Have Statins Met Our Expectations?

A Comparison of Expected Health Gains from Statins with Epidemiological Trends in Austria

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

Final Report

Ludwig Boltzmann Institut
Health Technology Assessment

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Vienna, October 2008

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List of Abbreviations

CHD	Coronary Heart Disease
CVD	Cardio Vascular Disease
DDD	Defined Daily Doses
MI	Myocardial Infarction
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 disease

Cholesterol lowering pharmacological interventions (statins) have been increasingly used to prevent CVD. In a previous study, the potential population health gains from 11 years of statin use in secondary prevention in Austria were calculated. The model used was based on the efficacy of statins derived from clinical studies. The results need to be verified with observed CVD epidemiology.

previous research evaluated potential health gains from prevention with statins

Research question:

The study aims to analyse whether the expected health gains from statins in secondary prevention of cardiovascular diseases (derived from modelling) can also be observed in Austrian cardiovascular disease epidemiology.

this study asks whether expected health gains are real

Method:

method:

A literature search was conducted to identify international epidemiological trends of CVD and the statins' role in these.

identifying international CVD trends in literature,

Expected health gains from statins in Austria were derived from an earlier study.

Austrian cardiovascular disease epidemiology was analysed descriptively based on administrative hospital data (as proxy for morbidity) and on mortality data. Statistical tests are used to analyse the influence of statins on Austrian CVD mortality.

expected health gains in Austria are contrasted with epidemiology

Results:

International trends:

international trends:

Western Europe has experienced downward trends in age-adjusted CVD mortality. Addressing risk factors seems to have a greater impact on the trend than improving treatment. However, the trend towards increasing prevalence of some risk factors (e.g. obesity) may offset some of the positive effects.

decreasing CVD mortality

Despite the benefits attributed to lowering cholesterol with statins, tackling other risk factors (e.g. smoking) and implementing specific types of treatment/management (e.g. hospital resuscitation after myocardial infarction) has shown a greater effect on reduced mortality than the use of statins.

smoking and disease management have greater influence than statins

Expected health gains in Austria:

expected health gains:

In roughly 600,000 patients who took statins between 1996 and 2006 about 26,600 cases of MI and roughly 10,200 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.

between 1996 and 2006: minus 26,600 MIs, 10,200 fatal CHDs and 7,000 revascularsations

68,000 (fatal) cases despite 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.

observed CVD trends:

Observed CVD trends in Austria:

+75% discharges after MI and + 194% administered PCIs,

From the age of 50 and over, discharge rates for those who were hospitalised for CVD rose steadily. Discharges of MI patients rose from 21,218 in 1996 to 37,064 in 2006 (+75 %). For angina pectoris, discharges also rose slightly, while in the case of stroke, data are unclear. In terms of revascularisation, the number of percutaneous coronary interventions (PCI) has also risen considerably (from 5,506 in 1995 to 16,153 in 2005/+ 194 %), while the number of conducted coronary artery bypass grafting (CABG) slightly decreased. Absolute numbers are in any case higher for men than for women.

slight decrease in CABGs

CVD mortality rates declined in both sexes

Age standardized CVD mortality rate fell by 59 % between 1970 and 2005. The decline is similar for men and women. Twenty percent of all deaths and 40 % of all cardiovascular deaths are due to CHD. Most of the mortality cases in CVD occur above the age of 65.

contrasting the results:

Contrasting the results

morbidity: health gains in model inconsistent with rising hospitalisation

While model outputs demonstrated decreasing numbers of CVD cases and revascularisation procedures when statin takers were compared with those not taking statins, hospital discharges indicate an overall increase in CVD morbidity.

mortality: corresponding decreasing trends and…

On the contrary, CVD mortality rates per 100,000 person years were decreasing in both the model as well as observed mortality when compared to the reference year 1994. The trend between model results and observed mortality is particularly consistent for reductions in CHD and MI mortality rates.

…stronger mortality decline after statin launch

Furthermore, the average decline in relative mortality changes per year and in annual mortality rates per 100,000 is stronger in the period after the launch of statins than before. The difference is statistically significant for both males and females with regard to CHD mortality overall and to MI mortality in particular, but not in the case of cerebrovascular deaths.

Sensitivity analysis:

more CHD health gains in sensitivity analysis -> less correspondence with observed CHD mortality reduction

Observed CVD mortality was contrasted with model mortality outputs according to varying gender and age distribution of statin takers in the model. While CVD mortality rate reductions in model and observed mortality were more consistent in sensitivity analysis, CHD mortality rate reduction was higher in sensitivity analysis and, thus, less consistent with observed mortality.

Discussion:

morbidity trends in model and real life not consistent, yet…

In terms of morbidity, potential health gains from statins have been shown for non-fatal MI in particular. Additionally, some revascularisation interventions seem to have been avoided due to statins. In contrast to the model results, hospital data showed rising numbers of discharges for MI and increasing numbers of revascularisation interventions.

…role of statins unclear

Although this indicates that potential health gains from statins may be smaller in real-life than in clinical studies, interpretation regarding the role of statins is limited, as the state of hospital discharges without statins is un-

known. Additionally, several other factors may influence hospital admissions such as economic incentives, changes in disease management, aging of the population etc.

statin-induced mortality reduction more likely, but causal relationship not known

With respect to mortality, mortality rate reductions in the model results and in observed mortality are more consistent, especially in the case of CHD mortality. Although it was additionally demonstrated that the decline in mortality was faster in the time period after the launch of statins than before, a causal relationship between the utilisation of statins and observed mortality changes cannot be substantiated. This is because other factors may also have influenced mortality as demonstrated in international studies.

limitation: data quality

General limitations of the study are related to restricted data quality, especially regarding morbidity data and statin utilisation data, thus leaving considerable room for uncertainty.

Conclusion:

statin-related mortality reduction likely, morbidity and cost benefit less clear

Tentative evidence exists that statins seem to have contributed to decreasing CHD mortality in Austria while the benefits with respect to CHD morbidity and related revascularisation interventions are less explicit. Hence, repeatedly mentioned cost saving potentials in economic evaluations need to be treated with caution.

whether health gains are sufficient requires debate

Yet, even if mortality gains exist, several hundred thousand patients need to be treated life-long in order to achieve this benefit. Whether this relation is acceptable is subject to public discussion.

better morbidity data and patient-level statin data required

Improving morbidity data quality and gathering detailed patient-level data from statin patients have been identified as top-priorities for obtaining more definite results.

1 Introduction

CVD: high burden of disease in Europe

Cardiovascular diseases (CVD) belong to the most prevalent diseases in industrial countries. They result in high morbidity and mortality rates. CVD comprises several types of disease which include coronary heart disease (CHD), cerebrovascular disease, and peripheral-artery disease (PAD). CHD includes 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.

statins dominate pharmacological prevention interventions

Several risk factors have been identified which seem to be associated with CVD. One of them is an elevated blood cholesterol level. A number of primary and secondary prevention strategies have been created 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 beginning of the 1990s and have since then dominated the market of cholesterol lowering drugs.

statins: efficacious and cost-effective in literature

Not only has the use of statins proven to be efficacious in clinical studies, statins have also been described as cost-effective in economic evaluations. One reason for the latter is that clinical studies have shown 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. In 2000, expenditure for statins in EU-15 countries and Norway already was equal to € 4 billion and had risen to over € 20 billion between 2000 and 2004 [2]. Prescription and expenditure have also increased dramatically in Austria since 1995.

increasing prescriptions and expenditures

study aims: comparing expected heath gains with observational data

In a previous study [3], the potential population health gains from 11 years of statin use in Austria were calculated by using a mathematical model. The model was based on the efficacy of statins in terms of cardiovascular morbidity and mortality derived from clinical studies. The current study aims at comparing the expected health gains with the actual epidemiological trends in Austria in order to address the question whether expected effects can be confirmed by observational data.

structure of report

After defining the precise research question, the report continues with a description of the methods applied in the study (chapter 3). In chapter 4, an overview of international trends in cardiovascular epidemiology is presented. The research question requires taking into consideration other factors which may have influenced cardiovascular epidemiology in Austria. Thus, determinants of epidemiological trends identified in relevant literature and the role of statins in these trends are included this chapter. Chapter 5 presents the expected health gains from statins generally and in Austria specifically by summarising the main results from clinical studies and from the Austrian modelling approach. In chapter 6, epidemiological CVD trends in Austria are described based on data sources which were available. In chapter 7, these results are finally contrasted with those from chapter 5 and complemented by a sensitivity analysis in chapter 8 in order to reach a conclusion on whether the expected health gains from statins can be confirmed by epidemiological trends in Austria.

