Chapter 4 introduces the model and its methodological characteristics. In chapter 5, the results will be presented. A discussion of the results and of the limitation of the method is provided in chapter 6. The report closes with concluding remarks for decision makers and researchers.

2 Research Question

The study aims at

study aims:

1. Evaluating expected health gains from statins compared to standard advice without statins in the *secondary prevention of CVD* in Austria based on the actual number of patients with coronary heart disease (CHD) who have been treated with statins. The calculations will additionally address the number of (reduced) hospital interventions linked with statin prescriptions.

expected population health gains

2. Evaluating the *10-year and life-time cost-utility* of statin therapy compared to standard advice without statins in the secondary prevention of CVD for patients with CHD in Austria from the perspective of the public payers.

10-year and life-time cost-utility

The specific research questions are:

research questions:

1. What are the annual sizes of 'statin patient cohorts' in Austria?

amount of statin patients?

2. What is the 11-year effectiveness (1997 to 2007) in terms of population health of statins compared to standard advice only for the following clinical parameters?

11-year population health gains?

   a. Non-lethal cardiovascular events (myocardial infarction, stable and unstable angina, stroke)
   b. Hospital interventions (percutaneous coronary intervention, coronary artery bypass grafting)
   c. CHD/CVD-specific mortality

3. What is the life-time effectiveness of statins compared to standard advice only in terms of quality-adjusted life years gained (QALY)?

life-time effectiveness?

4. What are the 10-year and life-time
   a. Costs for the health care system (direct costs only) and the
   b. Incremental cost-utility ratios

of statins compared to standard advice only

cost and cost-utility?

The analysis is restricted to secondary prevention of CVD for patients with clinically manifest CHD. In terms of definition, CHD is defined as clinically manifest MI, stable or unstable angina (including fatal events). CVD is defined as either CHD or stroke with a history of CHD (including fatal events).

definition

CHD & CVD

3 Background

3.1 Public Health Background

CVD: 4.3 million deaths per year in Europe

Diseases of the heart and circulatory system (cardiovascular diseases or CVD) are among the three most frequent causes of death in industrial countries and constitute one of the most significant causes of morbidity [3]. According to the 'European Cardiovascular Statistics', every year in Europe 4.3 million people die from CVD [4]. This accounts for almost half of all deaths in Europe.

CVD = CHD, cerebrovascular disease, PAD

CVD comprises several types of disease including coronary heart disease (CHD), cerebrovascular disease, and peripheral-artery disease (PAD). CHD encompasses myocardial infarction (MI), stable and unstable angina (SA and USA) as well as other chronic heart diseases. Concerning the burden of disease, in Europe just under half of all deaths from CVD are from CHD. Additionally, CHD is by itself the single most common cause of death in Europe, accounting for 1.92 million deaths each year [4]. This demonstrates the significance of CHD among CVD.

half of CVD deaths caused by CHD

Austria:

almost half of deaths were caused by CVD, mostly CHD

Similar to other countries, cardio-vascular diseases are also a significant factor for all-cause-mortality in Austria. In 2006, 43.7 % (32,489 persons) of deaths were caused by cardio-vascular diseases [5]. In terms of frequency, CHD is also the most prevalent type of CVD in Austria. In 2006, 20.1 % (14,960) of all deaths were related to CHD. Eight percent of all deaths were caused by MI which equals 5,969 persons. With respect to gender, the death rate due to MI is twice as high for males as for females. However, with respect to all CVD deaths, women more frequently die from CVD than men (48.9 % versus 37.9 %) [5].

CVD death rate declined in the past 30 year…

Over the past 30 years death rates from CVD have been declining in most northern and western European countries. According to several studies, the highest proportion of decline in CHD (around two thirds) is attributable to reduced incidence rates while the remaining third is due to improved treatment [6, 7].

…also in Austria, particularly since the 1990ies

Like in most northern and western European countries, death rates from CVD have also been decreasing in Austria. Over the last ten years – between 1996 and 2006 – mortality due to CVD fell by 40.9 %. Standardised for age, mortality due to MI fell by 44.5 %. The trend has been increasingly evident since the beginnings of the 1990s [5].

increasing revascularisation rates

The significance of CVD is also reflected in hospital statistics. In all European countries, rates for revascularisation have increased since the 1990ies. In some countries, in Hungary for example the revascularisation rate has increased up to 20-fold [8]. However, hospital discharge rates as well as intervention rates vary considerably from country to country.

CVD hospital length of stay in Austria decreased but still longer than the average

In Austria, CVD-diagnoses accounted for 12.2 % of all hospital diagnoses in 2005. This was the largest proportion compared to other diagnostic groups. Although the mean length of stay for persons with a CVD diagnosis has continuously decreased for CVD (from 12 days in 2003 to 7.8 days in 2005), it is still higher than the average length of stay of 5.9 days. In 2005, around 3,800 men and 3,600 women per 100,000 inhabitants were treated for a type of CVD [5].

hyperlipidaemia (LDL) one of several risk factors

Several risk factors have been identified as causes for CVD. One of them is hyperlipidaemia, more precisely a high 'Low-Density-Lipoprotein-Level' (LDL). Causality between an increased level of serum cholesterol and increased risk for CVD has been shown in several studies, however, it has also been noted that by itself, serum cholesterol is a limited predictor for cardiovascular events[1][9]. Hyperlipidaemia is therefore only one of several risk factors which need to be considered in prevention programmes. In other words reducing cholesterol is only one out of several measures to reduce risk of morbidity and mortality.

pharmacological intervention to reduce serum-cholesterol: statins

Several measures have been developed to reduce serum-cholesterol. Some of them address the life-style (e. g. diet), while others are pharmacological interventions. One of the most important pharmacological interventions is the 'Hydroxymethylglutaryl-CoA Reductase Inhibitors' (HMG-CoA Reductase-Inhibitors), also called statins which were launched in the beginnings of the 1990ies. Since then the number of prescriptions and expenditure for statins have risen considerably. An OECD report from 2003 showed that from all of the pharmaceuticals used for the prevention and treatment of CVDs (e.g. ACE inhibitors), statins showed the highest rates of increase in costs and utilisation [10].

3.2 Medical Background

statins lower serum-LDL and have shown 'pleiotropic effects'

Statins inhibit the HMG-CoA which is an enzyme that is required for the synthesis of cholesterol. This results in reduced cholesterol production in the liver and subsequently LDL receptors are increasingly formed on the liver-cell surface. The circulating LDL adheres to these receptors. In addition, statins have shown so-called 'pleiotropic' effects which are not necessarily linked with cholesterol reduction. For example they have shown improved vessel function in vitro [i.e. 11, 12]. Whether these effects will also be verifiable in vivo remains to be seen. Statins are either produced via fungal fermentation or synthetically [13].

clinical studies: efficacy for CVD mortality and morbidity endpoints

Several studies have shown that statins are efficacious in terms of effects on surrogate endpoints (e.g. reduction of cholesterol level) and clinical endpoints (reduction of morbidity and mortality). In a meta-analysis from 2005, 31 randomised controlled trials were analysed, which investigated the effect of statins in patients with pre-existing and manifest CVD [14]. The meta-analysis showed a significant risk reduction of all-cause-mortality, of cardiovascular mortality and of fatal MI. However, the analysis did not show a significant risk reduction in fatal stroke. Yet, the study reported a significant reduction of non-fatal endpoints such as non-fatal stroke, non-fatal MI, unstable Angina and coronary revascularisation.

biggest effect size: CHD mortality + morbidity

In terms of absolute risk reduction, the biggest effect size was shown for the combined endpoint of CHD mortality and morbidity. Depending on the study, average absolute risk reduction was between 3 % (CARE study) and 8.57 % (4S-Study) corresponding to a number-needed to treat of 34 (22.8-95.5) and 12 (9-16.4) [14].

[1] For example, according to the British Regional Heart Survey only 42 % of men who developed CHD over a 15-year period had elevated cholesterol-levels above 6,5 mmol/l.

good safety profile

Statins have exhibitied a high level of safety. Nevertheless, some side-effects have been reported. The most frequently mentioned side-effect (1 out of 1,000 users) is myopathia which is manifested in muscle pain and amyasthenia. If undetected, this can lead to rhabdomyolysis and acute renal-failure. However, in clinical studies such serious side-effects have been rarely reported. In rare cases, liver-dysfunction, renal-failure, hypothyreosis and infectious diseases can occur [13]. Occasionally, patients suffered from headache, dizziness, rash, diarrhoea, abdominal pain or constipation [14]. The side-effects are usually dependent on drug doses and are reversible if the drug dose is reduced in sufficient time. To prevent liver and muscle damage diagnostic tests for liver- and muscle enzymes are recommended [13].

3.3 Economic Background

total costs of CVD in Europe : 190 billion €

CVDs are linked with a high burden of disease which also has economic implications. According to the European cardiovascular disease statistics [4], total cost of CVD in Europe has been estimated to be around 192 billion Euros in 2006. This represents a cost per capita of 391 Euros. Around two thirds of the costs occur within the health care sector where they account for 10 % of the total health care expenditure across the EU. The remainder are incurred by productivity losses and costs of informal care.

CHD in EU:
49 billion €

CHD is estimated to cost the EU economy around 49 billion Euros per year which accounts for just over one quarter of the overall CVD costs. From the total CHD costs, around half are due to direct health care costs, a third to productivity losses and 15 % are due to informal care for people with CHD [4].

Austria: 1.6 billion € (6 % of total health care budget)

For Austria, the same study reports CVD costs for the health care sector of 1.6 billion Euros or 6 % of the total health care budget for the year 2006. Inpatient care accounted for the highest proportion of 54 % (0.8 billion Euros) [4].

economic benefits from statin treatment expected

Consequently, prevention and treatment are not only seen in terms of clinical benefits but also with respect to economic benefits. In that context, several studies have presented economic evaluations of statins. Usually, evaluators conducted cost-effectiveness or cost-utility analyses. A systematic review of existing economic evaluations from 2005 reports thirty-five economic evaluations which address secondary prevention with statins [2].

favourable cost-effectiveness results in literature

In summary the studies have shown that outcome from life-long statin treatment ranges on average from 0.11 to 0.44 life years gained (LYG) per person (which equals 1.3 to 6 life months gained (LMG) per person) or from 0.13 to 0.49 quality adjusted life years (QALY) per person. Additional costs as well as incremental cost-effectiveness or cost-utility ratios mostly lie below 10,000 Euros per LYG or QALY. This has been estimated to be cost-effective when compared to other accepted medical interventions or to (informally) existing willingness-to-pay thresholds [e.g. 14, 15, 16-21].

reduction in hospital costs but additional costs not totally compexnated

Based on clinical studies, economic evaluations have shown reductions of hospital costs resulting in cost-offset of statin costs between 25 % and 85 %, however, additional costs for medication were not fully compensated by savings. The most favourable cost-effectiveness results are to be expected in

countries with high rates of hospital admissions and long lengths of stay because the potential for cost-offset is higher in those countries. Yet, authors have also reported that the increasing use of statins in an unselected study population may also lead to unfavourable cost-effectiveness results [2].

3.4 Current Service Provision: Use of Statins in Austria

3.4.1 Legal Regulations and Guidelines

1990ies: public coverage restricted to secondary prevention (manifest CHD)

In Austria, public reimbursement of licensed pharmaceuticals is regulated via a so-called positive list (Erstattungskodex/EKO). Statins have been included in the positive list of the social health insurance since the mid 1990s. The first regulation stipulated that statins are reimbursed when *used for secondary prevention in patients with diagnosed CHD and hypercholesterinaemia*.

In terms of definition, diagnosed CHD means [22]

- Clinically verified angina (electrocardiogram, ergometry or scintigraphy, probably coronary angiography) or
- Patients after myocardial infarction (MI) or
- Patients after percutaneous transluminal coronary angiography (PTCA) or
- Patients after coronary artery bypass grafting (CABG)
- Hypercholesterinaemia is defined as
- LDL cholesterol > 100 mg/dl
- Quotient total cholesterol/HDL > 3

change in 2004: reimbursed for patients with high risk for cardio-vascular events

This regulation was changed in 2004. Since then statins are reimbursed for *patients with clinically manifest atherosclerosis and/or diabetes with high risk for cardio-vascular events.*

Clinically manifest atherosclerosis is defined as

- Coronary heart disease (CHD)
- Cerebrovascular disease
- Peripheral artery disease (PAD)

guideline: life-style interventions & pharmacological treatment

Concerning guidelines for treatment in secondary prevention, pharmacological treatment is suggested in addition to life-style interventions (weight reduction, dietary advice, smoking prohibition, exercise). Pharmacological treatment is to be started at the lowest dose.

3.4.2 Volumes and Expenditure from a Historical Perspective

database: Federation of the Austrian Social Insurance Institutions

The estimation of volumes and expenditure is based on data from the Federation of the Austrian Social Insurance Institutions. This data provides the number of prescriptions and related expenditure for all types of statins between 1996 and 2006.

Table 3.4-1 gives an overview of all statins (including generics) which have been covered publicly between 1996 and 2006.

With respect to statin types, six types have been included in the positive list between 1996 and 2006. These are

1996-2006: 6 types of statins included in positive list

- Atorvastatin (Sortis ®)
- Fluvastatin (Lescol ®)
- Lovastatin (Mevacor ® + Generics)
- Pravastatin (Pravachol ®, Selipran ® + Generics)
- Rosuvastatin (Crestor ®)
- Simvastatin (Zocord ® + Generics)

Table 3.4-1: Licensed statins in Austrian positive list between 1996 and 2006

Active Ingredient	Trade name	Manufacturer
Atorvastatin	Sortis® Filmtabletten (10, 20, 40, 80 mg)	Pfizer
Fluvastatin	Lescol® 40 mg Kapseln	Novartis
	Lescol MR® 80 mg Filmtabletten	Novartis
Lovastatin	Mevacor® 20 mg Tabletten	Merck Sharp & Dohme
	Mevacor forte® 40 mg Tabletten	Merck Sharp & Dohme
	Generikum 'Alternova'20 mg Tabletten	Alternova
	Generikum 'Hexal' 20 mg Tabletten	Hexal
	Gnerikum 'Stada' 20 mg Tabletten	Stada
Pravastatin	Pravachol® Tabletten (20, 40 mg)	Bristol-Meyers Squibb
	Selipran® Tabletten (10, 20 mg)	Bristol-Meyers Squibb
	Generikum Sanaprav® Tabletten (20, 40 mg)	Sankyo
	Generikum Panchol® Tabletten (20, 40 mg)	Lannacher
	Generikum '1A Pharma' Tabletten (20, 30, 40 mg)	1A Pharma
	Generikum 'Alternava' Filmtabletten (20, 40 mg)	Alternova
	Generikum 'Genericon' Filmtabletten (20, 40 mg)	Generikon
	Generikum 'Hexal' Tabletten (20, 30, 40 mg)	Hexal
	Generikum 'Interpharm' Tabletten (20, 40 mg)	Interpharm
	Generikum 'Ranbaxy' Tabletten (20, 40 mg)	Ranbaxy
	Generikum 'ratiopharm' Tabletten (20, 40 mg)	Ratiopharm
	Generikum 'Sandoz' Tabletten (20, 40 mg)	Sandoz
	Generikum 'Stada' Filmtabletten (20, 40 mg)	Stada
Rosuvastatin	Crestor® Filmtabletten (5, 10, 20, 40 mg)	Astra Zeneca
Simvastatin	Zocord® Filmtabletten (20, 40, 80 mg)	Merck Sharp & Dohme
	Generikum Nyzoc® Filmtabletten (20, 40, mg)	Nycomed
	Generikum Gerosim® Filmtabletten (20, 40 mg)	Gerot
	Generikum Simvastad® Filmtabletten (20, 40 mg)	Stada
	Generikum '1A Pharma' Filmtabletten (20, 40 mg)	1A Pharma
	Generikum ,Alternova' Filmtabletten (20, 40 mg)	Alternova
	Generikum ,Genericon' Filmtabletten (20, 40 mg)	Genericon
	Generikum ,Hexal' Filmtabletten (10, 20, 30, 40 mg)	Hexal
	Generikum ,Interpharm' Filmtabletten (20, 40 mg)	Interpharm
	Generikum ,Merck' Filmtabletten (20, 40 mg)	Merck
	Generikum ,Ranbaxy' Filmtabletten (20, 40 mg)	Ranbaxy
	Generikum ,ratiopharm' Filmtabletten (20, 40 mg)	Ratiopharm
	Generikum ,Sandoz' Filmtabletten (20, 40 mg)	Sandoz
	Generikum Simvatin® Filmtabletten (20, 40 mg)	Biospray

Source: Federation of Austrian Social Insurance Institutions

Statins have been available in different doses since 1996. Table 3.4-2 gives an overview of available doses per type of statin.