2 Research Question

The aim of this study is to analyse whether the expected health gains from statins in secondary prevention of cardiovascular diseases can also be observed in Austrian cardiovascular disease epidemiology.

research questions:

In detail, the following research questions will be addressed

1. What is the trend in cardiovascular morbidity and mortality from an international perspective for the past twenty to thirty years; what are the factors behind this trend; and what role do statins play in all this?

cardiovascular epidemiology international?

2. What are the expected population health gains from statins in secondary prevention since their introduction in Austria in terms of
   - Cardiovascular morbidity (myocardial infarction, angina, stroke)
   - Cardiovascular mortality (fatal coronary heart disease, fatal stroke with history of coronary heart disease, fatal myocardial infarction)
   - Revascularisation interventions (percutaneous coronary intervention/ coronary artery bypass grafting)

expected health gains from 11 years of statin treatment in Austria?

3. What has been the epidemiological trend (particularly since the mid-1990s) in cardiovascular disease in Austria in terms of
   - Cardiovascular morbidity (myocardial infarction, angina, stroke)
   - Cardiovascular mortality (cardiovascular disease overall, coronary heart disease overall, myocardial infarction, cerebrovascular disease)
   - Revascularisation interventions

CVD epidemiology in Austria?

4. Can a consistency be observed between expected health gains and epidemiological trends?

consistency between expected and observed CVD trends?

3 Method

The research questions are addressed via a multi-step approach described below.

multi-step approach

3.1 Analysing the International Epidemiological Trends in Cardiovascular Disease

The first question is addressed by a literature review which is concerned with how the burden of CVD in general and coronary heart disease (CHD) in particular has developed from an international perspective. It uses a rough time frame of 1980 to 2000. Specific attention is paid to the role of statins in influencing the trends. The main focus of the review is on trends in Western Europe.

literature review to identify international trends in CVD

The literature search was done in the PubMed database, using key terms including 'cardiovascular disease', 'coronary heart disease', 'mortality', 'morbidity', 'trends' and 'Europe'. The literature search does not strive to fulfil the criteria of a systematic review but rather attempts to present an overview of epidemiological patterns and trends which will serve as background information. Approximately 60 seemingly relevant articles were collected and read. Irrelevant articles were then discarded, leaving approximately 40 containing relevant information. Useful data and information were extracted and summarised. Due to repetition in the literature, not all relevant articles were drawn upon in the final review. In addition to published articles, statistics from international agencies (WHO, OECD) were searched.

used for background information

sources: PubMed + international agencies

3.2 Analysing Expected Health Gains from Statins in Austria

This part of the report is based on the results of a previous study [3] which evaluated the population health gains expected from statins in secondary prevention by using an adapted Markov model from the UK. Model outputs related to cardiovascular morbidity and mortality have been linked with data on Austrian statin users from 1996 to 2006 in order to estimate potential population gains in cardiovascular health.

expected health gains are used from previous study

The methodology is described in detail in the corresponding study report [3]. In summary, the method involved the following steps:

summary of method:

- The number of Austrian statin takers was estimated by using the amount of statin prescriptions for calculating the total number of prescribed daily doses. These results were employed to calculate mortality adjusted annual cohorts, assuming that patients take the medication every day in the base case.

estimation of statin cohort based on number of prescriptions

estimation of health effects from statins based on adapted UK Markov model

- A mathematical model (Markov model) from the UK that predicts cardiovascular health effects from statin treatment compared to non-medical cholesterol lowering was adapted for the Austrian context. The following data sources were used:
  - Disease progression in the untreated cohort was based on UK CHD and stroke registries
  - The probability of dying was based on Austrian life tables
  - Calculation of statin treatment effects was based on a meta-analysis of clinical trials on statins. Relative risk reductions for various cardiovascular outcomes were applied

model outputs were linked to Austrian cohort sizes

- Model outputs for a fictitious cohort were linked to the estimated annual Austrian cohorts between 1996 and 2006: The cohorts from year 1 (1996) could benefit for 11 years whereas the last cohort (starting in 2006) could only benefit for one year. The results from each year were summarised for each outcome category of interest and compared to the alternative of not taking statins.

uncertainty tested in sensitivity analyses

- Sensitivity analyses were conducted to test for uncertainty of the results: The influence of compliance and different age and gender distribution of statin takers on cohort sizes and potential health gains were evaluated

3.3 Analysing Epidemiological Trends in Cardiovascular Diseases in Austria

data sources for Austrian CVD trends:

In order to analyse Austrian epidemiological trends in cardiovascular morbidity and mortality, several data sources are used: Since there are no 'official' morbidity data on a population basis available in Austria administrative hospital data are used as proxy for morbidity.

hospital data as proxy for morbidity

Data show the age- and gender-specific cases of discharges from patients diagnosed with angina pectoris, myocardial infarction (MI) or stroke as well as the number of revascularisation interventions with respect to percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG). These are used descriptively to identify trends in cardiovascular morbidity.

ICD-10 & MEL-codes

The following documented ICD-10 codes and the codes for specific services (MEL-codes) were used to define and select the diagnoses and interventions of interest:

- Angina: I20
- MI: I21-I24
- Stroke: I61, I63, I64, I66
- PCI: MEL-codes 6512-6514, 6520–6524, 6562
- CABG: MEL-codes 2386, 2391, 2396, 2404

Data which have originally been documented in ICD-9 codes have been transformed into ICD-10 by using official recoding tables from the Ministry of Health.

potential bias in hospital data

Overall trends as well as gender and age specific developments will be illustrated. Data are case-based and not person-based. Thus, persons who were hospitalised more than once are counted as separate cases each time in the statistics, a factor which introduces some bias.

mortality data from official statistics on causes of death

In terms of mortality, official statistics on causes of death [4] are used to describe trends in CVD mortality in Austria for different ages and gender. In detail, both, overall CVD mortality (I00-I99) as well as selected subgroups of CVD, such as fatal CHD (I20-I25), fatal MI (I21-I22) and fatal cerebrovascular diseases (I60-I69) are addressed in the analysis.

statistical analysis of mortality dynamic:

In addition to the description of the long-term mortality trend since 1970, a statistical analysis has been carried out in order to evaluate whether specific trends can be identified that may be correlated with the introduction of statins:

differences between time before and after statin launch identified,

In detail, changes in mortality rates and in relative mortality per year were identified for the selected groups of CVD under evaluation. An analysis was made whether the development from 1970 to 1998 was different from the trend since 1998 when statins would have been likely to have had an impact. 1998 has been chosen because, first of all, in clinical studies Kaplan-Meier curves have shown a time-lag in mortality impact of at least 1.5 years [e.g. 5]. Second, the number of prescriptions was low at the beginning and, third, studies have shown that it usually takes three years from the launch of new drugs till their maximum impact on survival rates [6].

testing for statistically significant differences between time periods

The results are demonstrated descriptively and additionally, a selected number of statistical tests (t-test, Wilcoxon-test) was applied to assess statistical significance of the observed differences.

comparison of mortality rate reduction in model and observational data

For contrasting mortality outcomes in the population health model with observed mortality, changes in overall CVD mortality rates, CHD mortality rates, MI mortality rates and cerebrovascular mortality rates (cases per 100,000 years) based on the reference year of 1995 have been calculated.

sensitivity analysis to test for uncertainty

Since a previous report showed considerable variation in mortality outcomes in the population model depending on the assumptions applied for gender and age-characteristics in statin users [3], sensitivity analysis was conducted to address uncertainty in model-based mortality rate reduction.

4 International Trends in Cardiovascular Morbidity and Mortality and the Role of Statins

4.1 Methods Used in the Literature

data sources for CVD epidemiology internationally:

WHO, death registers, national statistics, RCT, observational studies

This section briefly describes the sources and statistical methods used to answer the question of epidemiological trends and their determinants in the literature published. The sources of data were varied. Mortality data from the World Health Organisation was used frequently [7-9]. In other studies, registers were used [10, 11], such as causes of death registers and hospital discharge registers. Other common sources are official national statistics [1, 11-14]. Other less common sources were surveys, clinical audits, controlled trials and meta-analyses, social insurance data and observational studies.

articles focus on mortality

Most articles focus on the identification of CVD mortality rather than morbidity trends. Much of the literature is descriptive combined with the statistical method of regression analysis (e.g. Poisson or linear regression) [7, 8, 11, 12, 15].

often used: IMPACT model

To analyse the influence and effectiveness of cardiology treatments and risk factor changes in observed CHD mortality trends, much of the literature used the so-called IMPACT model [1, 10, 12-14, 16]. The model has been progressively developed and revised since 1996 and has been utilised in numerous country-specific analyses. The model includes details of all major population risk factor trends (smoking, total cholesterol, hypertension, obesity, diabetes, physical activity etc.) and information about the use of cardiological treatments. This information is linked with the effectiveness of treatments and risk factor reductions based on clinical trials, meta-analyses and cohort studies.

calculation of deaths prevented by various prevention + treatment measures

The model calculates the number of CHD deaths that would be expected in a later time period if the mortality rate in the base period had remained unchanged. The number of actual deaths in the later period is subtracted from the number of deaths in the base period to give the number of deaths prevented. Furthermore, the number of deaths prevented by each type of risk factor reduction and treatment is analysed. For risk factor changes, regression coefficients from MONICA (Multinational Monitoring of Trends and Determinants in Cardiovascular Diseases) analyses and large cohort studies for smoking, cholesterol and blood pressure tend to be used. The studies also include sensitivity analyses due to the uncertainty surrounding certain values. Overall, the IMPACT model tends to explain approximately 90% of CHD mortality decreases.

4.2 Epidemiological Trends in Western Europe

4.2.1 Overall Trends

Western Europe: decline in mortality rates since mid-1970s

As stated above, most of the literature addresses mortality trends, while morbidity is only rarely covered. The literature consistently argues that Western Europe has experienced downward trends in age-adjusted total CVD mortality since the mid-1970s. On average, age-standardised mortality rates for total CVD in men declined by ~50% (~1.8% per year) in the period 1970 to 2000. The corresponding figures for women were ~60% and ~2% [7].

trend appears in CVD and CHD mortality

This trend is little changed by looking at different types of CVD. CHD mortality in men fell by 39% from 1975 to 1995, from 163 per 100,000 to 99 per 100,000. In women, the corresponding decline was 55% [9]. Stroke mortality has decreased by 60% in men and by 65% in women on average since 1970 [7].

decline started in Western Europe…

…25 years later followed by Eastern Europe

Clear parallels tend to exist between Western Europe as a whole and its individual countries. However, in contrast to Western Europe, cardiovascular mortality in Eastern Europe has typically been higher, reaching a peak in the period 1990-94. This was followed by a decline in much of Eastern Europe including Poland, Hungary and the Baltic States [7]. The broad consensus across the literature is that the decline in CVD mortality started approximately 25 years later in Eastern than in Western Europe. The decline in Eastern Europe has however, been faster than that in Western Europe. Russia is the exception, as it has experienced particularly high rates of CVD mortality as well as increasing CHD mortality trends. Figure 4.2-1 shows the trends since 1972 for selected European countries.

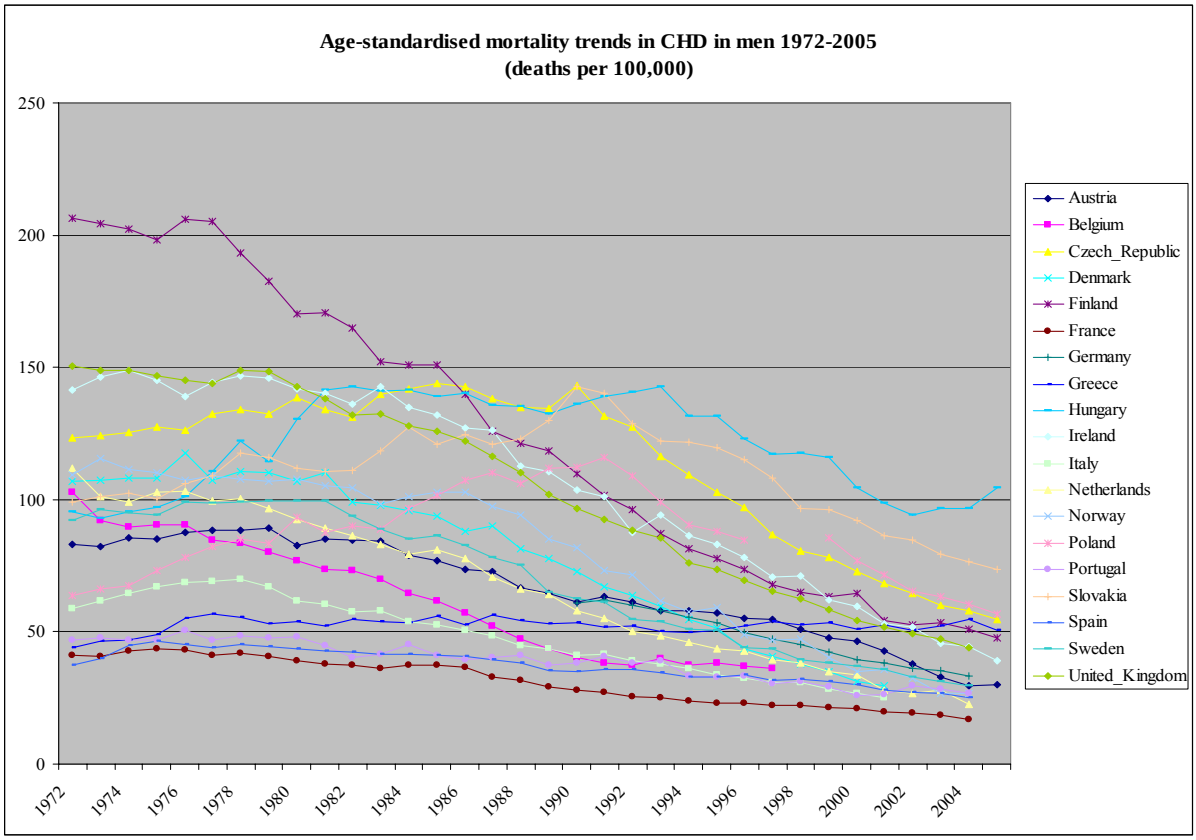

Figure 4.2-1: Age standardised death rates from CHD for men aged 35-74 in selected European countries 1972 - 2006

Source: [17]

mortality rates are lower in women than in men…

In nearly all studies, CVD mortality rates are substantially lower in women than in men. However, this is primarily related to CHD only. For example, in the Ghent-Charleroi CHD study [15], the weighted sex ratio (M/F) in Ghent was 3.2 for total attack rates, 3.8 for non-fatal attack rates, and 2.7 for fatal attack rates. Similarly, in the Netherlands, the age specific incidence of hospitalisation for a first acute myocardial infarction (AMI) was higher in men than in women and increased with age, up to 90 years [18]. Also comparable are figures for Denmark and Sweden, where the male/female rate ratios of the incidence of first AMI are 2.28 and 2.17 respectively [19].

… but 55% of all female deaths caused by CVD

Despite this substantial disparity, CVD continues to be the leading cause of death in women as well as men in most industrialised countries [20]. Fifty-five percent of all females' deaths are caused by CVD [21]. Also, women's lesser CVD risk may merely be an illusion, arising from the age-specific analysis used in most CVD mortality trend studies. Stramba-Badiale et al. [21] put forward the idea that women are not at less risk from CVD overall, but rather women's CVD risk is simply delayed by 10 years.

women´s risk delayed by 10 years

gap between men and women becomes smaller for aged 65 and younger

Some say that the recent decline in CVD mortality in Europe has been lower in women than in men [21]. For example, in the Netherlands, the gap between men and women at risk from dying from CHD has become smaller in recent years for those aged 65 years and younger [11]. This is probably the case in terms of absolute numbers. However, in relative terms, this seems unlikely to be the case, at least for Europe as a whole.

socioeconomic status affects mortality

An analysis of the effect of socioeconomic status on CHD in Western Europe shows that, in the ten populations studied, CHD mortality was higher among those with lower socioeconomic status than those with a high socioeconomic status among men and women aged 30-59 and >60 [22]. In most of the countries those of lower socioeconomic status were around 50% more likely to die from CHD. This can be regarded as a reflection of risk factors, with the better educated being more likely to cut down on, for example, smoking and consuming unhealthy foods. Another factor could be varying standards of treatment, with those of lower socioeconomic status receiving poorer or less treatment.