Table 3.4-2: Available doses per type of statin

Dose/Type of Statin	5 mg	10 mg	20 mg	30 mg	40 mg	80 mg
Atorvastatin		X	X		X	X
Fluvastatin					X	X
Lovastatin			X		X	
Pravastatin		X	X	X	X	
Simvastatin		X	X	X	X	X
Rosuvastatin	X	X	X		X	

differences between prescribed doses

The number of prescriptions varies considerably between different doses available. As shown in Table 3.4-3 for the year 2006, some doses hardly ever have been prescribed (e.g. rosuvastatin 5 mg) while others have been prescribed more frequently (e.g. simvastatin or pravastatin 20 mg and 40 mg, fluvastatin 80 mg).

Table 3.4-3: Number of statins prescribed in 2006 per doses and type of statin

	Number of prescriptions					
Dose/Type of Statin	**5 mg**	**10 mg**	**20 mg**	**30 mg**	**40 mg**	**80 mg**
Atorvastatin	0	333,771	84,748	0	26,762	9,343
Fluvastatin	0	0	0	0	171,118	337,254
Lovastatin	0	0	21,566	0	64	0
Pravastatin	0	46	259,112	3,038	123,650	0
Simvastatin	0	172	1,131,848	25,914	769,782	311
Rosuvastatin	17	54,896	12,291	0	2,710	0

number of prescription rose sharply

mostly prescribed type: Simvastatin

Figure 3.4-1 shows the numbers of total prescriptions for each type of statin between 1996 and 2006. The number of prescriptions has risen from 432,170 in 1996 to 3,468,303 in 2006. In terms of statin type simvastatin accounts for the greatest proportion of statins prescribed (40%), followed by atorvastatin (28.5 %). Pravastatin and fluvastatin account for 16.7 and 11.3 % respectively whereas lovastatin (2.9 %) and rosuvastatin (0.5 %) play a marginal role with respect to volume.

2006: 3.1% of all prescriptions due to statins

Concerning the overall number of prescriptions for pharmaceuticals that rose from 93.2 millions in 1996 to 107.7 millions in 2006 in Austria [23, 24], statins accounted for 0.5 % in 1996. The proportion constantly increased up to 3.1 % in 2006.

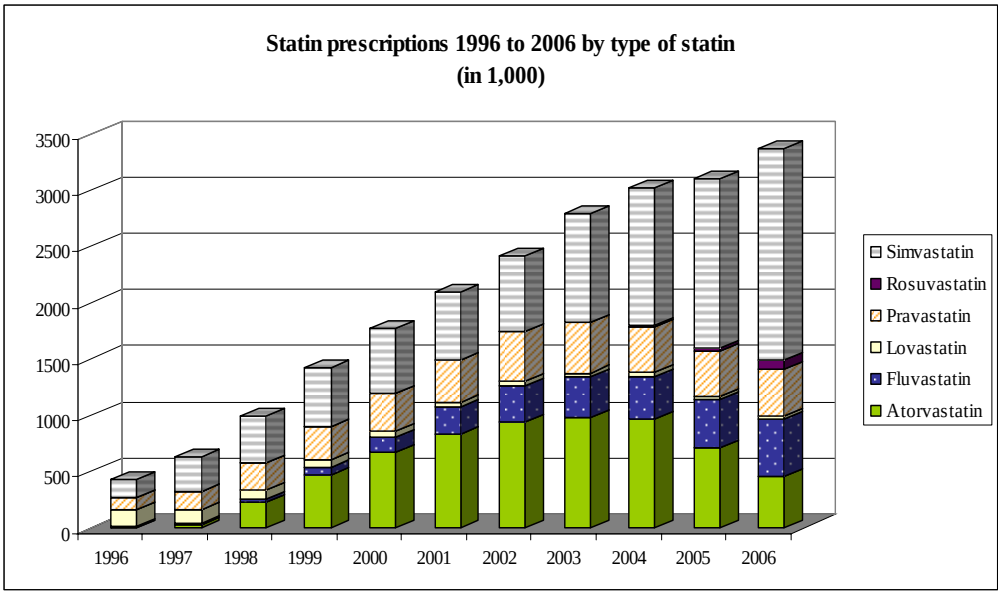

Figure 3.4-1: Statin prescriptions 1996 to 2006 by type of statin

expenditure: strong increase until 2003, then slight decrease because of generics

As shown in Figure 3.4-2, expenditure for statins has also risen considerably since the mid-1990s. In 1996 the social insurance institutions paid around 17 million Euros for statins. Expenditure peaked in 2003 where 94 million Euros were spent on statins. In 2006 expenditure for statins decreased to around 76 million Euros. The decrease was due to the introduction of generics. Total expenditure between 1996 and 2006 were 705,228,505 Euros. Again, simvastatin and atorvastatin account for the biggest proportion of expenditure, followed by pravastatin and fluvastatin. The costs per prescription were 39.40 Euros in 1996 and decreased to 22.50 Euros in 2006 (see Figure 3.4-3).

2006: 3 % of total pharmaceutical expenditure due to statins

In terms of overall expenditure for pharmaceuticals in Austria that increased from 1.4 billion in 1996 to 2.6 billion in 2006 [23, 24], the proportion paid for statins rose from 1.2 % in 1996 to 4.1 % in 2002. Since then, the share paid for statins has slightly decreased. In 2006 statins accounted for 2.9 % of total expenditure for pharmaceuticals.

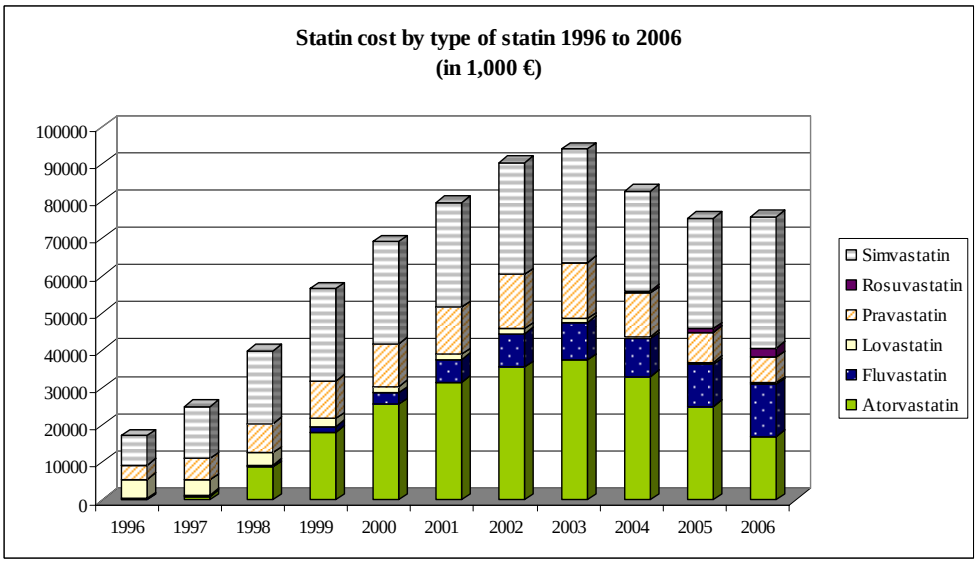

Figure 3.4-2: Statin costs 1996 to 2006 by type of statin

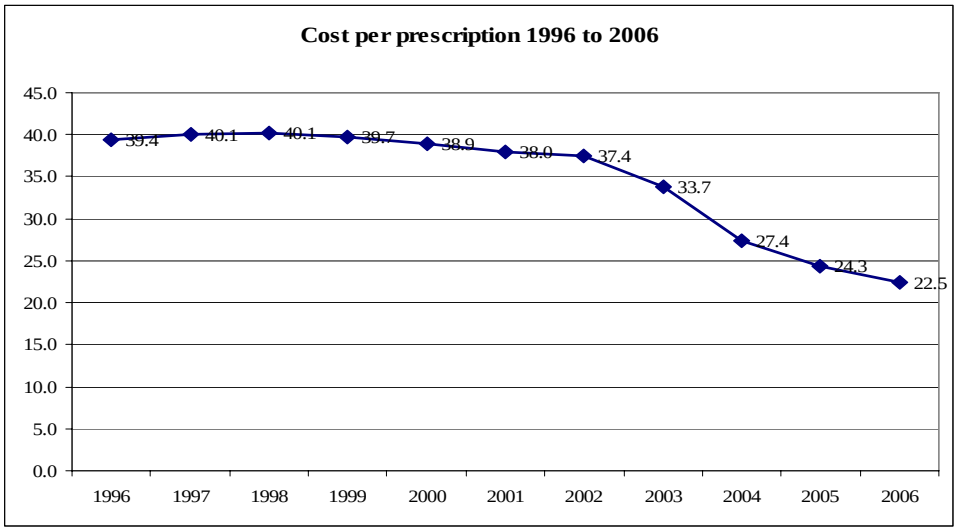

Figure 3.4-3: Cost per prescription 1996 to 2006

171 million prescribed daily doses in 2006

According to the defined daily doses for each type of statin, the total number of prescribed daily doses of statins can be calculated. Figure 3.4-4 shows that the total number of prescribed daily doses rose more than tenfold from around 13 million in 1996 to 170.8 million in 2006.

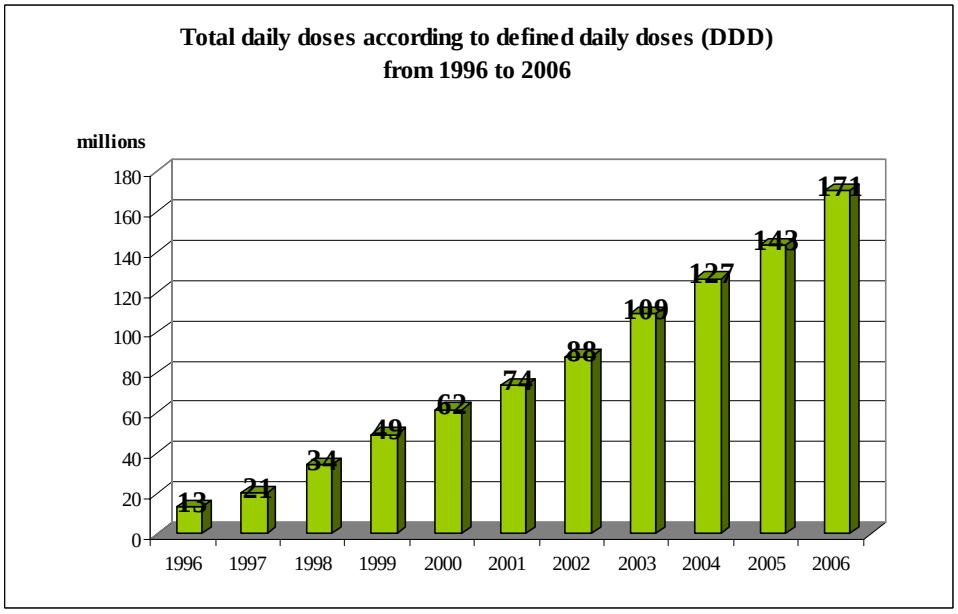

Figure 3.4-4: Total daily doses according to defined daily doses (DDD) from 1996 to 2006

lipid lowering drugs for around 65% of MI-patients in Austria

According to Gouya et al. (2007) [25], data from the Austrian province 'Burgenland' showed that from all 207 patients discharged after an MI in 2003, 68% were prescribed a lipid lowering agent. The frequency of lipid lowering drug prescription was significantly lower in women than in men. Similarly, Winkelmayer et al. [26] found from data covering three quarters of the insured population in Austria that 67 % of patients who were discharged after an MI were prescribed a lipid lowering agent within 120 days. The oldest patients (>90 years) were less likely to receive statins, however, gender did not have a significant influence on prescriptions in that study.

4 Method

4.1 Overview

adaptation of validated Markov-model from UK because…

For the study a Markov-model which has been developed and validated at the University of Sheffield/School of Health and Related Research (ScHARR) was adapted for the context of the Austrian health care system and for the specific research questions to be addressed. This model was chosen for several reasons

…appropriate for disease type,

- A Markov-model is appropriate for diseases with recurring events, for diseases involving risks that continue or increase over time and where the probability of an event occurring changes depending on the time since a previous event. This fits well with the characteristics of CVD.

similar research questions,

- The ScHARR model addresses a similar research question which should allow for adaptation, thus, avoiding duplication and redundancies.

data based on meta-analyses,

- Effectiveness data in the ScHARR model are based on a meta-analysis and, thus, synthesise the available evidence.

fulfils methodological standards

- The model generally fulfils the standards of modelling for economic evaluations.

data sources:

The model parameters are based on the following data sources:

UK data for…

patient characteristics,

- Due to absence of valid Austrian data, initial distribution into different health states and demographic characteristics of the cohort were adapted from the ScHARR model which is based on British registry data.

transitional probabilities,

- Progression between health states:
  - Transitional probabilities for MI, angina and stroke health states were used from the ScHARR model. They were derived from UK registry data for MI and stroke health states and from secondary literature for angina health states.
  - Progression to the health state 'mortality other cause' are based on Austrian life tables.

Austrian life tables

statin efficacy: UK meta-analysis

- Effectiveness of statin therapy with respect to morbidity and mortality was based on the ScHARR meta-analysis of clinical statin trials.
- Effectiveness of statin therapy with respect to reduced hospital interventions was based on Austrian data on the provision of revascularisation procedures.

QALYs: from UK model

- QALYs were based on data from the ScHARR model.

cost data: social insurance data + hospital financing data (LKF)

- Statin prices were based on Austrian volumes and prices of statins according to the social insurance data.
- Costs of health states:
  - Costs of inpatient care were based on data from the performance-oriented hospital financing system/LKF (a form of DRG system).
  - Costs for outpatient care were calculated according to social insurance data (Honorarordnungsdatenbank).

simulation results used to calculate population health gains for Austria

The results of the simulation are related to the actual sizes of annual Austrian statin patient cohorts according to social insurance data. The aim was to calculate the present aggregated absolute effects of statin therapy for all secondary prevention patients who have been prescribed statins since their introduction in the Austrian health care system between 1996 and 2006.

additionally: QALYs & cost-utility

Additionally, for every therapy strategy the model predicts the quality-adjusted life years gained the cost as well as the incremental cost-utility ratio for a life-time and a 10-year perspective.

The model will be described in more detail in the following chapters.

4.2 Therapy Strategies

therapy strategies:

The evaluation compares the costs and benefits associated with statin treatment versus no statin treatment. As lipid-regulating drug therapy should be combined with advice on diet or lifestyle measures and, if appropriate, other risk-reducing measures (e.g. reduction of blood pressure), it is assumed that all patients entering the model have been given standard advice regarding dietary control and other appropriate measures. The 'statin group' additionally receives statins.

'NoStatins' (standard advice)

Hence, the decision analytic health economic model compares the following therapy strategies:

versus

1. NoStatin

   Non-medical lipid-lowering therapy (standard advice only)

statin therapy (statins + standard advice)

2. Statin

   Statin therapy according to doses used in trials + standard advice

4.3 Outcome Parameters and Time Horizon

medical parameters

Both, medical and economic outcome parameters were calculated. Medical parameters were:

- Clinical events (non-lethal MI, stable and unstable Angina, stroke with history CHD),
- Revascularisation interventions (CABG, PCI),
- CHD- and cerebrovascular-specific mortality,
- Quality adjusted life years gained (QALYs).

economic parameters

Economic outcome parameters were:

- Direct medical costs in Euros (2007 prices or inflated),
- Discounted incremental cost-utility ratio in Euros per QALY.

health gains for 1997 to 2007

Cardiovascular health outcomes were calculated for the years 1997 to 2007 (11 years). Costs, quality adjusted life-years and cost-utility ratios were calculated for life-time and for a ten-year time horizon.

4.4 Perspective

public payer perspective

As the report aims to support decisions of public payers, costs and effects were calculated from the perspective of the public payers in the Austrian health care system. Thus, only direct costs have been included in the cost calculation while indirect costs from lost productivity (due to illness, premature death and informal care) or costs incurred directly by patients have not been taken into account. As shown in chapter 3.3, the latter can be substantial, thus by excluding them we will not be able to demonstrate the overall societal costs and potential cost-savings.

4.5 Discounting

discount rate: 5 %

Guidelines on economic evaluation state that, according to economic theory, results from economic evaluations, need to be discounted [e.g.27]. According to an Austrian consensus paper on economic evaluations, for the cost-utility analyses, a discount rate of 5 % is applied to costs and health benefits respectively [28]. The discount rate is varied between 0 % and 5 % to test for uncertainty and to inform decision makers on discounted and undiscounted results.

no discounting for epidemiological results

The calculation of expected population health gains for the years 1997 to 2007 addresses epidemiological outcomes only and results therefore have not been discounted.

4.6 Model Structure

model structure:

Figure 4.6-1 shows the structure used for calculating the outcome parameters. The model is based on annual cycles.

patients start in one of three different CHD-conditions (secondary prevention)

As described in chapter 3.4.1, the first Austrian guidelines on statin therapy for the secondary prevention of CVD state that statins are indicated for patients with hypercholesterinaemia and manifest CHD (defined as angina, MI and status post PCI or CABG). According to these guidelines, in the base case, analysis patients can start in three 'secondary prevention health states' being 'stable angina', 'unstable angina' or 'first myocardial infarction'. Per definition patients in these health states have experienced the according event in the previous year.

different probabilities to move into more severe health states…

Patients who have suffered from stable angina can then either move to 'unstable angina' or to 'post stable angina'. Furthermore, they can experience their first MI. Patients who start in the health state 'unstable angina' (meaning they have experienced unstable angina in the previous year) can either move to 'post unstable angina' or to 'first MI'. Finally, patients who start in the health state 'first MI' can either experience a subsequent MI in the first year or they move to the health state 'no subsequent MI first year'.