CVD mortality in older age groups often overlooked

Finally, with respect to age groups, the focus on age standardised mortality rates masks probable variation in CVD mortality trends between different age groups. Also, people in older age groups are frequently excluded from studies. Less encouraging CVD trends among older people may be hidden as a result of such exclusions. The situation in North Karelia shows that CVD mortality has fallen less in older age groups [12]. This indicates the need for caution; because a decrease in the CVD mortality rate in a young age group cannot be extrapolated to changes of the same magnitude in other age groups.

WHO MONICA project: incidence of coronary events falling in Northern and Western Europe

but not necessarily in Southern, Central and Eastern Europe

As previously mentioned, the PubMed search yielded few results for studies on European CVD morbidity trends: The WHO MONICA project examined the incidence of major coronary events in 29 populations in 16 European countries; however data are more than ten years old. Nevertheless, the project has shown that the incidence of coronary events is higher in MONICA project populations in Northern, Central and Eastern Europe than in Southern and Western Europe. Results from the project have also shown that the incidence of coronary events is falling in MONICA project populations in Northern and Western Europe but not necessarily in the populations in Southern, Central and Eastern Europe. For example incidence rates for women aged 35 to 64 living in North Karelia (Finland) fell by 5.1 % per year between 1983 and 1992, but rose by 2.7 % per year for women living in Kaunas (Lithuania) [17].

knowledge gap for morbidity trend in older age groups

Yet, for analysing overall population morbidity trends, these results have to be handled with care because they only include age groups from 35 to 64 and may thus mask an increasing trend in morbidity in older age groups. For example, Reitsma, Dalstra et al. [11] found an increase in hospital admissions due to chronic cases. While the incidence of CVD fell, chronic CVD rose by 5.1% per year due to the longer survival of patients as a result of better treatment. This idea of an increasing burden is supported by projections outlined by Kromhout [23], who estimates that from 1994 to 2015 the number of prevalent cases of CHD and stroke will increase by 35-45% in spite of decreasing age-standardised mortality rates. This would be due to the aging of the population and a decline in case fatality in CVD patients.

increasing morbidity in older people likely

declining mortality, increasing morbidity

Hence, the declining CVD mortality trends do not necessarily indicate a fall in CVD morbidity. Where mortality is lowered by means of improved treatment or risk factor reduction, morbidity may increase, as CVD patients may remain chronically ill or experience reoccurring illness. Thus, despite falling CVD mortality, the burden of CVD in Western Europe may be increasing.

4.2.2 Determinants of Change

determinants of change: reduction of risk factors + improvements in treatment

All relevant studies identify two key factors which have contributed to the fall in mortality from CVD, namely reductions in the prevalence of risk factors and improvements in treatments. Other influential factors such as changes in diagnoses are given little to no attention.

Addressing risk factors has greater impact than treatment

Figure 4.2-2 below gives an indication of the relative contributions of risk factor changes and treatments to decreases in the CVD mortality rate, as identified in various countries and studies. According to figure 4.2-2, reduction in risk factors accounted for between 44 % and 76% of the decrease in deaths from coronary heart disease in the latter two or three decades of the twentieth century. The corresponding figure for treatments is 23 % to 47%. Thus addressing risk factors seems to have had a greater impact on CVD mortality rates than treatment.

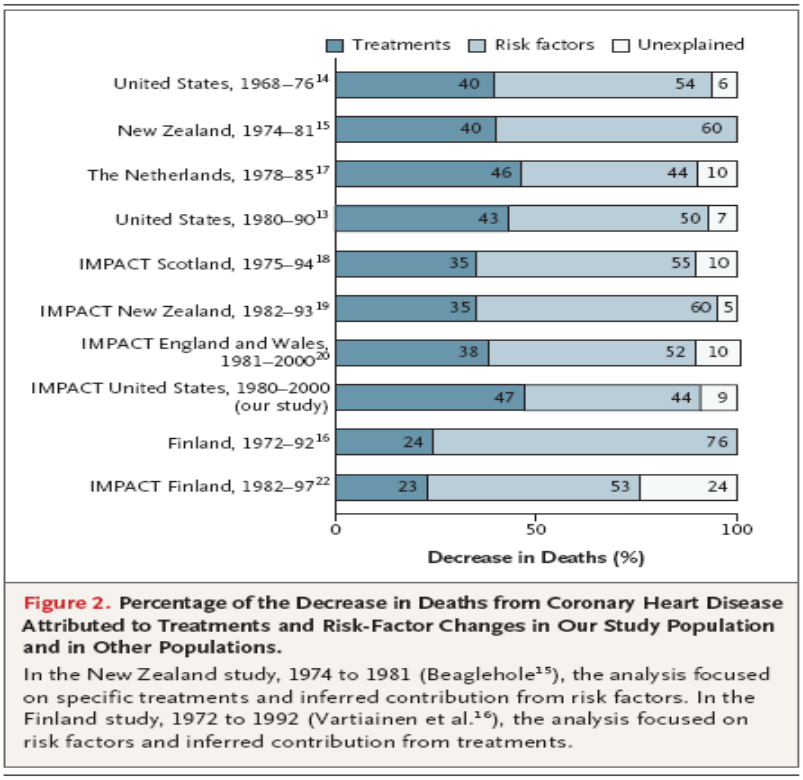

Figure 2. Percentage of the Decrease in Deaths from Coronary Heart Disease Attributed to Treatments and Risk-Factor Changes in Our Study Population and in Other Populations.

In the New Zealand study, 1974 to 1981 (Beaglehole[15]), the analysis focused on specific treatments and inferred contribution from risk factors. In the Finland study, 1972 to 1992 (Vartiainen et al.[16]), the analysis focused on risk factors and inferred contribution from treatments.

Figure 4.2-2: Explanation of the decrease in deaths from coronary disease, 1980-2000

Source [1]

'classical risk factors':

hypertension, elevated lipids, smoking, diabetes, obesity account for 80% of CVD

The mention of causally linked risk factors throughout the literature seems to suggest a consensus regarding their effects on CVD. They are frequently referred to as 'classical risk factors'. Table 4.2-1 summarises the major risk factors that have been associated with CVD, although some of them (e.g. elevated homocystein) are still under debate. Risk factors such as hypertension, elevated lipids, smoking, obesity or diabetes are suspected to account for some 80% of cardiovascular diseases [24]. In terms of elevated blood cholesterol, research from the WHO highlights that over 60 % of CHD and around

40 % of ischemic stroke in developed countries is due to elevated blood cholesterol levels [17].

cholesterol lowering and smoking are key prevention factors, yet…

In turn, falling elevated cholesterol and reduced smoking prevalence are repeatedly identified as the key factors in the decrease in CVD mortality in Europe. Diet is frequently cited as a reason for consistently low rates of CVD mortality in southern Europe, where high consumption of monounsaturated fats such as olive oil and antioxidants in fruit and vegetables is common [e.g.25].

…poor predictors for occurrence of events

However, the risk factors by themselves are often poor predictors of who will go on to have a CVD event as Ebrahim et al. [26] have shown for blood cholesterol.

Table 4.2-1: Proven and putative risk markers for cardiovascular disease

Proven and Putative Risk Markers for Cardiovascular Diseases
Risk factors that are casually linked:
Tobacco consumption
Elevated LDL
Low HDL
High blood pressure
Elevated glucose
Physical inactivity
Obesity
Diet*
Risk markers that show associations:
Low socioeconomic status*
Elevated prothrombotic factors: fibrinogen, PAI-1
Markers of infection or inflammation
Elevated homocysteine
Elevated lipoprotein(a)
Psychological factors (depression, proneness to anger, hostility, stress, acute life-events) and breakdown in social structures (loss of social support and cohesion)*
* Predisposing risk factors: A predisposing risk factor is presumed to work, at least in part, through an impact on other risk factors that act directly. For example, obesity raises blood pressure, causes dyslipidemia, and increases blood glucose. That some of the predisposing risk factors also have direct effects is probable.
PAI: plasminogen activator inhibitor

Source: [27]

With respect to specific countries, an interesting example is Finland where a community-prevention program in North Karelia was implemented in 1972 in order to change risk factors and health behaviours. From 1968-71 to 1995, age-standardised CHD mortality in North Karelia fell by 73%, the corresponding figure for the whole of Finland was 65% [12]. Further reductions were observed after this period. It is estimated that of the 55% reduction in CHD and stroke mortality in Finland from 1972 to 1992, three quarters are attributable to a reduction in cholesterol (13% in men and 18% in women), blood pressure reductions and decreases in smoking levels [12], while only 23% of the mortality reduction in CHD is attributable to improved CHD treatments [10]. Thus, the Finnish case appears to correspond with that of the rest of Europe, in which improvements in three key risk factors proved crucial.

crucial factors in Finland:

reduction in cholesterol, blood pressure, smoking

Similarly, in England and Wales estimates showed that approximately 60% of the CHD mortality decrease is attributable to risk factors, and 40% to cardiological treatments [7]. A significant (34%) reduction in smoking led to 48% of the reduction in CHD deaths. Blood pressure and cholesterol each contributed to around 10% (Table 4.2-2).

England & Wales:

reduction in smoking led to 48% reduction in CHD deaths

Table 4.2-2: Deaths prevented or postponed as a result of population risk factor changes in England and Wales 1981-2000

Risk factors	% Change in Risk Factor 1981-2000	ß Coefficient	Deaths Prevented or Postponed (No.) Best Estimate	Minimum Estimate	Maximum Estimate	Proportion of Overall Deaths Prevented or Postponed, % Best Estimate
Smoking	- 34.0	0.51	29,715	20,037	44,677	48.1
Population blood pressure	-7.7	0.67	5,868	4,246	15,469	9.5
Cholesterol	-4.2	2.46	7,900	5,284	16,692	9.6
		Relative Risk				
Deprivation	-6.6	1.24	2,126	1,063	3,189	3.4
Physical activity	-30.6	0.5	-2,662	-1,491	-3,460	-4.3
Obesity	+186.2	1.57	-2,097	-1,339	-2,587	-3.4
Diabetes	+65.6	4.24	-2,888	-2,567	-4,685	-4.7
Total risk factor effects	…	…	35, 944	23,123	62,195	58.2

Source: [28]

The negative effects of low physical activity, obesity and diabetes are causes for concern. Figure 4.2-3 emphasises the fact that while focusing on risk factors overall has had a positive effect on CVD mortality rates, some risk factors are contributing in a negative way. For example, in England and Wales between 1981 and 2000, certain risk factors developed in an adverse fashion, thus causing additional CHD deaths. The increasing prevalence of risk factors such as obesity, diabetes and physical inactivity have counterbalanced some of the positive effects of, for example, falling cholesterol and smoking.

negative effects (overweight, diabetes and physical inactivity)…

…may counterbalance positive effects

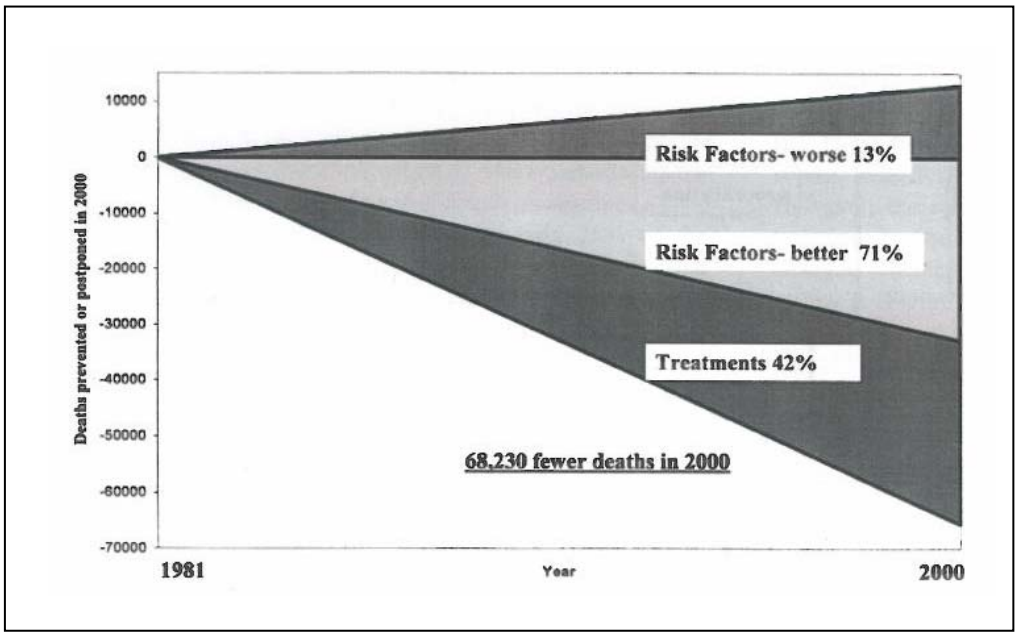

Figure 4.2-3: Explanation of the decline in CHD mortality in England and Wales

Source: [28]

which effect has reduced blood cholesterol?

Although a reduction in blood cholesterol seems to play a significant role in its effect on mortality trends, previous studies do not specify the extent the deaths prevented can be attributed to cholesterol lowering drugs. Also unclear is the role of other measures in primary and secondary prevention in reducing elevated blood cholesterol.

statins in secondary prevention more effective than in primary prevention

Along these lines, Unal et al. [14] provide an overview of the roles of primary and secondary prevention in the reduction of risk factors. Primary prevention, as shown in Table 4.2-3, was four times more effective than secondary prevention in the period 1981-2000. However, the amount of deaths prevented by statin treatments (2,135) is considerably higher in secondary prevention (1,990 or 93 %) than in primary prevention (145 or 7 %).

biggest effect from cholesterol lowering in primary prevention: diet,

in secondary prevention: statins

With respect to cholesterol lowering, in primary prevention improved diet seems to have a considerably higher impact on the prevention or postponement of deaths than statin treatment. From 4,710 estimated deaths prevented due to cholesterol lowering in primary prevention 4,565 (97 %) were attributed to diet, while only 145 (3 %) were attributed to statins. On the contrary, in secondary prevention, from 3,190 deaths prevented due to cholesterol lowering, 1,990 (62 %) were attributed to statins compared to 1,205 (38 %) which were attributed to improved diet. The more favourable impact of statins in secondary prevention is most likely a reflection of better treatment uptake (Table 4.2-3).

greatest impact overall: reduced smoking

However, of all the measures addressing risk factors, the highest number of the deaths prevented can be attributed to a change in smoking behaviour in both primary and secondary prevention. In the former, smoking behaviour changes accounted for more than two thirds of all deaths prevented as opposed to less than 1 % due to statin treatments. In the latter, whereas changes in smoking behaviour accounted for 57 % of deaths prevented, the

lowering of cholesterol through the use of statins accounted for 23 % (Table 4.2-3).