Patients in the health state 'post stable angina' can either remain in that state, move to 'unstable angina' or to 'first MI'. Similarly, patients in the health state 'post unstable angina' can remain in that state or move to 'first MI'. Additionally, patients can move to 'stroke' from all MI health states. In other words, CVD outcomes are only considered for patients with a history of MI.

…or to die

Finally patients can move to 'coronary heart disease death', 'cardiovascular death with history of coronary heart disease' or 'death from other causes' from all health states.

frequency of revascularisation based on Austrian service patterns

Revascularisation interventions are not directly predicted by the model. Thus they have been calculated by relating the model outputs for 'stable angina', 'unstable angina' and 'MI' to the typical patterns of revascularisation intervention provision in Austria based on published literature and expert opinion (see 4.9 for details).

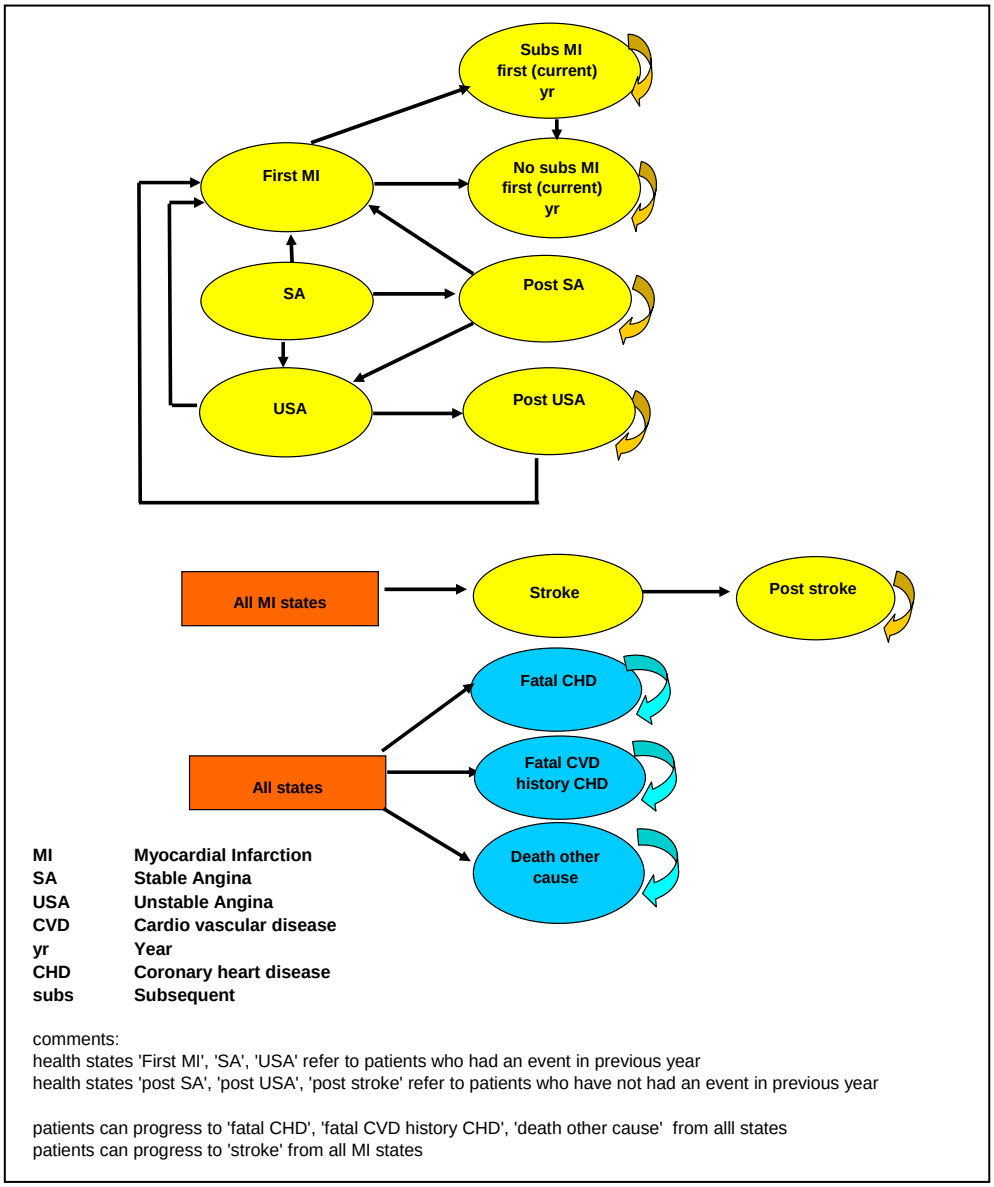

Figure 4.6-1: Model structure

4.7 Model Parameters

4.7.1 Transition Probabilities

transition probabilities based on UK data

Transitions from and to the different health states are based on the ScHARR-model (table 4.7-1). UK registries were used to calculate transitional probabilities for patients with manifest CHD (Nottingham Heart Attack Register; South London Stroke Register) [29, 30]. Where registry data were not available (progression from stable angina to unstable angina, MI or CHD death) secondary data from the literature were used [31].

age-specific transitions used

The ScHARR model takes into account that the probability of experiencing further events after primary events is strongly correlated with age (for example multivariate regression analysis showed that for patients experiencing an MI the mean probability of a second event within 1 year is 5.4 % at age 45 and 29.8 % at age 85). Logistic and multivariate regression analyses of the observational data mentioned above were used to retain age specific probabilities which feed into the model [14]. Table 4.7-1 presents the transitional probabilities for the untreated population by age.

Table 4.7-1: Annual transitional probabilities by age in the untreated population

	Unstable Angina	Non fatal MI	Stroke	CHD death	CVD death history CHD
Markov model health states for age 45					
Stable angina	0.0013	0.0032		0.0009	
Unstable angina (1st year)		0.4950		0.0362	0.0016
Unstable angina (subs yr)		0.0186		0.0081	0.0004
MI (1st yr)		0.1280	0.0015	0.0167	0.0007
MI (subs yr)		0.0162	0.0004	0.0052	0.0002
Stroke (1st year)		0.0016	0.0459	0.0111	0.0111
Stroke (subs yr)		0.0016	0.0186	0.0049	0.0049
Markov model health states for age 55					
Stable angina	0.0029	0.0062		0.0035	
Unstable angina (1st year)		0.0497		0.0617	0.0004
Unstable angina (subs yr)		0.0348		0.0100	0.0007
MI (1st yr)		0.1152	0.0032	0.0319	0.0002
MI (subs yr)		0.0179	0.0010	0.0091	0.0013
Stroke (1st yr)		0.0031	0.0459	0.0111	0.0046
Stroke (subs yr)		0.0031	0.0186	0.0049	0.0021
Markov model health states for age 65					
Stable angina	0.0060	0.0110		0.0070	
Unstable angina (1st year)		0.0488		0.1031	0.0046
Unstable angina (subs yr)		0.0632		0.0119	0.0005
MI (1st yr)		0.1019	0.0068	0.0599	0.0027
MI (subs yr)		0.0185	0.0022	0.0152	0.0007
Stroke (1st yr)		0.0055	0.0423	0.0260	0.0260
Stroke (subs yr)		0.0055	0.0223	0.0104	0.0104
Markov model health states for age 75					
Stable angina	0.0091	0.0158		0.0070	
Unstable angina (1st year)		0.0466		0.1671	0.0074
Unstable angina (subs yr)		0.1122		0.0139	0.0006
MI (1st yr)		0.0874	0.0141	0.1088	0.0048
MI (subs yr)		0.0178	0.0047	0.0235	0.0010
Stroke (1st yr)		0.0080	0.0446	0.0206	0.0586
Stroke (subs yr)		0.0080	0.0246	0.0206	0.0206
Markov model health states for age 85					
Stable angina	0.0122	0.0207		0.0070	
Unstable angins (1st yr)		0.0425		0.2587	0.0115
Unstable angina (subs yr)		0.1955		0.0160	0.0007
MI (1st yr)		0.0711	0.0278	0.1875	0.0083
MI (subs yr)		0.0160	0.0091	0.0340	0.0015
Stroke (1st yr)		0.0104	0.0446	0.0185	0.1215
Stroke (subs yr)		0.0104	0.0252	0.1215	0.0375

Source: Ward et al. [14]

4.7.2 Demographic and Clinical Characteristics of the Study Population

distribution into health states based on UK data

In the absence of Austrian prevalence data, distribution of patients into primary event states was based on the ScHARR model which used heart disease registries for this purpose [29]. Distribution into the health states changes according to gender and age as shown in Table 4.7-2.

Table 4.7-2: Distribution into CHD health states for different ages and gender

Age males	Stable Angina	Unstable Angina	Myocard. Infarction	Age females	Stable Angina	Unstable Angina	Myocard. Infarction
30	46%	12%	42%	30	45%	12%	43%
45	38%	13%	49%	45	47%	16%	36%
55	46%	10%	44%	55	57%	12%	30%
65	41%	16%	43%	65	46%	18%	36%
75	40%	17%	42%	75	51%	22%	28%

background mortality from Austrian life-tables

Background mortality has been adjusted to Austria by using age and gender-specific death rates from Statistik Austria [32].

age and gender characteristics of Austrian statin takers according to gamma distribution

To calculate population health gains for Austria the model was run with and without statin therapy for both genders and for each year of age (from age 31 to 99) separately. These simulation results are then projected to all Austrian statin patients. In the absence of age and gender characteristics of Austrian patients taking statins, Austrian patients using statins were distributed into different ages by applying a gamma distribution based on an expected value of 60 and a standard deviation of 8 in the base case. Furthermore, international experience [14] has shown that the relation between male and female statin taker is 60:40. These parameters were varied in sensitivity analyses (see 4.11).

4.7.3 Effectiveness of Statin Therapy

meta-analysis for relative risks of statin therapy

In the ScHARR model, a standard meta-analysis based on a systematic literature review up to the year 2004 was conducted to calculate the relative risks of statin therapy for the health states of interest. The results are shown in Table 4.7-3. Benefits of statin therapy have been modelled by adjusting the probabilities for events in the model with relative risks observed in the meta-analysis. The model assumes that the relative risks reported in the trials continue over lifetime since no evidence exists suggesting that the effect diminishes over time. The ScHARR meta-analysis did not include data on the efficacy of lovastatin. However, as shown in chapter 3.4, this type of statin has hardly been prescribed in Austria. Thus, specific efficacy data on lovastatin have not been taken into consideration.

Table 4.7-3: Relative risk values and sources

Health State	Mean RR	Source
Stable Angina	0.69	ScHARR RevMan Meta Analysis [14]
Unstable Angina	0.82	ScHARR RevMan Meta Analysis [14]
Non fatal MI	0.57	ScHARR RevMan Meta Analysis [14]
Fatal CHD event	0.72	ScHARR RevMan Meta Analysis [14]
Non fatal Stroke history CHD	0.66	ScHARR RevMan Meta Analysis [14]
Fatal CVD history CHD	1.00	ScHARR RevMan Meta Analysis [14]

literature update for 2004-2007:

no changes required

To check the availability of more recent efficacy data addressing the relevant clinical endpoints of cardiovascular morbidity and mortality a systematic literature review has been conducted for the years 2004 to 2007 (The search strategy and the selection of references are shown in the appendix). The review showed that trial analyses for specific subgroups (gender, patients with diabetes) have been published since 2004. However, no publication was available which would have required changes in the meta-analysis results from ScHARR since these address the general relative risks for the selected health states without focussing on specific subgroups.

4.7.4 Quality of Life Data

QALY:

combines life expectancy and health related quality of life

In addition to the illustration of health outcomes in the form of physical units (morbidity, mortality), health outcomes are calculated in the form of the generic indicator 'quality adjusted life years' (QALY). The principle of QALYs is that life expectancy and health related quality of life that result from the medical technologies under evaluation are combined into a single outcome index. QALYS will be used as the denominator in the cost-utility analyses in chapter 5.4 (see [27] for more details on the method).

data used from UK model

In order to calculate QALYs, quality of life data (utility values) are required. According to methodological standards of cost-utility analysis these data may be transferred from one county to another if no country-specific data are available [27]. Hence, age-related quality of life data (utility values) for the overall population and for the health states under investigation have been used from the ScHARR model. These are based on UK data (Table 4.7-4; Table 4.7-5).

Table 4.7-4: Utility values by age

Utility values by age used in the ScHARR cost effectiveness model			
Age (years)	utility	age	utility
45	0.869	75	0.741
50	0.848	80	0.72
55	0.826	85	0.699
60	0.805	90	0.678
65	0.784	95	0.656
70	0.763	100	0.635

Source: Ward et al. [14] based on secondary literature from Kind et al. [33]

Table 4.7-5: Utilities for health states

Utilities for health states		
Health state	**Utility (mean)**	**Source**
		CHD
Stable angina	0.808	Ward et al. 2005 [14] based on secondary literature [34]
Unstable Angina	0.770	Ward et al. 2005 [14] based on secondary literature [35]
MI	0.760	Ward et al. 2005 [14] based on secondary literature [35]
		CVD
Stroke	0.629	Ward et al. 2005 [14] based on secondary literature [36]

Source: Ward et al. [14] based on secondary literature

4.7.5 Costs

only health care system costs (direct costs) included

Cost calculations are based on Austrian service patterns and unit costs. Information on typical services which are provided for the different health states has been obtained from medical experts. Only costs for the health care system (direct costs) have been included in the calculation. Costs are at 2007 prices and inflated where necessary.

social insurance tariffs for statin treatment costs and primary care

hospital reimbursement data (LKF) for hospital costs

Services for statin treatment as well as for treatment in the different health states are provided both in primary and in hospital care. In the absence of precise cost data, unit costs for these services are based on reimbursement-tariffs which are used as a proxy for actual costs. Being aware of their limitations, it is assumed that they roughly represent the magnitude of costs of the services analysed. Unit costs for primary care services are based on data from the Federation of the Austrian Social Insurance Institutions (database on tariffs/Honorarordnungsdatenbank). Unit costs for inpatient services are based on data from the Austrian performance-oriented hospital reimbursement system (LKF) which is a form of diagnosis-related-group system (DRG). The average LKF points for selected hospital services, adjusted by a pre-defined factor that accounts for total costs (for example 1.7 for 2002) [37], are used as a proxy for the monetary value of interventions and treat-

ment. Table 4.7-6 gives an overview of the health services included and the unit costs applied. The sources used for each category are presented in the appendix (chapter 9).

MI and stroke more expensive in first year

Overall, service patterns and related unit costs for four different health states (stable angina, unstable angina, MI, stroke) have been included in the model. For some health states (MI, stroke) first year costs are higher than the costs in subsequent years.

stable angina: 860 € / year,

MI 1st year: 5,300 €

stroke 1st year: 6,400 €

Treatment of stable angina has been calculated to cost on average 860 Euros for both first and subsequent years. Basic primary care costs for the treatment of unstable angina are assumed to be the same as for stable angina. On average, treatment for myocardial infarction costs 5,265 Euros in the first year and 860 Euros in subsequent years. Treatment of stroke has been calculated to cost 6,381 Euros in the first year and 1,831 Euros thereafter.

Table 4.7-6: Resource types and unit costs (base case analysis)

Statin treatment		***Type of resources used***	***costs per year (weighted average)***
		Medication costs (see following table for details)	341
		GP visits + Monitoring	287
Health States		***Type of resources used***	***costs per year (2007 €)***
Stable Angina	1st year	Internal medicine (incl. ECG, Ergo, Echo)	314
		Medication	485
		Laboratory	60
		total	**860**
	subsequent year	like 1st year	860
Unstable Angina	1st year	Primary care = stable angina	860
	subsequent year	Primary care = stable angina	860
MI	1st year	Hospital costs (average)	4,835
		Primary care =stable angina	860
		total	**5,265**
	subsequent year	Primary care =stable angina	860
	fatal event	Hospital costs (average)	4,835
Stroke	1 st year	Hospital costs (average)	3,897
		Primary care (=stable angina+ neurologist+physiotherapy)	2,484
		total	**6,381**
	subsequent year	Primary care (=stable angina+neurologist)	1,183
	fatal event	Hospital costs	3,897

Ergo: Ergometry; ECG: Electrocardiogram; Echo: Echocardiography; Source: Social Insurance database on tariffs, LKF-database; own calculation;

statin treatment

341 € / year plus 278 € regular GP visit

The annual costs for statin treatment (Table 4.7-7) are based on the overall costs spent for each type of statin between 1996 and 2006. A weighted average of 341 Euros has been calculated according to the proportion each type of statin that had been prescribed. Additionally, costs of 278 Euros per year for regular GP visits and monitoring have been included. Costs for the handling of potential side-effects of statin therapy have been neglected due to their minor significance in clinical studies.

details in the appendix

Full details on services included, unit costs and data sources are provided in the appendix.