Table 4.2-3: Fall in CHD mortality attributable to changes in risk factors in people with and without recognised CHD: England and Wales 1981-2000

Risk factor	Change in population risk Factor level (%)	Deaths Prevented or Postponed				Total
		Primary prevention*		Secondary prevention**		
		No (min-max) †	%	No (min-max) †	%	
Smoking :						
Overall	-35	24,680 (16,935-36,420)	83	5,035 (3,100-8,255)	17	29,715 (20,035-44,675)
Cholesterol:						
Overall	-4.2	4 ,710 (3,335-10,060)	60	3,190 (1,950-6,635)	40	7,900(5,285-16,695)
Attributable to diet		4 ,565 (3,290-9,650)	79	1,205 (645-2,455)	21	5,770 (3,935-12,105)
Attributable to statins		145 (45-410)	7	1,990 (1,305-4,180)	93	2,135 (1,350-4,590)
Blood pressure:						
Overall	-7.7	7,235 (3,965-14,525)	93	520 (285-940)	7	7,755 (4,250-15,460)
Secular trend		5,345 (3,125-11,740)		520 (285-940)		5,870 (3,410-12,680)
Antihypertensive treatment		1,890 (840-2,785)		‡		1,890 (875-3,165)
All three major risk factors		36,625 (24,235-61,005)	81	8,745 (5 335-15 830)	19	45,370 (29,570-76,835)

** primary prevention = in healthy people; **secondary prevention = in people with coronary heart disease; † all numbers rounded to nearest 5; min-max = minimum and maximum estimates; ‡ antihypertensive treatment was subsumed in secondary prevention medication component of IMPACT model; source: [14]*

England and Wales

Table 4.2-4 provides an additional perspective and gives a comprehensive list of the treatments available for CHD which could have had an impact on the declining CVD mortality rates in the last few decades in England and Wales.

from deaths prevented in secondary prevention, statins account for 0.7 %

From several treatment types available, statins have been identified to account for an absolute risk reduction for CVD deaths of 0.018 in secondary prevention in England and Wales. From a minimum of 2,850 deaths prevented or postponed due to secondary prevention after myocardial infarction, statins have accounted for 432 (25 %). If a maximum estimate of 5,095 deaths prevented/postponed is assumed, statins are expected to account for 1,341 (11%). From all deaths prevented in secondary prevention, statins account for 0.7 %. Considerably more deaths prevented are attributed to Aspirin or ß-Blockers. Contrary to the case for secondary prevention, in primary prevention statins have been estimated to account for an absolute risk reduction of 0.002 and an overall proportion of deaths prevented or postponed of 0.2 %.

from deaths prevented after MI, statins account for 11 %-25 %

Table 4.2-4: CHD deaths prevented or postponed by medical and surgical treatment in England and Wales 1981-2000

Treatment	Patients Eligible	Treatment Uptake %	Absolute Risk Reduction	Deaths Prevented or Postponed			Proportion of Overall Deaths Prevented or Postponed, %
				Best Estimate	Minimum Estimate	Maximum Estimate	Best Estimate
Acute myocardial infarction	66,196		0.110	4,779	3,118	7,928	**7.7**
Community resuscitation	3,045	48	0.208	799	742	958	1.3
Hospital resuscitation	7,282	99	0.033	1,453	680	2,185	2.4
Thrombolysis		46	0.024	1,321	493	1,636	2.1
Aspirin		94	0.057	1,949	1,132	2,780	3.2
Primary angioplasty		1	0.008	38	13	207	0.1
β-Blockers		4	0.011	21	11	38	0.0
ACE Inhibitors		19		172	47	123	0.3
Total secondary prevention				6,899	4,587	12,670	**11.2**
Secondary prevention after infarction	313,378			3,844	2,850	5,059	6.2
Aspirin		56	0.009	1,263	641	1,991	2.0
β-Blockers		34	0.014	969	569	1,636	1.6
ACE inhibitors		19	0.014	442	336	1,439	0.7
Statins		25	0.018	459	432	1,341	0.7
Warfarin		4	0.009	100	58	233	0.2
Rehabilitation		23	0.017	673	304	1,231	1.1
Secondary prevention after revascularization	315,680		0.028	3,055	1,737	7,610	4.9
Chronic angina				3,424	1,907	5,889	**5.5**
CABG surgery (1990-2000)	187,416	100	0.009	1,935	1,124	2,375	3.0
Angioplasty (1880-2000)	112,404	100	0.005	559	160	814	0.8
Aspirin in community	1,763,633	55	0.001	1,104	627	2,117	1.6
Unstable angina	67,376			912	620	1,622	**1.5**
Aspirin and heparin		59	0.012	467	334	718	0.8
Aspirin alone		30	0.013	234	127	657	0.4
Platelet llb/lla inhibitors		48	0.007	211	158	247	0.3
Heart failure			…	7,760	5,957	17,356	**12.6**
Hospital	34,689	62	…	4,756	4,228	11,762	7.5
Community	242,088	56		3,211	1,802	5,997	5.0
Hypertension treatment	13,352,868	53	0.001	1,888	875	3,166	**3.1**
Statins for primary prevention	7,630,759	3	0.002	143	47	410	**0.2**
Total treatment effects, 2000				***25,805***	***17, 110***	***49,042***	***41.80***

Source:[28]

4.3 Conclusion

decreasing CVD mortality rates in men and women

Studies consistently show that Western Europe has experienced downward trends in age-adjusted CVD mortality. This is true for both men and women. The trend in Eastern European countries has started later than in Western Europe except for Russia where mortality rates have been increasing.

fewer studies about CVD morbidity trends

While studies on trends in CVD mortality seem to be common, less information on CVD morbidity trends was found. Generally favourable trends in CVD mortality identified in this review, however, could conceivably be masking less favourable trends in CVD morbidity, due to the improved treatments and the lowering of case fatality rates. Thus, the overall burden of CVD may be underestimated.

mostly CHD studies: trend in overall CVD less clear

Furthermore, many studies focus on declining CHD mortality trends. Ignoring other types of CVD may lead one to under- or overestimate the overall burden, because other types of CVD may not show the same trends. However, while this needs to be kept in mind, the CHD trends seem to be more or less in line with the CVD statistics that are available, and therefore the inference could very well be correct that trends in al or most types of CVD are favourable whenever CHD trends are favourable.

positive trend may be offset in long-run

Tackling risk factors seems to have a greater impact on the downward trend than improving treatment. However, the trend towards increasing prevalence of some risk factors (e.g. obesity) may offset some of the positive effects.

statins have shown benefits, but…

…other measures showed a greater impact

While in overall terms, primary prevention seems to have a greater impact on mortality reduction than secondary prevention, in the case of statins, the number of deaths prevented is considered higher in secondary prevention than in primary prevention. Yet, despite the obvious benefits that have been attributed to statins, focusing on other risk factors (e.g. smoking) and implementing specific types of treatment/management (e.g. hospital resuscitation after myocardial infarction) have shown a greater effect on mortality reduction than the use of statins.

5 Expected Gains in Cardiovascular Health from Statins in Austria

5.1 The Role of Statins in the Prevention of CVD

5.1.1 Efficacy in Clinical Trials

statin trials:

The efficacy of statins in terms of surrogate endpoints (reduction of serum cholesterol) and clinical endpoints (reduction in morbidity, mortality and revascularisation procedures) has been evaluated in several trials.

in secondary prevention relative risk reduction of cardiovascular mortality and morbidity

Although not all statin types have demonstrated significant effects for all relevant patient outcomes[1], the meta-analysis by Ward et al. [30] has established that overall statins in secondary prevention have significantly reduced the relative risk for all-cause mortality, CVD mortality, CHD mortality and fatal MI in clinical trials. Furthermore, relative risks have been reduced for nonfatal stroke, unstable angina, hospitalisation for stable angina and revascularisation interventions (Table 5.5-1).

absolute risk reduction on average 3% - 9%

In terms of absolute risk reduction, the greatest effect size occurred 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) [30].

The medical background on statins has been described in more detail in previous reports [3, 31].

[1] e.g. in patients with stable coronary heart disease, only the statins simvastatin and pravastatin showed benefits with respect to a life-prolonging effect [29] IQWIG. Evaluation of the effects of statin (with particular consideration of atorvastatin). Köln: IQWIG; 2006.