Table 4.7-7: Statin costs

Statin costs per year according to price per daily dose (€)						
year	Atorvastatin	Fluvastatin	Lovastatin	Pravastatin	Simvastatin	Rosuvastatin
1996	0.00	328.73	669.11	444.16	424.74	0.00
1997	404.70	321.38	654.67	421.41	421.96	0.00
1998	414.63	320.68	650.05	416.87	421.21	0.00
1999	414.77	320.68	601.03	415.06	418.91	0.00
2000	407.70	317.93	579.55	408.39	414.22	0.00
2001	405.91	279.78	576.06	400.46	409.13	0.00
2002	402.79	258.42	576.33	400.04	376.60	0.00
2003	394.44	251.76	575.16	399.58	242.15	328.75
2004	351.78	225.00	381.33	336.62	157.05	338.45
2005	334.79	218.28	348.67	214.07	131.45	328.70
2006	302.11	213.83	347.77	149.75	120.26	330.23
Average (€)						
	383.36	277.86	541.79	364.22	321.61	331.53
Proportion of total prescriptions (%)						
	25	11	1	13	49	1
Weighted average for all types between 1996 and 2006 (€)						
	340.96					

Source: Social insurance database; own calculations

two types of cost calculations:

On the basis of these data, two different types of cost calculations were undertaken:

budget impact 1996-2007 for Austrian statin population

Firstly, the budget impact over time with respect to total net costs for the Austrian statin population (in comparison to the 'NoStatin' group) was assessed (see 5.3.1). Unfortunately, the cost outputs in the model are overall aggregate values. A differentiation between statin costs and costs for the selected health states as well as the potential cost containment was therefore only possible via a rough estimation.

While outcomes for each statin cohort have been analysed for the years thereafter (e.g. outcomes for statin taker from 1996 are presented from 1997 onwards for the following 10 years until 2007; see 4.9), cost calculation has to reflect that costs were already incurred in 1996. Thus, the budget impact is presented for 1996 to 2007 (12 years). Since no data on statin expenditure was available for 2007, expenditure from 2006 was extrapolated for one year. According to the guidelines for budget-impact analysis [38], results for this analysis are presented undiscounted.

life time cost per person for statin and 'NoStatin' group

The second type of cost calculation is an analysis of life-time costs per person for the statin and the 'NoStatin' group. This is again based on the model outputs and will be used in order to calculate incremental cost-utility ratios. According to the guidelines on economic evaluation [27], results are presented discounted and undiscounted (see 5.3.2).

4.8 Calculation of the Cohort Sizes

calculation of cohort size:

As has been outlined in chapter 2, one aim of the study is to estimate the population-wide health gains that can be expected from the use of statins between 1996 and 2006 in Austria. This requires relating the model results from fictitious cohorts of various ages and gender to the actual number of patients who have taken statins in the observed time period.

no patient-level data available, thus…

Chapter 3.4.2 details how many statins were been prescribed between 1996 and 2006. In the absence of more precise data on the actual number and demographic characteristics of patients who have been prescribed these drugs, the number of patients was calculated with the following approach:

…calculation of total number of daily doses from number of prescribed statins,

Firstly, the total number of daily doses (DDD) was calculated from the total number of prescribed statins for each year according to the defined daily dose. Secondly, the total daily doses were divided by 365 in order to obtain an estimation of the annual total number of patients who could in theory have taken statins while assuming that they took the statins regularly over the entire year. However, this assumption is varied in sensitivity analysis. It is furthermore assumed that once a patient starts taking statins in secondary prevention, medication lasts life-long. Thus, in order to estimate the number of patients who start taking statins each subsequent year of interest, the number of patients from previous years is subtracted.

division by 365,

taking into account that patients die,

Additionally, calculations have taken into account that some of the initial patients will die throughout the 11-year period of observation resulting in changes in the subsequent cohort sizes. Hence, the annual number of 'new statin takers' was adjusted to take into consideration those who have died. The probability of dying was based on the model outputs for the statin cohort using the results from the health states 'CHD death', 'CVD death/history CHD' and 'death other cause'. Half-cycle corrections were conducted to account for the fact that patients die continuously throughout the year and not necessarily at the end of a cycle.

calculation of mortality adjusted 'new statin takers' per year

4.9 Calculation of Population Health Gains

calculation of population health gains for:

The model predicts results for various cardiovascular health states and fatal events of interest. As specified in chapter 4.6, these are 'stable angina', 'unstable angina', 'first MI', 'subsequent MI in first year', 'stroke/history CHD', 'CHD death' and 'CVD death/history CHD'. Outcomes are predicted for untreated and for treated cohorts for various ages and for males and females separately. Model outputs for stable angina, unstable angina and MI represent the total number of persons in the health state of interest. In epidemiological terms, this corresponds to the prevalence for these health states. On

prevalence of stable angina, unstable angina, myocardial infarction

incidence of fatal events

the contrary, fatal events are predicted as new events occurring, thus indicating incidence.

first: calculation of age and gender specific model outputs for year 1 to 12

For each year of age as well as for males and females the model results for the first 12 years with and without statin treatment were used for further calculations: The age and gender specific results from the model were multiplied by the probabilities of being in the various ages (these have been obtained by gamma-distribution as explained in chapter 4.7.2). This yielded the Austrian age and gender specific probabilities for each health states of interest and the probabilities of experiencing a fatal event.

second: calculation of CVD prevalence and occurrence of fatal events per person + half-cycle correction

Next, for each health state and fatal event the prevalence or events per person for the years 1 to 12 was calculated by aggregating the corresponding results from each year of age (described in the previous paragraph). The results of this calculation – adjusted by half-cycle correction – represent the total prevalence for the health states and the occurrence of events per persons for 11 years (1997 to 2007).

third: multiplying the results per person with annual cohorts

In the following step, the number of persons in each year's Austrian cohort was multiplied by the prevalence and fatal events per person. The cohort from 1996 can benefit from treatment for 11 years while the cohort starting in 2006 can only benefit from one year of treatment. In other words, for each cohort, outcomes were taken into account from the subsequent years onwards (for example, for the 1996-cohort outcomes from 1997 to 2007 were illustrated).

fourth: summarising the results for each health state and year

Finally, the total number of persons in each health state of interest and the total number of events were summarised for each year. Total health gains were estimated by calculating the differences in outcomes between the treated and the untreated group.

additionally: calculation of fatal MIs and revascularisations

Besides the health states and fatal events mentioned, some additional outcome parameters not directly predicted by the model are relevant. These are 'fatal MI' and 'revascularisation interventions'.

MI based on gender specific MI proportion in Austria

The number of fatal MIs was calculated by applying the gender specific proportions of fatal MIs from all CHD deaths in Austria. The figures used were based on mortality data from Statistik Austria showing that from all CHD deaths in Austria between 1995 and 2007 MIs accounted on average for 45 %. This corresponds to 53 % and 39 % in males and females respectively [39].

revascularisation based on utilisation patterns (expert info)

The calculation of the number of revascularisation interventions was based on the revascularisation intervention patterns in Austria according to secondary data and expert information. Table 4.9-1 shows the parameter values used to calculate the number of PCIs and CABGs in patients with stable angina, unstable angina or MI.

Table 4.9-1: Revascularisation interventions in Austria

	Interventions post event	
State	**PCI in %**	**CABG in %**
(first) MI*	33	18
SA**	7	3.5
USA***	65	15
post MI #	0	0
post SA##	7.5	7.5
post USA ###	8	2
subs MI 1st year §	30	21

Source: secondary literature; expert interviews

** 33 % receive PCI within 6 months [40]; later on no further PCI; within 8 months 17 % of patients received CABG in Austria [40]; overall no more than 20 % of patients receive CABG within year 1 -> for model: estimation that 18 % receive CABG in year 1*

*** Within 4 weeks of SA diagnosis 8 % have PCI and 8 % have CABG planned or performed [41]; in total no more than 10 % receive PCI and max. 5 % receive CABG in year 1 -> for model: estimation that 7 % receive PCI and 3.5 % receive CABG in year 1*

**** 80 % receive revascularisation; from those 80 % receive PCI and 20 % CABG*

 # no further PCI is performed and CABG is almost negligible (= 1 in 1000);

5 to 10 % receive revascularisation in year 2 -> estimation in model: 7.5 % receive PCI and 7.5 % receive CABG in year 2

all of those remaining (if technically possible) receive revascularisation procedure (10 % remain without revasc.)

§ compared to first MI slightly fewer PCI and slightly more CABGs

4.10 Model Validation

internal, technical and external validation

Extensive model validation had already been carried out for the original model. Thus, it is assumed that the model is valid with respect to technical and internal validity. For external validation model results were contrasted with epidemiological data. As this issue has been addressed as a separate research question in a subsequent project, the results have been presented in the corresponding report [42].

4.11 Sensitivity Analysis

sensitivity analysis in original model:

In the original model, extensive sensitivity analyses had been performed to account for uncertainty. Both one-way (varying each parameter one at a time) and probabilistic sensitivity analyses were performed. In detail, for secondary prevention, the influence of statin costs, health state costs, discount rate, utilities, relative risks of statin treatment, compliance (defined as the extent to which the medication is taken each day as prescribed), incidence/prevalence of CVD and timeframe of the model on the cost-effectiveness results have been tested.

statin costs, discount rate and model timeframe had greatest influcence

The results showed that statin costs, discount rate and the model timeframe had the biggest influence on the results: Higher statin costs, a higher discount rate and a shorter model timeframe increased the cost-utility ratios noticeably, while the model was robust to changes in relative risks, cost of health states, health state utilities and assumptions on incidence, prevalence and compliance [14].

sensitivity analysis in adapted model:

On the basis of these results the following univariate sensitivity analyses were performed for the 'Austrian model':

influence of health state costs, statin costs, discount rates and compliance on cost-utility,

Firstly, the influence of health state costs, statin costs, discount rates and compliance on the cost-utility ratios were tested because these have either been changed in the Austrian model or/and have shown to have a significant influence in the British model. The model time-frame, which has also proven to have considerable bearing on the results in the ScHARR model, has been addressed as a separate research question and therefore has been presented under the base case results in chapter 5.4.

effect of compliance on cohort size and health gains,

The effect of compliance was tested in further analyses: First, since reduced compliance (in the form of not picking up prescriptions) may mean that more patients would have been able to receive statins from the overall number of prescribed statins, the impact of compliance on cohort size was analysed. Based on data on total prescribed doses of statins, the number of persons who would have been able to take statins was calculated assuming different compliance scenarios according to the evidence from the UK [14] (see chapter 5.5). Second, how this impacts on the results in terms of population health gains has been evaluated.

effect of gender and age of statin takers on cohort size and health gains

Finally, the applied age and gender distribution of Austrian statin patients was varied to assess its effects on the results in terms of cohort size and population health gains. The distribution was varied according to the age and gender distribution in hospital discharge data for myocardial infarction because these are considered to be representative for persons who take statins.

4.12 Software

software: ECXEL

The original model has been calculated with Microsoft EXCEL. This software has also been used for the adapted version.

5 Results

5.1 Cohort Size

Table 5.1-1 shows the results from the cohort size calculation as described in chapter 4.8. Column two represents the total number of daily doses based on prescribed statins and defined daily doses. The figure rises from 13 million to around 171 million daily doses in 2006.

overall daily doses increased from 13 to 171 million

Column three shows the total number of patients when all take statins regularly throughout a year. Hence around 35,600 patients started taking statins in 1996. In 2006, the total number of patients would have increased more than tenfold to around 468,000. Column four shows the number of new patients per year taking statins which rose from 35,600 to 74,700.

annual patients (unadjusted) rose from 35,000 to 74,700

In column five, the amount of new patients per year have been adjusted to reflect mortality meaning that annual cohorts are in fact slightly greater in number. According to the base case calculation, 36,300 persons started taking statins in 1996. In 2006, there were almost three times more persons (108,000) starting statin therapy. Overall, there would have been almost 600,000 persons who had taken statins between 1996 and 2006 including those who died. This corresponds to around 7.5 % of the Austrian population.

mortality adjusted number rose from 36,300 to 108,000

in total: ~ 600,000 over 11 years

Table 5.1-1: Cohort size

Year	Total DD for all types of statins	cohort size cumulated (total DD/365)	new patients per year	new patients per year mortality adjusted	mortality adjusted cohort size cumulated
1996	13,008,421	35,640	35,640	36,257	36,257
1997	20,511,480	56,196	20,556	22,035	58,293
1998	34,051,918	93,293	37,097	39,799	98,092
1999	49,334,692	135,164	41,871	46,571	144,663
2000	61,699,193	169,039	33,875	40,166	184,829
2001	73,682,604	201,870	32,831	40,559	225,388
2002	88,031,836	241,183	39,313	49,445	274,834
2003	109,392,667	299,706	58,523	73,301	348,135
2004	126,826,414	347,470	47,764	66,767	414,901
2005	143,489,059	393,121	45,651	67,522	482,424
2006	170,753,792	467,819	74,698	108,024	590,448

Source: Social insurance data, own calculations; DD: daily dose

5.2 Effectiveness of Statin Therapy

5.2.1 Expected Health Gains for Austrian Patients from 1997 to 2007

Prevalence of Angina, MI and Stroke

prevalence of angina, MI and stroke:

Table 5.2-1 compares statin treatment with no statin treatment for the health states stable angina, MI and stroke showing the absolute annual amount of persons for each. Health gains are displayed as absolute differences between the untreated and treated population.

more cases of stable angina in statin group

In terms of stable angina, the model actually predicts an increase for the statin group. This is because patients who do not take statins progress more quickly to more severe health states.

USA 2007: minus 175 cases in 108,000 statin takers

Furthermore, the model estimates that in the 36,000 persons who took statins in 1996, 52 cases of unstable angina occurred in 1997 compared with 64 cases if these persons had not taken statins. Hence, there were 11 fewer cases of experienced unstable angina in 1997. The health gains from taking statins continuously increased resulting in minus 175 fewer cases in 2007 in around 108,000 patients who took statins in 2006.

MI 2007: minus 5,200 cases in 108,000 statin takers

7,100 MIs still occurring in 2007

In terms of MI, in the 36,000 persons who took statins in the first year, 755 cases of MI occurred in 1997 compared with 1,354 if these persons had not taken statins. Consequently, there were 599 fewer cases of MI due to statins in 1997. In 2007, 5,234 fewer MIs occurred as the amount of persons using statins increased. However, the model also predicted that despite taking statins, around 7,100 MIs in 108,000 statin takers occurred in 2007.

strokes 2007: minus 240 cases

Finally, whereas the model predicted for 1997 that 56 cases of stroke occured in patients with a history of CHD without statins, it foresaw 39 stroke cases for those on statins. Thus, strokes were reduced by 17 in the first-year cohort. In 2007, statin treatment resulted in 239 fewer strokes in patients with a history of CHD. Yet, around 490 strokes were estimated despite taking statins compared to 725 strokes in the untreated cohort in 2007.

overall: 28,600 fewer CVD cases in 600,000 statin takers in 11 years

number needed to treat: 21

Overall, by 2006, around 600,000 persons were estimated to have taken statins over 11 years. In these, 28,600 fewer cases of unstable angina (860), MI (26,600) or stroke (1,100) and roughly 6,100 more cases of stable angina occurred. In other words, 21 persons had to be treated with statins in order to avoid or postpone one patient going into a CVD health state. At the same time, about 42,000 cases of unstable angina (4,400), MI (35,200) or stroke (2,300) occurred despite statins.

Table 5.2-1: Absolute number of cases in different health states in 'Statin' and 'NoStatin' group

Year	SA untreated	SA treated	Health gains	USA untreated	USA treated	Health gains	MI untreated	MI treated	Health gains	Stroke untreated	Stroke treated	Health gains
1997	15923	16306	107	64	52	-11	1354	755	-599	56	39	-17
1998	25525	25890	243	104	86	-18	1531	843	-688	69	47	-23
1999	42395	43251	476	176	146	-31	2560	1428	-1132	118	80	-38
2000	61954	63274	807	262	217	-45	3540	1979	-1560	169	114	-55
2001	78393	79959	1211	338	281	-57	4126	2320	-1805	207	139	-68
2002	94385	96399	1694	416	347	-69	4620	2604	-2016	253	170	-83
2003	113551	116395	2280	510	426	-84	5834	3325	-2509	316	212	-104
2004	142123	146584	3029	647	541	-106	7573	4322	-3250	413	278	-136
2005	167922	173064	3896	774	649	-125	8615	4933	-3681	489	328	-162
2006	193154	199230	4893	904	760	-144	9747	5615	-4132	574	384	-190
2007	232053	242723	6115	1105	930	-175	12359	7125	-5234	725	487	-239

MI: myocardial infarction; SA: stable angina; USA: unstable angina;

Figure 5.2-1 shows the changes in the health states of interest graphically.

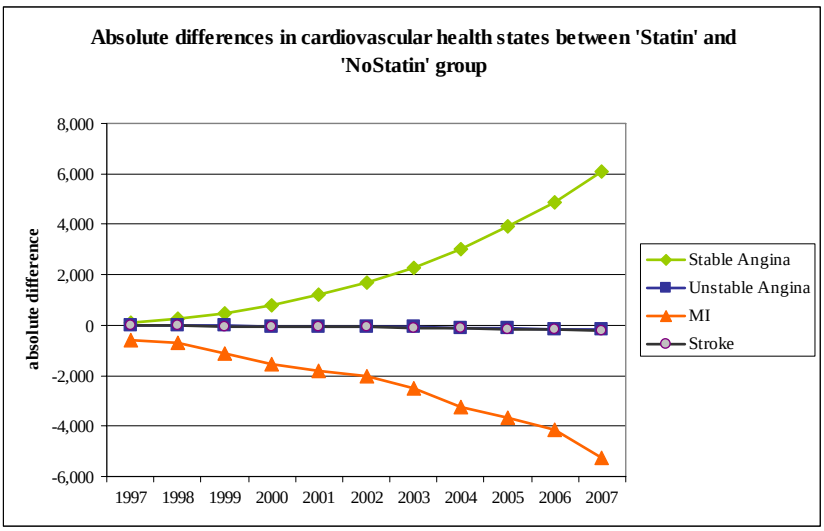

Figure 5.2-1: Differences in cardiovascular health states between 'Statin' and 'NoStatin' group (absolute numbers)

MI: myocardial infarction

As shown in Figure 5.2-2, more health gains are observable in men than in women. The gender difference is largest with respect to the number of persons experiencing an MI.

more health gains in males than in females

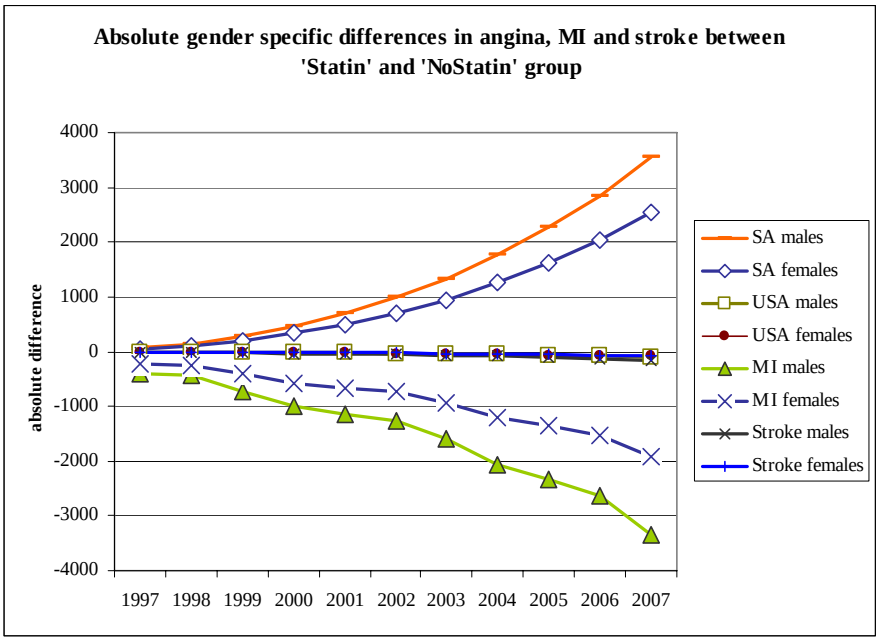

Figure 5.2-2: Gender specific differences for angina, MI and stroke between 'Statin' and 'NoStatin' group (absolute numbers)

MI: myocardial infarction; SA: stable angina; USA: unstable angina

Fatal Events

fatal CVD events:

Table 5.2-2 shows the absolute number of fatal events for the two treatment alternatives according to the model results. While the model demonstrates that 763 patients from around 36,000 would have died of CHD without statin treatment in 1997, treatment reduced fatal CHD events to 539 which corresponds to 224 fewer CHD deaths. Furthermore, the model shows that in 2007, comparing those on no medication to the 108,000 estimated statin takers, 2,061 fewer persons died of CHD. However, around 4,900 died of CHD despite taking statins.

2007: minus 2,700 fatal CHDs in 108,000 statin patients

fatal MI 2007: minus 980

From all CHD deaths avoided or postponed, 107 and 982 are related to fatal MI in 1997 and 2007 respectively.

cerebrovascular death: almost no benefit

Furthermore, the model shows that health gains with respect to fatal cerebrovascular diseases for patients with a history of CHD are considerably lower than for fatal CHD. In the first year of observation, almost no difference between taking statins and not taking statins can be observed. In 2007, 26 fewer patients died in the statin group.

in total: 10,300 fewer fatal events

number needed to treat: 59

Overall, by 2007, a total number of around 600,000 patients who were estimated to have taken statins between 1996 and 2006 can be weighed against 10,300 avoided/postponed fatal CVD events. Put differently, 59 persons had to take statins between 1996 and 2006 in order to avoid or delay one fatal CVD event. Despite statin treatment 24,000 fatal CHDs and 1,400 fatal cerebrovascular events occurred.

Table 5.2-2: Absolute number of fatal events in treated and untreated population

Year	CHD death untreated	CHD death treated	Health gains	cerebrov. death untreat.	cerebrov. death treated	Health gains	fatal MI untreated	fatal MI treated	Health gains
1997	763	539	-224	33	32	-1	365	258	-107
1998	805	560	-246	35	33	-2	385	268	-118
1999	1375	963	-412	59	56	-3	657	460	-197
2000	1893	1324	-569	82	77	-5	905	633	-272
2001	2197	1534	-662	96	89	-7	1050	733	-316
2002	2589	1812	-778	114	106	-8	1236	865	-371
2003	3175	2225	-950	142	131	-11	1516	1063	-453
2004	4167	2924	-1243	187	173	-14	1989	1396	-592
2005	4747	3328	-1419	216	199	-17	2265	1588	-676
2006	5422	3806	-1616	250	229	-21	2585	1816	-769
2007	6947	4886	-2061	321	295	-26	3312	2330	-982

CHD: coronary heart disease; cerebrov. death: cerebrovascular death; MI: myocardial infarction; untreat.: untreated

Figure 5.2-3 presents the reduction in fatal events graphically.

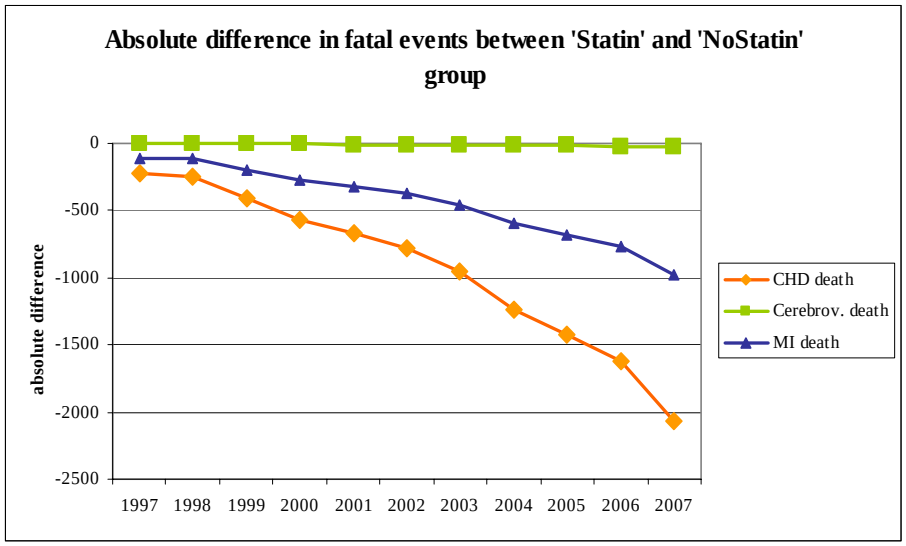

Figure 5.2-3: Difference in fatal events between 'Statin' and 'NoStatin' group (absolute numbers)

CHD: coronary heart disease; cerebrov. death: cerebrovascular death; MI: myocardial infarction

fewer fatal events in males than in females

Similar to the numbers of angina, MI and stroke more fatal events are avoided in men than in women (Figure 5.2-4).

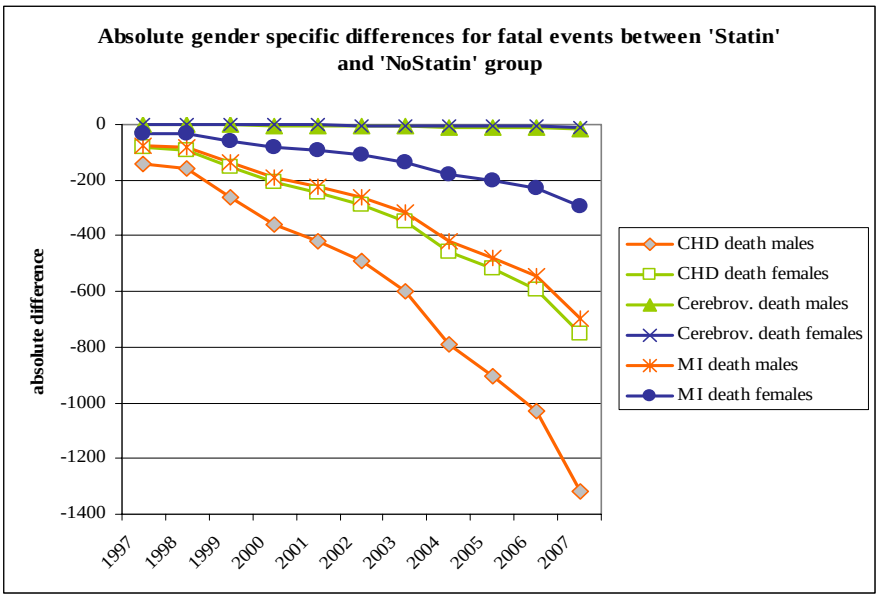

Figure 5.2-4: Gender specific differences in fatal events between 'Statin' and 'NoStatin' group (absolute numbers)

CHD: coronary heart disease; Cerebrov. death: cerebrovascular death; MI: myocardial infarction

Revascularisation

reduction of revascularisation expected…

Since revascularisation procedures are closely linked to the diagnosis of angina or MI, reduced occurrence of these types of coronary heart disease will probably result in reduced numbers of revascularisation procedures.

…and shown in model, however…

As Table 5.2-3 demonstrates, health gains obtained from statins result in a reduction of both, PCI as well as CABG in the model. Compared to 'no statin' in 'statin takers' 162 fewer PCIs and 110 fewer CABGs were performed in 1997. In 2007, 632 PCIs and 447 CABGs were avoided according to the base case analysis in the model. However, despite statins, the performance of 1,800 PCIs and 1,500 CABGS was estimated for 1997 and delivery of 25,750 PCIs as well as 20,200 CABGs was predicted for 2007.

overall reduction in revascularisation interventions low

The number of revascularisation interventions avoided is low compared to health gains in MI described earlier. However, since the number of stable angina increases and revascularisation interventions are also provided for people with stable angina the overall reduction in revascularisation interventions is predicted to be low in the model.

86 patients to be treated to avoid one revascularisation intervention

Overall, by 2007, a total number of around 600,000 patients who were estimated to have taken statins between 1996 and 2006 can be weighed against around 7,000 revascularisation interventions avoided corresponding to treating 86 patients in order to avoid one revascularisation intervention. 231,000 revascularisation interventions were carried out in spite of statin treatment in the same time period.

Table 5.2-3: Absolute number of revascularisation interventions in treated and untreated population

Year	PCI untreated	PCI treated	Health gains	CABG untreated	CABG treated	Health gains
1997	1992	1830	-162	1578	1469	-110
1998	2959	2794	-165	2368	2255	-112
1999	4929	4669	-260	3948	3771	-177
2000	7124	6790	-334	5719	5491	-228
2001	8857	8515	-342	7133	6897	-236
2002	10582	10231	-350	8541	8297	-244
2003	12735	12349	-387	10290	10020	-271
2004	16079	15585	-495	12991	12644	-346
2005	18826	18332	-494	15235	14887	-348
2006	21545	21064	-482	17460	17118	-342
2007	26374	25742	-632	21360	20913	-447

CABG: coronary artery bypass grafting; PCI: percutaneous coronary intervention

The reduction is also demonstrated in Figure 5.2-5

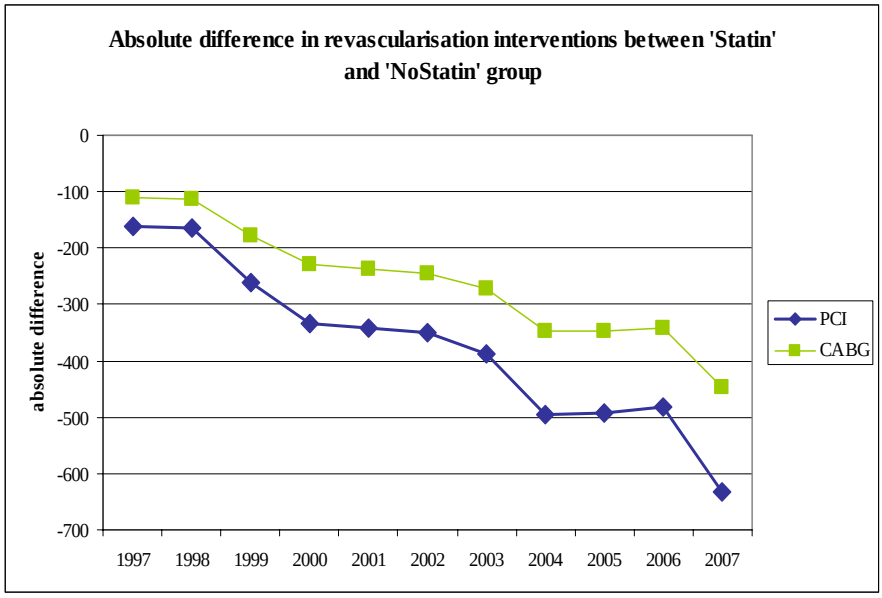

Figure 5.2-5: Difference in revascularisation interventions between 'Statin' and 'NoStatin' group (absolute numbers)

CABG: coronary artery bypass grafting; PCI: percutaneous coronary intervention

reduction of interventions higher in males than in females

Figure 5.2-6 demonstrates the reduction in revascularisation interventions for males and females. Again, a higher number of interventions are avoided in males than in females.

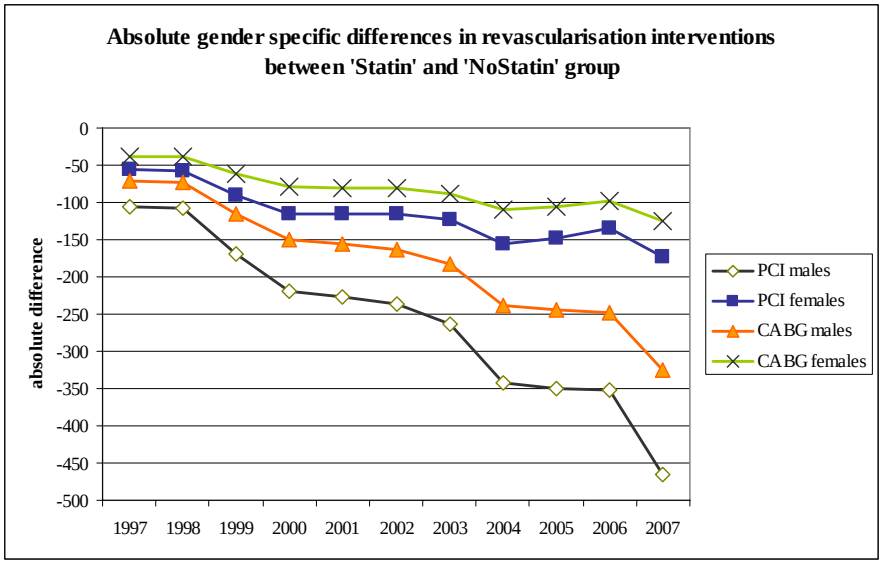

Figure 5.2-6: Gender specific differences in revascularisation interventions between 'Statin' and 'NoStatin' group (absolute numbers)

CABG: coronary artery bypass grafting; PCI: percutaneous coronary intervention

5.2.2 Life-time Effectiveness

QALYs for life-time effectiveness

In addition to the 11-year health gains in terms of population health, life-time effectiveness of statin therapy in terms of QALYs has been calculated. In contrast to the previous results, gains in QALYs are presented in the form of individual averages per person included. This enables better comparison with international results.

average quality adjusted life months gained per person (undiscounted): 3.2 to 13.6 (males); 3.7 to 15.8 (females)

Table 5.2-4 and Table 5.2-5 show the discounted and undiscounted life-time effectiveness in terms of QALYs per person for different ages. Compared to not taking statins, the gain in QALYs for the statin cohort in the model is highest for the youngest age groups and decreases with increasing age. The average gain in undiscounted QALYs for male statin taker is 1.13 (13.6 quality adjusted life months) per person at the age of 45. Undiscounted QALYs gained per male person decrease to 0.27 (3.2 quality adjusted life months) at the age of 85. Females gain on average 1.32 undiscounted QALYs (15.8 quality adjusted life months) per person at the age of 45 and 0.31 QALYs (3.7 quality adjusted life months) at the age of 85.