Table 5.1-1: Relative risks of events from meta-analyses of clinical trials

Outcome	All studies	Secondary Prevention CHD	Secondary Prevention CVD
All-cause mortality	**0.84 (0.78-0.90)**	**0.79 (0.70-0.90)**	**0.80 (0.71-0.90)**
CVD mortality	**0.79 (0.74- 0.85)**	**0.75 (0.68-0.83)**	**0.75 (0.68-0.83)**
CHD mortality	**0.77 (0.72-0.83)**	**0.72 (0.64-0.80)**	**0.72 (0.64-0.80)**
Stroke mortality	0.92 (0.74-1.14)	1.07 (0.67-1.71)	1.08 (0.67-1.72)
Nonfatal stroke	**0.75 (0.63-0.90)**	**0.75 (0.59-0.95)**	**0.75 (0.59-0.95)**
TIA	**0.79 (0.68-0.91)**	0.66 (0.37-1.17)	0.66 (0.37-1.17)
Fatal MI	**0.54 (0.44-0.67)**	**0.57 (0.45-0.72**	**0.57 (0.45-0.72)**
Nonfatal MI	**0.70 (0.63-0.77)**	**0.69 (0.59-0.79)**	**0.69 (0.61-0.78)**
Stable angina (SA)	**0.59 (0.38-0.90)**	No data	No data
Unstable angina (USA)	**0.82 (0.74-0.90)**	**0.82 (0.72-0.94)**	**0.82 (0.72-0.94)**
Patients hospitalised for SA	**0.88 (0.84-0.94)**	**0.90 (0.84-0.97)**	**0.90 (0.84-0.97)**
CABG	**0.74 (0.67-0.82)**	**0.76 (0.66-0.87)**	**0.76 (0.66-0.87)**
PTCA	**0.78 (0.67-0.90)**	**0.79 (0.67-0.94)**	**0.79 (0.67-0.94)**
CABG+PTCA	**0.75 (0.70-0.81)**	**0.77 (0.69-0.85)**	**0.77(0.69-0.85)**
CHD death + nonfatal MI	**0.74 (0.71-0.77)**	**0.73 (0.68-0.80)**	**0.74(0.69-0.79)**

Source: Ward et al. [30]; Statistically significant results in bold

CABG: coronary artery bypass grafting; CHD: coronary heart disease; CVD: cardiovascular disease; MI: myocardial infarction; PTCA: percutaneous transluminal coronary angiography; TIA: transient ischemic attack

5.1.2 Statin Treatment in Austria

number of statin prescriptions rises

As has been described by Zechmeister et al. 2008 [3], statins have been reimbursed by the social insurance since the mid 1990s. Until 2004, reimbursement was restricted to secondary prevention only. The number of prescriptions has risen from 432,170 in 1996 to 3,468,303 in 2006. In terms of statin type, simvastatin accounted for the biggest proportion of statins prescribed (40%), followed by atorvastatin (28.5 %). Pravastatin and fluvastatin accounted for 16.7 and 11.3 % respectively whereas lovastatin (2.9 %) and rosuvastatin (0.5 %) played a marginal role with respect to volumes.

simvastatin dominant

initially rising expenditures, later decreasing because of generics

Additionally, expenditure for statins has also risen notably since the mid-1990s. In 1996, around 17 million Euros were paid for statins by the social insurance institutions. Expenditure peaked in 2003 when 94 million Euros were spent on statins. In 2006 expenditure for statins decreased to around 76 million Euros due to the introduction of generics. Again, simvastatin and atorvastatin accounted for the biggest proportion of spending, followed by pravastatin and fluvastatin. The cost per prescription was 39.4 Euros in 1996 and decreased to 22.5 Euros in 2006. In relation to overall expenditure for pharmaceuticals in Austria, the proportion paid for statins rose from 1.2 % in 1996 to 4.1 % in 2002. Since then, the proportion has slightly decreased. In 2006 statins accounted for 2.9 % [32, 33].

on average: € 60 million per year

not every patient eligible gets statins

According to recently published data [34, 35], not all patients who could be treated with statins are prescribed the drugs. In particular, studies have shown that only around a third of those patients who are discharged after an MI are prescribed lipid lowering drugs.

5.2 Expected Health Gains from Statin Treatment in Austria

calculation of health gains with adapted Markov model

As described in the method section (chapter 3.2), in a previous study [3], statin treatment has been compared with the alternative of no medical cholesterol-lowering therapy in terms of cardiovascular disease outcomes. Model outputs from an adapted Markov model have been used to calculate population health gains based on the number of persons who have taken statins in Austria between 1996 and 2006.

reduced morbidity, mortality and revascularisation analysed

The results of the report are summarised below. They represent the estimated cohort sizes in Austria as well as the population health gains which can be expected from statin therapy based on statin efficacy in clinical trials. Health gains are categorised into three groups that are, first, morbidity health gains (angina, MI, stroke), second, mortality health gains (fatal CHD, fatal MI, fatal cerebrovascular disease) and, third, reductions in revascularisation interventions (PCI, CABG).

5.2.1 Cohort Size in Austria

cohort size of Austrian statin takers: between 600,000 and 750,000

Based on the number of statin prescriptions and the corresponding daily doses prescribed, it was estimated how many persons took statins between 1996 and 2006 in Austria. According to the base case calculation, 36,000 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. The results are subject to some uncertainty. Applying a different gender and age distribution (one that is close to the persons hospitalised for an MI in Austria) resulted in a total cohort of about 750,000 persons between 1996 and 2006.

5.2.2 Prevalence of Angina, MI and Stroke

statin patients remain longer in less severe health state

In terms of stable angina (SA), the model actually predicted an increase for the statin group since patients who take statins remain longer in that health state than persons who do not take statins and progress more quickly to more severe health states (Figure 5.2-1).

in 108,000 statin takers in 2007: 180 fewer cases of unstable angina,

Furthermore, the model demonstrated that had around 36,000 persons in 1997 taken statins, this would have resulted in 11 fewer cases of unstable angina (USA) in Austria. The health gains steadily increased rising to minus 175 fewer cases in 2007 in around 108,000 patients (Figure 5.2-1).

5,200 fewer cases of MI, yet…

… 7,000 MIs occured despite statins

In terms of MI, of the 36,000 persons who took statins in the first year, 755 cases of MI occurred in 1997 compared with 1,354 had these persons not taken statins. Consequently, statin treatment resulted in 599 fewer cases of MI. Until 2007, the difference between taking statin and not taking the medication rose to 5,234 fewer MIs. However, the model also predicted that despite taking statins, around 7,100 MIs in 108,000 statin takers occurred in 2007 (Figure 5.2-1).

stroke: minus 240 cases in 2007

Finally, the model forecasted 56 cases of stroke in patients with a history of CHD not on statins, as opposed to 39 stroke cases for those who did take the medication in 1996. Thus, strokes were reduced by 17 in the first year. In 2007, statin treatment resulted in 239 fewer strokes in patients with a history of CHD. However, around 490 strokes were estimated despite taking statins compared to 725 strokes in the untreated cohort (Figure 5.2-1).

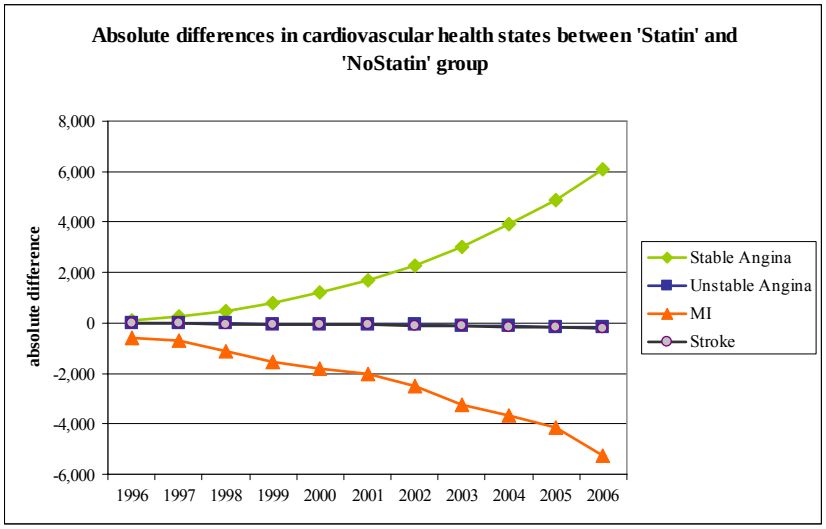

Figure 5.2-1: Differences in cardiovascular health states between 'Statin' and 'NoStatin' group (absolute numbers)

MI: myocardial infarction;

5.2.3 Fatal Events

In 108,000 statin takers in 2007: minus 2,000 fatal CHDs

Figure 5.2-2 shows the absolute differences in the number of fatal events for the two treatment alternatives. 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. In 2007, compared to no medication, of 108,000 estimated statin takers 2,061 fewer persons died because of CHD according to the model. However, around 4,900 died of CHD despite taking statins.

mostly MIs

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

reduction in fatal cerebrovascular events low

Furthermore, for patients with a history of CHD, the model showed a considerably lower reduction of fatal cerebrovascular events than fatal events of 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 as compared to the group not on statins.