Table 5.2-4: Life-time quality adjusted life years gained per person in different ages (undiscounted)

Gender	Age	QALYs NoStatin/person	QALYs Statin/person	Incremtenal QALYs/person
Male	45	19.34	20.48	1.13
	55	13.87	14.79	0.92
	65	8.98	9.70	0.72
	75	5.29	5.76	0.47
	85	2.63	2.90	0.27
Female	45	21.80	23.11	1.32
	55	16.12	17.22	1.10
	65	10.43	11.34	0.92
	75	6.36	6.95	0.58
	85	3.18	3.49	0.31

NoStatin: no statin therapy; Statin: statin therapy; QALYs: quality adjusted life years

discounted quality adjusted life months: 2.51 to 4.07 (males); 2.35 to 4.19 (females)

As expected, QALY values are lower when discounting is applied (table 5.2-5). They range from 0.37 incremental discounted QALYs in males aged 65 to 0.21 incremental discounted QALYs in men aged 85 (4.07 to 2.51 quality adjusted life months). In females, the values range from 0.44 incremental discounted QALYs in 65 years old women to 0.20 incremental discounted QALYs in 85 years old (4.19 to 2.35 quality adjusted life months).

Table 5.2-5: Life-time quality adjusted life years per person in different ages (discounted at 5 %)

Gender	Age	QALYs NoStatin/person	QALYs Statin/person	Incremtenal QALYs/person
Male	45	10.20	10.54	0.34
	55	8.30	8.66	0.36
	65	6.12	6.49	0.37
	75	4.07	4.37	0.31
	85	2.25	2.46	0.21
Female	45	10.88	11.23	0.35
	55	9.15	9.53	0.39
	65	6.81	7.25	0.44
	75	4.18	4.47	0.29
	85	2.34	2.53	0.20

NoStatin: no statin therapy; Statin: statin therapy; QALYs: quality adjusted life years

5.3 Costs of Statin Therapy

2 different types of cost calculation

As described in chapter 4.7.5, two different types of cost calculations have been undertaken: First, the budget impact over time for the Austrian statin population (in comparison to the 'NoStatin' group) has been assessed (see 5.3.1). Second, in order to calculate cost-utility ratios, life-time absolute and incremental costs (discounted and undiscounted) per person for the statin and the 'NoStatin' group have been computed (see 5.3.2).

5.3.1 Population Costs (Budet Impact)

statin treatment results in health gains but…

…costs can´t be compensated by saving costs elsewhere

Although it has been shown in chapter 5.2.1 that statin treatment seems to results in some health gains (especially in the case of MIs and CHD death), overall costs are higher in the statin group than in the 'NoStatin' group. Hence, additional costs from statin treatment cannot be totally compensated by cost savings elsewhere.

increasing cohorts cause increasing costs

Figure 5.3-1 shows that the total net costs in the treated cohort have risen from 33 million Euros in 1996 to around 680 million Euros in 2007. If the same cohort had been untreated, costs would have been 16 million Euros in 1996 and roughly 470 million Euros in 2006. The reason for the overall cost increases is the annual growth cohort size.

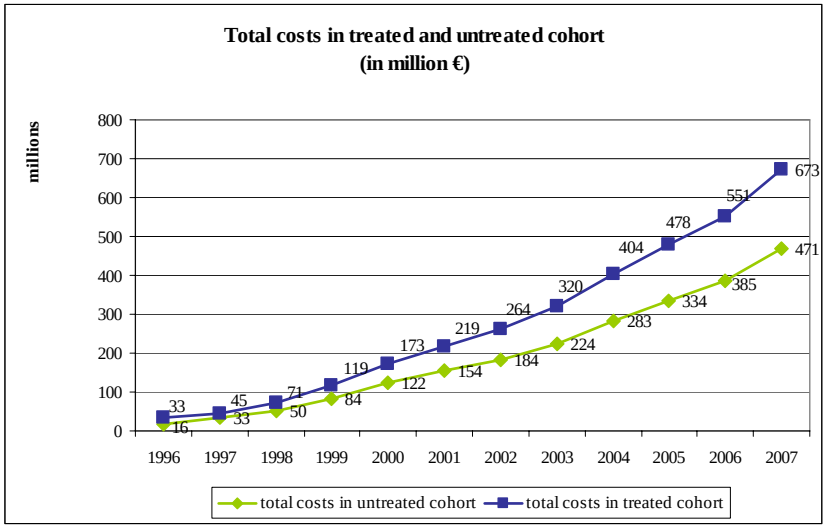

Figure 5.3-1: Total costs in treated and untreated cohort (in million €)

disaggregated costs for treated cohort:

Figure 5.3-2 shows the estimated net costs for the treated cohort disaggregated into costs for statins and net costs for treating the various CVD conditions. The third category shows the potential cost containment for each year in terms of health state costs.

1996: 17 million € statin costs + 33 million € health state costs

2007: 76 million € statin costs + 600 million € health state costs, 105 million € savings

From total net costs of 33 million Euros in 1996, 17 million Euros were related to statins and 16 million Euros to costs for treating the CVD health states under evaluation. Potential cost-containment is shown to have begun in 1997, when reduced cardiovascular events resulted in cost reduction of 8 million Euros. Total net costs rose to 673 million Euros in 2007 from which 76 million Euros were related to statin treatment and 597 million Euros to health state costs. Potential cost containment is estimated to have been 105 million Euros by then.

savings are partly consumed by increasing demand elsewhere

In comparison to total net costs, cost containment seems comparably low. However, as shown in chapter 5.2.1, for some health conditions, the number of cases is actually increasing and therefore consuming some of the savings made elsewhere. Furthermore, as mentioned, several persons are taking statins in order to gain the benefit of one event avoided, leaving less room for cost containment.

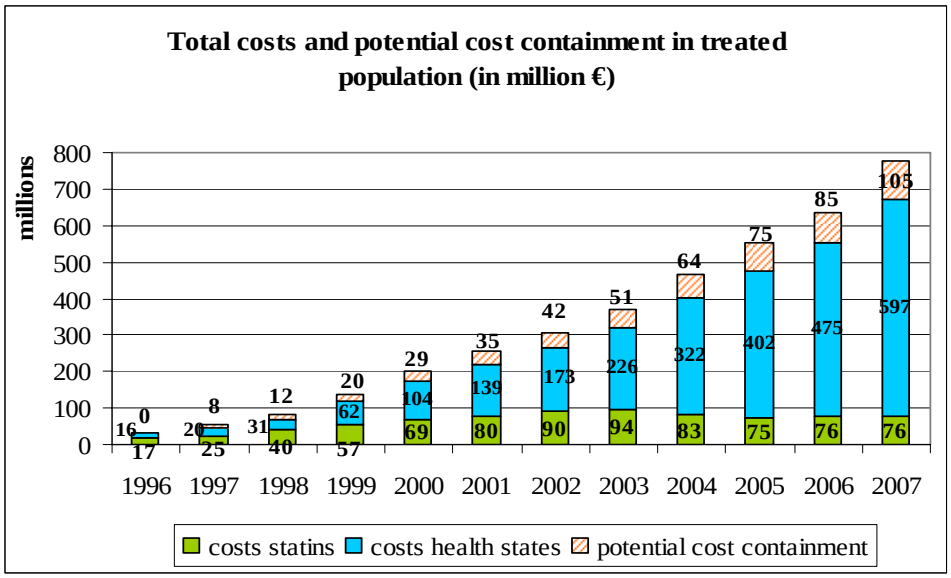

Figure 5.3-2: Total costs and potential cost containment in treated population

5.3.2 Lifetime Costs for Cost-Utility Analysis

Table 5.3-1 and Table 5.3-2 show the undiscounted and discounted costs per person for the statin group compared to the 'NoStatin' group. Undiscounted incremental costs are highest in the youngest age group of 45 accounting for 16,700 Euros and 18,200 Euros for males and females respectively. They decrease to 2,900 Euros in 85 year old males and to 3,200 Euros in 85 year old females.

undiscounted lifetime costs: males: 2.900 to 16.700 €; females: 3.200 to 18.200 €

Table 5.3-1: Lifetime costs per person undiscounted (in €)

Gender	Age	Costs No Statin	Costs Statin	Incremental costs
Male	45	30,148	46,827	16,679
	55	22,990	35,138	12,148
	65	16,694	25,227	8,532
	75	11,403	16,749	5,346
	85	7,236	10,130	2,895
Female	45	33,472	51,692	18,220
	55	26,117	39,646	13,529
	65	19,140	28,989	9,848
	75	13,038	19,152	6,114
	85	7,946	11,192	3,246

NoStatin: no statin therapy; Statin: statin therapy;

The same pattern relates to discounted costs. Incremental discounted costs are 7,900 Euros for males aged 45 and 2,400 Euros for males aged 85. The corresponding figures for females are 8,000 Euros and 2,500 Euros respectively.

discounted lifetime costs: lower but same pattern

Table 5.3-2: Lifetime costs per person discounted at 5 % (in €)

Gender	Age	Costs No Statin	Costs Statin	Incremental costs
Male	45	15,662	23,539	7,877
	55	13,673	20,281	6,608
	65	11,455	16,815	5,360
	75	8,931	12,795	3,864
	85	6,355	8,731	2,376
Female	45	16,105	24,161	8,056
	55	14,418	21,312	6,894
	65	12,458	18,317	5,859
	75	8,942	12,886	3,944
	85	6,287	8,732	2,445

NoStatin: no statin therapy; Statin: statin therapy;

5.4 Cost-Utility Analysis

Table 5.4-1 shows the costs, QALYs and cost-utility results for the base case analysis discounted at a rate of 5 % for different ages and gender. Results are presented as averages per person.

discounted costs:

males: 2,400 to 7,900 €
females: 2,500 to 8,000 €

As shown in chapter 5.3.2, in comparison with no statin therapy, statin therapy results in discounted incremental costs between 2,400 Euros and 7,800 Euros for males and between 2,500 Euros and 8,000 Euros for females. Incremental costs decrease with age in both males and females.

discounted QALYs:
males: 0.21 to 0.37
females: 0.20 to 0.44

Additionally, it was demonstrated in chapter 5.2.2 that average discounted QALYs gained per person due to statins compared with 'NoStatin' range from 0.21 to 0.37 (2.51 to 4.07 quality adjusted life months) in males and from 0.20 to 0.44 (2.35 to 4.19 quality adjusted life months) in females.

ICUR: males: 11,400 to 23,200 €/QALY

females: 12,500 to 23,000 €/QALY

Discounted incremental cost-utility-ratios (ICUR) range from around 11,400 Euros per QALY to 23,200 Euros per QALY for males and from 12,500 Euros per QALY to 23,000 Euros per QALY for females. ICURs decrease with increasing age. In other words, depending on the age of the patients, between 11,400 Euros and 23,200 Euros are required to gain one extra QALY with statin therapy.

Table 5.4-1: Base case analysis: discounted incremental costs, QALYs and ICUR per person (discount rate: 5 %) for different ages and gender

Gender	Age	Incremental costs	Incremtenal QALYs	ICUR
Male	45	7,877	0.34	23,217
	55	6,608	0.36	18,228
	65	5,360	0.37	14,400
	75	3,864	0.31	12,633
	85	2,376	0.21	11,366
Female	45	8,056	0.35	23,057
	55	6,894	0.39	17,800
	65	5,859	0.44	13,311
	75	3,944	0.29	13,803
	85	2,445	0.20	12,508

ICUR: incremental cost-utility ratio; NoStatin: no statin therapy; Statin: statin therapy; QALYs: quality adjusted life years;

much higher ICURs for 10-year time horizon

The results differ considerably when a 10-year time horizon is considered. While in 85-years-olds, ICURs are similar to the base case analysis, Table 5.4-2 shows that ICURs are rising significantly in the younger age groups for which 65,600 Euros have to be paid per extra QALY gained in males aged 45 and 74,000 Euros per extra QALY gained in females aged 45. This is around three times more than in the base case.

Table 5.4-2: 10-year time horizon analysis: discounted incremental costs, QALYs and ICUR per person (discount rate: 5 %) for different ages and gender

Gender	Age	Incremental costs	Incremtenal QALYs	ICUR
Male	45	3,867	0.06	65,578
	55	3,621	0.09	40,464
	65	3,408	0.15	23,132
	75	2,983	0.19	15,664
	85	2,207	0.18	11,931
Female	45	3,777	0.05	73,903
	55	3,535	0.07	47,309
	65	3,443	0.15	23,120
	75	3,029	0.19	15,684
	85	2,266	0.17	13,180

ICUR: incremental cost-utility ratio; NoStatin: no statin therapy; Statin: statin therapy; QALYs: quality adjusted life years;

5.5 Sensitivity Analysis

sensitivity analysis tested health state and statin costs, discount rate + compliance

As has been mentioned in chapter 4.11, first, the influence of health state costs, statin costs, discount rates and compliance on the cost-utility ratios were tested. These had either been changed in the Austrian model or/and had shown a significant influence in the British model. The results of the one-way sensitivity analysis are presented in Table 5.5-1.

biggest influence: statin costs and discount rate

Similar to the British model, increasing or reducing health state costs by 20 % had only a marginal influence on the ICURs. The influence is bigger when statin costs are decreased, especially in the younger ages and at a reduction of 40 %. In both cases ICUR decreases by around 30 %, thus becoming more favourable. As expected, discounting has also a considerable influence. Particularly in the younger age groups, lower discount rates result in lower ICURs of up to minus 40 % because of the longer time period these persons take statins.

compliance: higher ICUR in lower age groups

Finally, the influence of compliance on the ICUR is tested. The UK analysis has shown that when lower rates of compliance are accompanied by lower costs of treatment with patients failing to pick up their prescriptions, the impact on cost-effectiveness is limited [14]. Thus, for the Austrian sensitivity analysis the worst case of patients collecting prescriptions but failing to take the medication (thus incurring full costs) is assumed for two different compliance scenarios according to the evidence from the UK-analysis [14] (see Table 5.5-2). Sensitivity analysis shows some impact in the younger age groups. Generally, the lower the compliance the higher are the ICURs with a maximum of plus 48 %.

In summary, even the highest ICURs in sensitivity analyses do not exceed 35,000 Euros per QALY.

Table 5.5-1: Summary of costs per QALY results of the one-way sensitivity analyses

Sensitivity analysis		**Min**	**Max**	**Min**	**Max**
				€/QALY	
	Sex	Male	Male	Female	Female
	Age	85	45	85	45
	Base case	11,366	23,217	12,508	23,057
Health state costs					
	+ 20 %	11,089	23,035	12,212	22,921
	- 20 %	11,644	23,399	12,804	23,193
Statin costs					
	- 20 %	9,726	20,134	10,716	19,884
	- 40 %	8,086	17,051	8,924	16,711
Discounting					
	No discounting	10,755	14,726	11,832	13,830
	Discount rate 1 %	10,878	16,144	11,968	15,302
	Discount rate 3 %	11,123	19,418	12,239	18,814
Compliance					
	Scenario 1	13,829	30,144	15,177	30,006
	Scenario 2	15,020	34,111	16,473	34,023

Table 5.5-2: Compliance in different scenarios

year	Scenario 1 (% compliance)*	Scenario 2 (% compliance)
1	0.90	0.85
2	0.80	0.78
3	0.78	0.70
4	0.75	0.66
5	0.75	0.65
all subsequent years	as year 5	as year 5

**defined as the extent to which the medication is taken each day as prescribed; Source: Ward et al. [14]*

influence of compliance on cohort size and health gains

Second, two further factors of compliance are reviewed – the influence of compliance on cohort size and how this effects results in terms of population health. The compliance scenarios chosen are the same as described above (Table 5.5-2).

Based on the compliance rates in scenarios 1 and 2, cohort sizes have been adjusted resulting in the following mortality adjusted numbers of annual statin patients (Table 5.5-3).

Table 5.5-3: Cohort sizes according to different compliance scenarios

Year	Total DD/365	Cohort size base case	Cohort size scenario 1	Cohort size scenario 2
1996	35,640	36,257	38,101	39,097
1997	56,196	22,035	27,113	28,367
1998	93,293	39,799	46,994	48,321
1999	135,164	46,571	56,446	60,679
2000	169,039	40,166	52,263	57,183
2001	201,870	40,559	53,211	59,356
2002	241,183	49,445	62,880	70,060
2003	299,706	73,301	88,859	97,152
2004	347,470	66,767	84,863	93,941
2005	393,121	67,522	87,295	97,345
2006	467,819	108,024	125,655	137,649

cohort size increases with decreasing compliance by 5 % to 27 %

Annual mortality adjusted cohort sizes increase with decreasing compliance rates. In Scenario 1, cohort size rises from around 38,100 persons in 1996 to 125,700 in 2006. This corresponds to an increase of 5 % and 16 % respectively compared to the basecase. In scenario 2, the first cohort comprises roughly 39,100 persons while the 2006 cohort consists of 137,600 persons representing an increase of 7 % and 27 % respectively compared to the basecase.

higher number of statin takers is partly counterbalanced by lower effectiveness, yet…

With respect to cardiovascular health states of unstable angina, MI and stroke, model outcomes show that although more patients are taking statins overall and could therefore benefit from the treatment, the bearing on health gains is partly counterbalanced by lower effectiveness of the medication when people stop taking statins over time. The lower the compliance rates, the lower are the health gains (see Table 5.5-4, Table 5.5-5, Table 5.5-6).

…more health gains in MI…

Yet, while the effect on unstable angina and stroke is minor, a significant impact is related to MI health gains (Table 5.5-5), where compliance scenarios 1 and 2 result in around 200 and 300 fewer MIs avoided respectively.

Table 5.5-4: Impact on unstable angina health gains in different compliance scenarios (absolute numbers)

Year	Health gains USA base case	scenario 1	Diff.	scenario 2	Diff.
1997	11	10	-1	10	-2
1998	18	16	-2	16	-2
1999	31	28	-3	26	-4
2000	45	41	-4	39	-6
2001	57	53	-4	51	-7
2002	69	65	-4	62	-7
2003	84	79	-5	76	-8
2004	106	100	-6	95	-10
2005	125	118	-7	113	-12
2006	144	136	-8	131	-13
2007	175	164	-11	157	-17

Diff: difference; USA: unstable angina

Table 5.5-5: Impact on myocardial infarction health gains in different compliance scenarios (absolute numbers)

Year	Health gains MI base case	scenario 1	Diff.	scenario 2	Diff.
1997	599	552	-47	533	-66
1998	688	666	-23	648	-41
1999	1132	1097	-36	1046	-86
2000	1560	1520	-41	1474	-86
2001	1805	1783	-22	1735	-71
2002	2016	2005	-11	1964	-53
2003	2509	2477	-32	2422	-87
2004	3250	3183	-67	3111	-139
2005	3681	3619	-62	3541	-140
2006	4132	4072	-61	3984	-149
2007	5234	5044	-190	4932	-302

Diff.: difference; MI: myocardial infarction

Table 5.5-6: Impact on stroke health gains in different compliance scenarios (absolute numbers)

Year	Health gains stroke base case	scenario 1	Diff.	scenario 2	Diff.
1997	17	16	-1	15	-2
1998	23	22	-1	21	-2
1999	38	36	-1	34	-3
2000	55	53	-2	51	-4
2001	68	66	-2	64	-4
2002	83	81	-2	78	-5
2003	104	101	-3	97	-7
2004	136	132	-4	126	-9
2005	162	157	-4	151	-11
2006	190	185	-5	177	-12
2007	239	230	-9	220	-19

Diff.: difference

…and fewer fatal CHD events

Additionally, reduced compliance results in fewer fatal events avoided. This is primarily the case for CHD, where in compliance scenario 1 and 2, up to 70 and 130 fewer CHD deaths are avoided respectively (Table 5.5-7). Moreover, the model predicts that compared to the base case, up to 30 and 60 fewer fatal MIs respectively would occur (Table 5.5-9). Yet, with respect to fatal stroke with a history of CHD, the impact from different compliance scenarios is negligible (Table 5.5-8)

Table 5.5-7: Impact on reduced CHD death in different compliance scenarios (absolute numbers)

Year	Health gains CHD death base case	scenario 1	Diff.	screnario 2	Diff.
1997	224	207	-17	198	-26
1998	246	240	-5	232	-14
1999	412	402	-10	381	-31
2000	569	558	-11	538	-31
2001	662	658	-5	636	-26
2002	778	773	-5	749	-28
2003	950	939	-10	912	-38
2004	1243	1219	-23	1182	-61
2005	1419	1398	-21	1356	-62
2006	1616	1594	-22	1546	-69
2007	2061	1991	-70	1929	-132

Diff.: difference; CHD: coronary heart disease

Table 5.5-8: Impact on avoided cerebrovascular deaths with history CHD in different compliance scenarios (absolute numbers)

Year	Health gains cerebrov. death base case	scenario 1	Diff.	scenario 2	Diff.
1997	1	1	0	1	0
1998	2	2	0	2	0
1999	3	3	0	3	0
2000	5	5	0	5	0
2001	7	7	0	6	0
2002	8	8	0	8	0
2003	11	10	0	10	-1
2004	14	13	0	13	-1
2005	17	17	0	16	-1
2006	21	20	-1	19	-2
2007	26	25	-1	23	-3

Cerebrov. death: cerebrovascular death; Diff.: difference

Table 5.5-9: Impact on reduced fatal MI in different compliance scenarios (absolute numbers)

Year	Health gains Fatal MI basecase	scenario 1	Diff.	scenario 2	Diff.
1997	107	99	-8	94	-13
1998	118	115	-3	111	-7
1999	197	192	-5	182	-15
2000	272	267	-5	257	-16
2001	316	314	-2	303	-13
2002	371	369	-2	357	-14
2003	453	448	-5	434	-19
2004	592	581	-11	562	-30
2005	676	666	-10	645	-31
2006	769	759	-10	735	-34
2007	982	948	-33	917	-64

Diff.: difference; MI: myocardial infarction

impact of compliance on revascularisation low

Furthermore, the impact of compliance scenario 1 and 2 on reduced revascularisation interventions is analysed. Model outputs show that the impact is minor. In some years slightly more interventions are avoided in the sensitivity analysis scenarios (especially in the case of CABG) while in some years reduced compliance results in slightly more revascularisation interventions than in the base case (Table 5.5-10).

Table 5.5-10: Impact on revascularisation interventions in different compliance scenarios (absolute numbers)

Year	Reduced interventions PCI base case	scenario 1	Diff.	scenario 2	Diff.	Reduced interventions CABG base case	scenario 1	Diff.	scenario 2	Diff.
1997	162	149	-13	144	-18	110	101	-9	98	-12
1998	165	160	-5	157	-9	112	110	-2	107	-5
1999	260	252	-8	240	-20	177	173	-4	166	-11
2000	334	326	-8	318	-16	228	226	-3	220	-8
2001	342	341	-1	335	-8	236	238	3	234	-1
2002	350	352	2	347	-3	244	249	5	246	3
2003	387	387	1	384	-3	271	276	5	274	4
2004	495	489	-6	483	-11	346	348	1	345	-1
2005	494	493	-1	490	-4	348	354	6	353	6
2006	482	486	4	484	2	342	352	10	353	11
2007	632	606	-26	603	-30	447	437	-10	437	-9

CABG: coronary artery bypass grafting; Diff.: difference; PCI: percutaneous coronary intervention

influence of varied gender and age distribution of statin takers:

Finally, the applied age and gender distribution of Austrian statin patients is varied and the influence on the results in terms of cohort size and population health gains is evaluated. The distribution is changed according to the age and gender distribution in hospital discharge data for myocardial infarction as these can be expected to be representative for persons who take statins.

distribution adjusted to discharge data

In contrast to the base case analysis, an expected value of 75 and a standard deviation of 14 was chosen in the gamma-distribution in the sensitivity analysis as this results in an age distribution which is close to the distribution of discharged patients after an MI. The ratio between males and females was chosen at 62:38, again representing the gender ratio of discharge data.

results: bigger cohorts and…

As presented in Table 5.5-11, after mortality adjustment, the alternative age and gender distribution results in more new patients per year than in the base case. In 1996 there would be about 800 more patients while in 2006 the model predicts around 38,300 more patients. This is because discharge data showed a higher average age of discharged patients than assumed in the base case for statin takers. Thus, mortality is higher in the discharge patients. This affects the mortality adjusted cohort size because more statin patients are expected to die, thus increasing the total number of potential statin taker. Overall, there would be around 740,000 persons who have taken statins for secondary prevention between 1996 and 2006 in contrast to about 600,000 in the base case.

Table 5.5-11: Cohort size after varied gender and age distributioin

Year	Total DD for all types of statins	cohort size cumulated (total DD/365)	new patients per year	new patients per year mortality adjusted **base case**	mortality adjusted cohort size cumulated **base case**	new patients per year mortality adjusted **sensitiv. anal.**	mortality adjusted cohort size cumulated **sensitiv. anal.**
1996	13,008,421	35,640	35,640	36,257	36,257	37,060	37,060
1997	20,511,480	56,196	20,556	22,035	58,293	24,080	61,140
1998	34,051,918	93,293	37,097	39,799	98,092	43,632	104,772
1999	49,334,692	135,164	41,871	46,571	144,663	53,130	157,902
2000	61,699,193	169,039	33,875	40,166	184,829	48,817	206,719
2001	73,682,604	201,870	32,831	40,559	225,388	50,881	257,600
2002	88,031,836	241,183	39,313	49,445	274,834	62,423	320,023
2003	109,392,667	299,706	58,523	73,301	348,135	91,409	411,431
2004	126,826,414	347,470	47,764	66,767	414,901	89,630	501,061
2005	143,489,059	393,121	45,651	67,522	482,424	93,252	594,314
2006	170,753,792	467,819	74,698	108,024	590,448	146,352	740,666

DD: daily dose

…more health gains

Consequently, cohort size has an effect on the outcomes in terms of population health. Table 5.5-12 compares health gains between the statin and 'NoStatin' group in the base case with health gains in sensitivity analysis. It shows that the alternative gender and age distribution of statin patients results in higher health gains when the 'NoStatin' group is compared with the statin group than in the base case. The differences in terms of additional health gains are biggest in the case of MIs where up to 1,200 more MIs are avoided in the sensitivity analysis, followed by additional health gains in stroke prevalence and in unstable angina.

biggest differences for MIs, yet…

…similar number needed to treat

In total, about 740,000 statin taker between 1996 and 2006 can be weighed against around 35,200 fewer cases of unstable angina, MI or stroke between 1997 and 2007. This corresponds to 21 patients taking statins in order to achieve one fewer case of a CVD health state. The number needed to treat is similar to the base case. Hence, while the absolute number of CVD health states is lower in sensitivity analysis than in the base case, the number needed to treat remains unchanged because of the bigger cohort size.

Table 5.5-12: Impact on morbidity health gains from varied gender and age distribution in statin patients (absolute numbers)

Year	USA base case	USA sensit. anal.	Difference	MI base case	MI sensit. anal.	Difference	Stroke base case	Stroke sensit. analy.	Difference
1997	11	16	-5	599	613	-14	17	36	-18
1998	18	25	-7	688	771	-83	23	46	-23
1999	31	42	-11	1132	1268	-136	38	77	-40
2000	45	61	-16	1560	1786	-225	55	111	-57
2001	57	77	-20	1805	2121	-316	68	137	-69
2002	69	93	-24	2016	2393	-377	83	166	-83
2003	84	112	-28	2509	2973	-464	104	205	-101
2004	106	142	-37	3250	3853	-603	136	267	-131
2005	125	169	-44	3681	4471	-790	162	316	-155
2006	144	195	-52	4132	5078	-946	190	368	-178
2007	175	242	-67	5234	6488	-1254	239	469	-231

MI: myocardial infarction; sensit. analy.: sensitivity analysis; USA: unstable angina

fewer fatal events and lower number to treat in sensivitivty analysis

Absolute results are similar for fatal events. The reduction of fatal events is greater when running the model with varied gender and age distribution in sensitivity analysis than in the base case. This is particularly the case for fatal CHD (Table 5-5-13). Overall, about 740,000 statin takers between 1996 and 2006 can be weighed against around 17,500 fewer fatal CVD events between 1997 and 2007, corresponding to a number needed to treat of 42 to avoid one fatal event. This is lower than in the base case suggesting that the increase in mortality health gains is disproportionately higher than the increase in cohort size.

Table 5.5-13: Impact on mortality health gains from varied gender and age distribution in statin patients (absolute numbers)

Year	CHD death base case	CHD death sensit. analy.	Difference	Cerebrov. death base case	Cerebrov. death sensit. analy.	Difference	Fatal MI base case	Fatal MI sensit. analy.	Difference
1997	224	397	-173	1	3	-2	107	191	-84
1998	246	420	-174	2	8	-5	118	202	-84
1999	412	716	-303	3	11	-8	197	343	-146
2000	569	986	-416	5	17	-12	272	472	-200
2001	662	1136	-474	7	23	-16	316	544	-227
2002	778	1322	-544	8	27	-19	371	632	-261
2003	950	1611	-661	11	33	-23	453	770	-317
2004	1243	2129	-887	14	43	-29	592	1018	-426
2005	1419	2432	-1013	17	53	-35	676	1162	-486
2006	1616	2761	-1145	21	62	-41	769	1318	-549
2007	2061	3618	-1557	26	76	-50	982	1728	-747

cerebrov. death: cerebrovascular death; CHD: coronary heart disease; MI: myocardial infarction; sensit. analy.: sensitivity analysis

low influence on revascularisation

On the contrary, in the case of revascularisation interventions, the results are almost the same when comparing base case and sensitivity analysis. Slightly fewer interventions are reduced in the sensitivity analysis compared to the base case (Table 5.5-14).

Table 5.5-14: Impact on revascularisation interventions from varied gender and age distribution in statin patients (absolute numbers)

Year	PCI base case	PCI sensit. analy.	Difference	CABG base case	CABG sensit. analy.	Difference
1997	162	153	9	110	103	7
1998	165	164	2	112	110	2
1999	260	252	8	177	172	5
2000	334	324	9	228	223	5
2001	342	330	12	236	231	5
2002	350	329	22	244	234	10
2003	387	354	33	271	256	15
2004	495	457	38	346	329	18
2005	494	461	32	348	335	12
2006	482	442	39	342	327	15
2007	632	607	25	447	443	4

CABG: coronary artery bypass grafting; PCI: percutaneous coronary intervention; sensit. analy.: sensitivity analysis

6 Discussion

two issues analysed:

population health gains + cost-utility ratios

In this analysis we have addressed two major issues with respect to statin treatment in Austria. First, we analysed the expected population health gains from statin treatment between 1996 and 2006 in Austria in terms of different types of cardiovascular diseases and revascularisation interventions. Second, incremental cost-utility ratios for statin treatment compared to non-statin treatment for a life-time perspective and for a 10-year time horizon were evaluated.

1996-2006: 600,000 persons have taken statins

According to the base case results, overall around 600,000 persons took statins between 1996 and 2006 in Austria. This amount included those who had died within that time period.

26,600 MI avoided,

increasing prevalence of SA,

impact on stroke is lower than on CHD

With respect to population health gains in cardiovascular morbidity, base case model outputs showed that the biggest health gains could be expected with respect to MI. Between 600 and 5,000 MIs per year and 26,600 MIs in total were avoided or postponed in estimates comparing the statin group to the 'NoStatin' group in Austria. On the other hand, the model has shown that the prevalence of stable angina has risen in the statin group. This is probably due to the fact that the use of statins results in people staying longer in the less severe health state of stable angina. In terms of stroke, predicted health gains are considerably smaller. However, this is because only strokes with a history of CHD have been considered in the analysis. Moreover, efficacy data from clinical studies which are the basis for the model have shown that statins have a lower impact on stroke than on CHD.

10,200 avoided/postponed fatal events, most of them MI

no significant effects in fatal cerebrovascular events

Estimated health gains in terms of avoided/postponed fatal events are largest with respect to fatal CHD. In the base case, the proposed number of avoided or postponed CHD deaths between the statin and the 'NoStatin' group rose from 224 in 1997 to 2,061 in 2007 resulting in a total number of around 10,200 avoided/postponed fatal events for the whole period evaluated. Fatal MIs account for the biggest proportion of fatal CHDs avoided. The health gains in terms of reduced fatal cerebrovascular diseases for those with a history of CHD, however, are almost negligible. This is mainly due to the fact that statins have not shown a significant effect in the meta-analysis in terms of fatal cerebrovascular disease.

7,000 avoided revascularisation interventions

In terms of revascularisation, it was estimated that around 7,000 interventions were avoided in a total number of 600,000 persons who took statins compared to not taking statins.

more health gains for men –

less women taking statins

For all outcome parameters evaluated, health gains are lower for women than for men. This is consistent with the model parameters where, firstly, it has been assumed that slightly more men than women are taking statins and, second, that – based on epidemiological data – a higher proportion of men than of women undergo more severe health states.

despite statins cases of CVD occur

Apart from health gains, however, the model additionally demonstrated that in the 600,000 patients who took statins between 1996 and 2007, 4,400 cases of USA, 35,200 cases of MI and 2,300 cases of stroke were occurring. Furthermore, it was estimated that 24,000 fatal CHDs and 1,400 fatal cerebrovascular events occurred despite statin treatment. Finally, 231,000 revascularisation interventions were carried out in spite of statin treatment.

45,000 avoided CVD cases, events or revascularisations versus 300,000 cases still occurring

Thus, despite statin treatment, a considerable number of patients were in one of the health states evaluated, experienced a fatal CVD event or needed to undergo revascularisation. Overall, around 45,000 'avoided health states', events or interventions need to be measured up against around 300,000 cases in CVD morbidity health states (excluding stable angina), fatal events or interventions that still have occurred. Moreover, (fatal) events that can be avoided in one year may simply occur later on, thus postponing rather than truly avoiding the events.

number needed to treat consistent with literature

The number of persons that needed to be treated to achieve one fewer case of a CVD morbidity health state was 21. For avoiding one fatal event, 59 persons needed to be treated. For every revascularisation intervention avoided, 86 persons needed to take statins. These figures are consistent with the results from clinical studies which showed a number needed to treat of 34 (22.8-95.5) in the 4S-Study and of 12 (9-16.4) in the CARE study for the combined endpoint of CHD mortality and morbidity [14].

undiscounted QALYs: 0.27 to 1.13 (males); 0.31 to 1.32 (females)

Concerning life-time effectiveness, the model predicts average undiscounted incremental QALYs per person of 1.13 and 1.32 (13.6 and 15.8 quality adjusted life months) for the youngest age groups (45 years) of males and females respectively. QALYs decrease with age to 0.27 and 0.31 (3.2 and 3.7 quality adjusted life months) for males and females aged 85 respectively.

cost savings: 8 to 105 million €

Population net costs are higher in the treated cohort compared to the 'NoStatin' group. In the former, they ranged from 33 million Euros in 1996 to almost 700 million Euros in 2007. It has been estimated that potential cost savings ranged from 8 million Euros in 1997 to 105 million Euros in 2007. However, these results could not be derived from the model directly and are therefore subject to some uncertainty.

ICUR: below 30,000 €/QALY in life-time perspective

Base case incremental cost-utility-ratios are below 30,000 Euros per QALY gained in all age groups and in both, males and females. ICURs decrease with age which means that treating people in higher ages decreases the additional resources required to gain an extra QALY. With respect to gender, in younger age groups results are slightly more favourable in females than in males. This difference reverses at the age of 75 above which results are more favourable for males.

sensitivity analysis: results robust…

Results from the various one-way sensitivity analyses show that ICURs may be lower than in the base case (when lower discount rates and statin prices are assumed) but do not exceed 35,000 Euros per QALY even when factors with the opposite impact are varied (e.g. compliance). The results can therefore be considered as conservative as well as robust with respect to a theoretical willingness-to-pay-limit of 35,000 Euros per QALY. Yet, the analysis for a 10-year time frame has shown a different picture. Cost-utility addressed from a short time perspective results in considerably higher ICURs (above 50,000 Euros per QALY gained) in the younger age groups. Hence, overall cost-utility ratios can be considered as robust only when a lifetime approach including long-term treatment is guaranteed.

…but high ICURs in 10-year time frame

ICURs consistent with literature…

Cost-effectiveness results are consistent with those from the original model as well as with other international studies. Yet, when comparing age specific results, ratios are higher in younger age groups and lower in older age groups in the Austrian case than in the original UK model. This may be explained by differences in overall life-expectancy between the two countries. However, since ratios in all age groups are within a similar range for each country, the country-specific differences are considered to be of little consequence. Nonetheless, interpretation of cost-utility ratios is limited in Austria, since no threshold exists for what is to be considered a favourable cost-utility ratio in the Austrian health care system. One useful indicator may be that derived from international studies on statins in which – based on a utilitarian approach – results below 30,000 Euros per QALY have generally been considered favourable [2].

…but interpretation in Austria limited

limitations:

The study has several limitations:

many data not from Austria, yet…

First, the results on population health gains as well as the cost-utility ratios are based on the ScHARR Markov model which uses primarily UK data for populating the model. Wherever available, British data have been replaced with Austrian ones which is the case for life-expectancy data, data on health state costs and statin cost data. Yet, many other data were not available for Austria, such as utility data for the various health states included in the model, information on the initial distribution of patients into different health states and transitional probabilities for patients moving from one health state to another in the untreated cohort (including baseline risks). These issues –in particularly the lack of information on baseline risks [43] – are clearly a limitation of the model. However, sensitivity analysis in the UK study has shown that neither of these parameters had a major influence on the final results of their study. Thus, as it has been suggested in a methodological study on transferability [44], it can be assumed that uncertainty with respect to these limitations is low in the adapted Austrian model with respect to cost-utility results.

…influence on cost-utility results should be low

demographic characteristics of statin taker and compliance affect cohort size and health gains

On the contrary, sensitivity analysis for the population health gain model has shown that results are subject to considerable uncertainty. This is especially the case when the age and gender distribution of statin takers is varied. The variation applied does not only result in larger cohort sizes than in the base case, but subsequently influences population health gains which are also greater in sensitivity analysis than in the base case, indicating again a conservative approach. Varying compliance has some affect on the cohort size, too. Yet, health gains remain fairly stable as the potential health gains from more people taking statins is compensated by lower statin efficacy when it is assumed that these people are less compliant.

statin prescription data may include primary prevention cases

Not least, estimated cohort size and subsequent impacts on population health are very much dependent on the prescription data available. If statins prescribed were in fact less restricted to secondary prevention than the regulation in chapter 3.4.1 suggests, the cohort size (and the health impact) may be overestimated. Since the regulation for prescription was changed in 2004 to a more risk-related approach, there will certainly have been be a number of prescriptions for patients who did not fall within our definition of secondary prevention from 2004 to 2006. This again suggests a possible overestimation of population health gains.

cost data suboptimal but little impact on robustness of results expected

Another limitation is related to the health state cost data used in the model. Data are based on administrative prices and not on precise cost calculation which is suboptimal. Yet, no other data have been available and, moreover, variation of health state costs has not had a significant influence on the results in sensitivity analysis. Furthermore, the costs for statin treatment are based on a weighted average of expenditure for different types of statins between 1996 and 2006. This seems appropriate for the population cost analysis which is done for the same time period. However, with respect to the life-time cost-utility analysis, ICURs may be overestimated as costs per prescription have decreased over time and may remain at a low level in the long run. As sensitivity analysis has shown, lower statin costs have resulted in lower (better) ICURs.

statin costs may overestimate ICUR

public payer perspective limits information

In relation to costs, it is also a limitation of the study that health care sector costs only have been included, thus we cannot depict the total societal consequences (e.g. informal care, productivity etc.) from statin therapy.

data from clinical studies may differ in routine practice

Furthermore, results are based on data from clinical studies which may differ in routine clinical practice. This is most important for compliance and the reduced effectiveness of statin therapy this relates to. Overall, the evidence available on compliance rates has been poor in quality. However, as the UK model illustrates, reduced compliance combined with failure to retrieve a prescription does not incur costs either and thus does not greatly influence the cost-effectiveness results. Only in the case of patients who fail to take medication but pick up prescriptions, cost-utility results are less favourable. On the contrary, as previously mentioned, compliance that is poor has been shown to have an impact on the cohort size in the population model but less on the estimated population health gains.

no differentiation between statin types

In terms of statin efficacy, differentiating the various statins on the basis of the evidence from the placebo-controlled trials used in the model was not possible. Hence, the combined evidence for each outcome was used in the model thus making a comparison of the results between different statins impossible as well.

long-time extrapolation increases uncertainty

Generally, a long extrapolation of clinical study results is required for cost-utility analyses over a life-time. This increases uncertainty - particularly in the younger age groups in which the data used for populating the model (e.g. distribution into different health states) are generally of lower quality than the data from older age groups [14].

further research requirements::

economic evaluation for primary prevention,

Finally, some further limitations indicate future research requirements. As outlined in the beginning of this report, our study was restricted to secondary prevention only. Because statins were more or less confined to secondary prevention in the period addressed in order to calculate population health gains, the focus chosen seems appropriate in that case. For the cost-utility analysis, it would be equally interesting to address primary prevention as well, especially since indications were extended in 2004 to include additional patients at risk of CVD.

sub-group analysis

Furthermore, in terms of sub-groups, the study was limited to age and gender specific outcomes but did not address disease-specific sub-groups such as people with diabetes. In the latter case, economic evaluations (especially in primary prevention) have usually shown more favourable results than when addressing the total population at risk [17]. Moreover, the study did not consider socio-economic variations in the uptake of or access to statins which may be another sub-group analysis of interest.

7 Conclusion

observable CHD health gains to be expected from statins, yet…

In summary, results suggest that prescribing statins to about 600,000 to 750,000 patients from 1996 to 2006 should have resulted in observable health gains compared to the alternative of not taking statins. This is especially the case for avoided non fatal MIs and reduced CHD mortality, while the impact on stroke (for those with a history of CHD), cerebrovascular mortality and revascularisation interventions is significantly smaller.

…only a proportion of statin takers benefit from treatment

However, the study also demonstrated that despite statin treatment, a considerable number of patients still were in one of the health states evaluated, experienced a fatal event or needed to undergo revascularisation. Overall, around 45,000 'avoided CVD health states', events or interventions need to be weighed against around 300,000 cases of CVD health states, fatal events or interventions that still occurred. The results are based on the effect size that statins have shown in clinical studies.

small cost-containment but ICUR below 30,000 € per QALY in the long run

Additionally, potential cost savings exist, yet they are small in comparison to the total costs involved. Nevertheless, cost-effectiveness ratios from statin therapy in comparison to non-medical treatment are below 35,000 Euros per QALY and can be considered as robust when a lifetime perspective is considered. Although interpretation of cost-utility results is limited in Austria, results below 35,000 Euros per QALY have been rated as cost-effective in most international studies. However, viewed from a short term perspective of ten years, cost-utility ratios are considerably higher than 35,000 Euros per QALY for most age groups.

results are sensitive to gender and age distribution of statin population

While cost-utility results have been shown to be robust (except for a 10-year time horizon), estimated population health gains are quite sensitive to the assumed variations in the gender and age distribution of statin taker in Austria. Health gains in base case results are lower than in sensitivity analysis results and can therefore be considered conservative. Consequently, the dimension of health gains is subject to considerable uncertainty and a precise number of events avoided cannot be calculated with the approach chosen. Additionally, the cohort size of Austrian statin takers also varies considerably in the sensitivity analyses applied, thus the 'true' size and characteristics of Austrian statin taker is also subject to some uncertainty. More detailed primary and patient-level data on statin prescription would help to overcome this limitation.

whether health gains are sufficient requires debate

Overall, whether the expected health gains are sufficient when considering the number of CVD events still occurring as well as the costs is a matter of political debate.

health impact has yet to be confirmed

Finally, the results are based on the outcomes of clinical studies on statins and whether the estimated 'theoretical' health gains from statins in this study correspond with observed cardiovascular epidemiology and real-life population health in Austria remains to be seen. This issue is addressed in a subsequent project which will be presented in a separate report [42].

8 References

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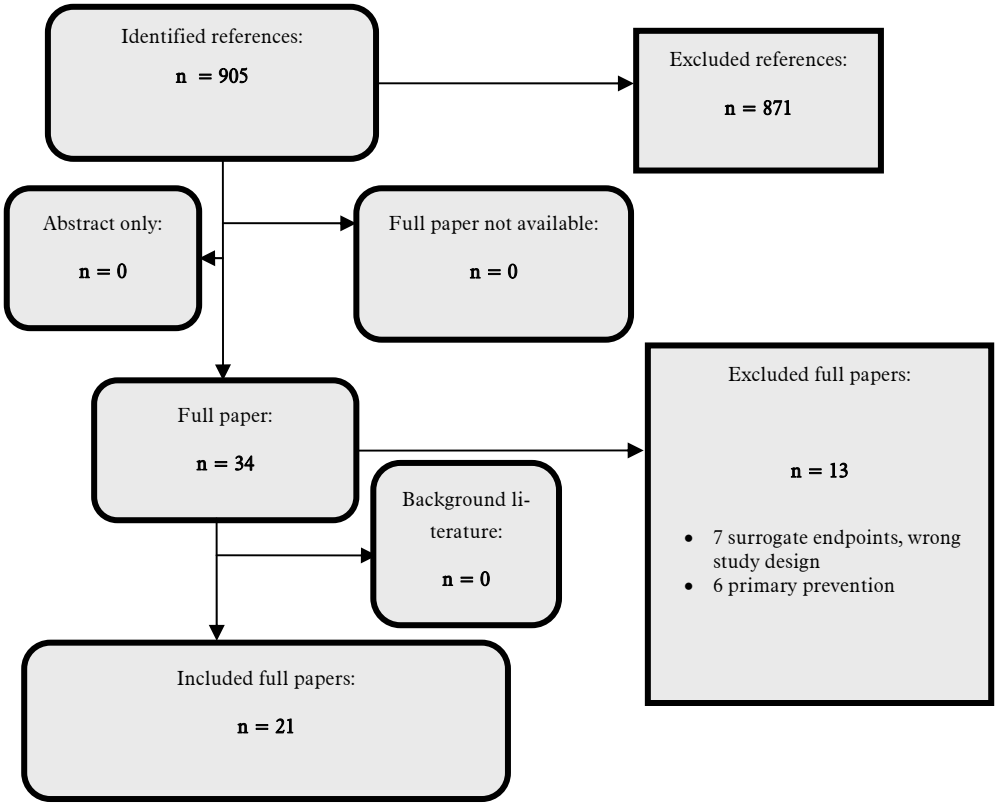
9 Appendix

Search Strategy Pubmed for statin efficacy update

1. statin*
2. simvastatin[tw]
3. pravastatin[tw]
4. lovastatin[tw]
5. fluvastatin[tw]
6. atorvastatin[tw]
7. rosuvastatin[tw]
8. hmg[tw]
9. co reductase inhibitor*[tw]
10. lipid lowering[tw]
11. OR/1-10
12. coronary disease/
13. (coronary OR heart OR arter*)[tw]
14. cerebrovascular disorder*
15. stroke/
16. OR/12-15



Search resulted in 905 hits (mostly: surrogate endpoints, combinations with ezetimib, treatment with statins for acute MI, aggressive cholesterol lowering, treatment to new targets)

34 were selected at abstract stage

Inclusion criteria: RCT or meta-analysis of RCT, outcome parameter clinically relevant (non-fatal CVD event, fatal CVD event, hospital intervention, adverse events, specific subgroupanalysis – especially gender and diabetes, adverse events, German and English language)

Exclusion criteria: other language, non-western countries (Asia), surrogate endpoints, economic evaluation

Table 9-1: Included studies in literature update

N =21	**Characteristics**
6	Adverse effects
1	Gender specific meta analysis
6	Outcomes for Diabetes
5	General Trials or Meta- Analysis
- 2	- Atorvastatin
- 2	- Fluvastatin
- 1	- Meta Analysis
3	Stroke Outcome

Table 9-2: Service patterns and unit costs

Health states/services	***Type of services used***	***Frequencies***	***Unit costs***	***Sources***	***comments***
Stable Angina	Primary care services: Specialist consultant (internal medicine) Medication Monitoring	Year 1: 2 specialist (internal medicine) visits + ECG + Ergo + Echo) Medication: Nitrat, ACE inhibitor, beta-blocker, aspirin (partly) Monitoring: 4 times a year; HDL, LDL, Total cholesterol, Triglycerid, Subsequent years: as year 1	Internal medicine: € 18.02 ECG: € 21.26 Ergometry: € 68.35 Echocardiography: € 49.58 Nitrate: € 11.37 ACE inhibitor: € 15.80 Beta-Blocker: € 11.73 Aspirin: € 0.05 HDL, LDL: € 4.86 Total Cholesterol: € 4.68 Triglycerids: € 5.57	Federation of the Austrian Social Insurance Funds-database (Honorarordnungs-datenbank)	Aspirin is only calculated for a part of the patients as it will mostly be paid out of pocket.
Unstable Angina	See stable angina	See stable angina	See stable angina		
Non-fatal MI	Hospital care Primary care services: Specialist consultant Medication Monitoring	Year 1: 1x hospital admission + Primary care services (see stable angina) Subsequent years: primary care services (see stable angina)	Hospital treatment: € 4,835 Primary care: see stable angina	LKF-data; Federation of the Austrian Social Insurance Funds-database (Honorarordnungs-datenbank)	
Fatal MI	Hospital care	1 x hospital admission	Hospital treatment: € 4,835	LKF-data;	

Non-fatal Stroke	Hospital care; Primary care services: Specialist consultant (Internal Medicine + Neurology) Medication Monitoring Physiotherapy	Year 1: hospital care Primary care services (see stable angina) + 2 times a year neurologist + 4x3x10 physiotherapy sessions Subsequent years: as year 1 but without hospital care and physiotherapy	Hospital treatment: € 3,897 Neurologist: € 18.02 Physiotherapy: € 1,301.35	LKF-data; Federation of the Austrian Social Insurance Funds-database (Honorarordnungs-datenbank)	
Fatal Stroke	Hospital care	1 hospital admission	Hospital treatment: € 3,897	LKF-data	
Statin therapy	Medication Monitoring	DD of Statins 1 GP visit per prescription Monitoring: GOT, GPT, Gamma-GT, Creatinin, CK, CK-MB	Statins per DD: € 0.93 (= € 340.96 per year (weighted average) GP: € 12.39 GP: € 12.39 GOT: € 6.12 GPT: € 5.98 Gamma-GT: € 6.17 Creatinin: € 4.35 Creatininkinase: € 4.67 CK-MB: € 7.21		

DD: daily dose; LKF: Leistungsorientierte Krankenanstaltenfinanzieru