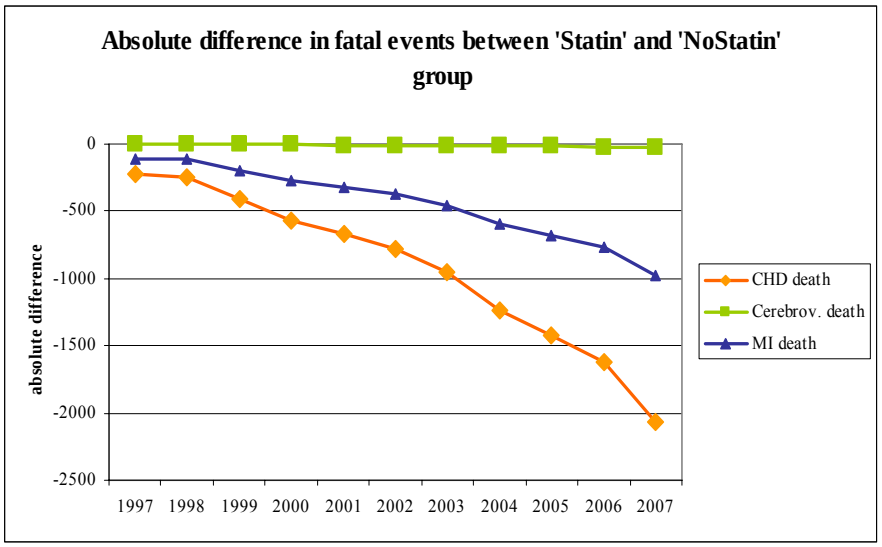

Figure 5.2-2: Difference in fatal events between 'Statin' and 'NoStatin' group (absolute numbers)

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

5.2.4 Revascularisation

fewer CHD cases = fewer revascularisation?

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

health gains results in revascularisation reduction, yet…

As Figure 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 the 'NoStatin' group, 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.

…reduction is low

Compared to health gains in MI described earlier, the number of revascularisation avoided has been low overall. However, since the amount of stable angina increases and revascularisation interventions are also provided for people with stable angina, the model predicts a low overall reduction in revascularisation interventions.

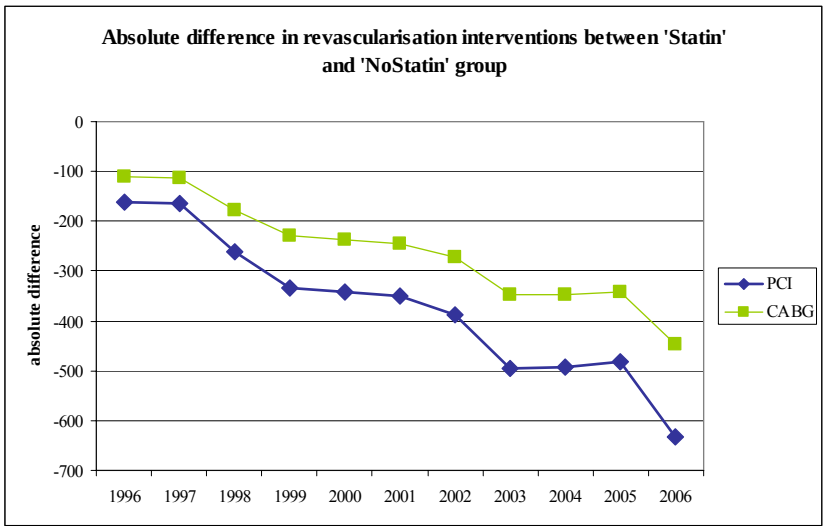

Figure 5.2-3: Difference in revascularisation interventions between 'Statin' and 'NoStatin' group (absolute numbers)

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

greater health gains in males than in females

As demonstrated in Figure 5.2-4 for the health states of angina, MI and stroke, health gains in the statin group are greater for males than for females. This is also the case for avoided fatal events (Figure 5.2-5)

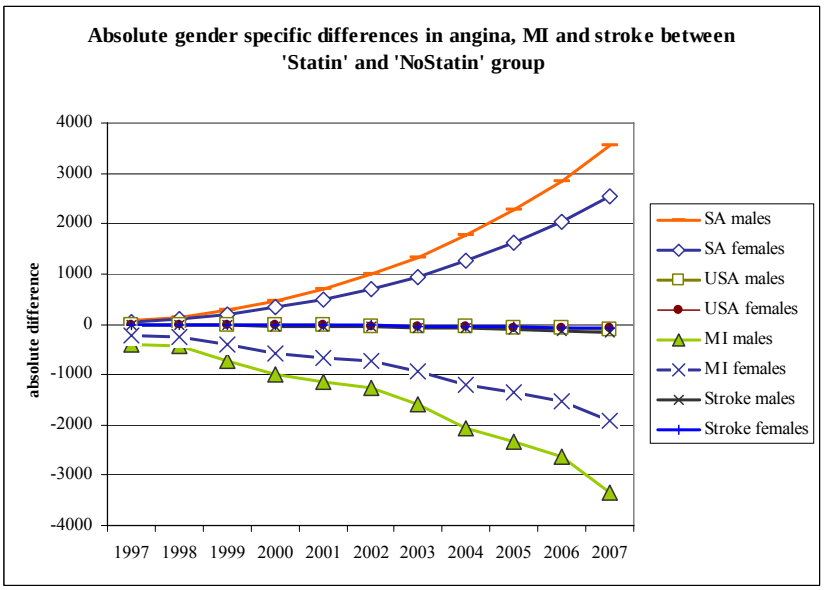

Figure 5.2-4: Gender specific differences for angina, MI and stroke between 'Statin' and 'NoStatin' group (absolute numbers)

MI: myocardial infarction, USA: unstable angina

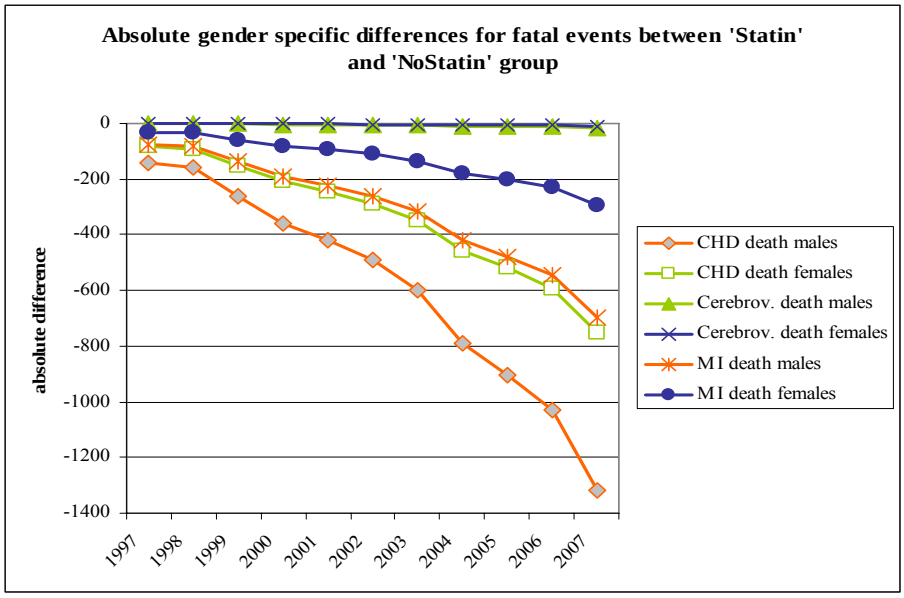

Figure 5.2-5: Gender specific differences in fatal events between 'Statin' and 'NoStatin' group (absolute numbers)

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

In total, in around 600,000 persons who were estimated to have taken statins over 11 years, health benefits of around 28,600 fewer cases of either unstable angina, MI or stroke and roughly 6,100 more cases of stable angina were predicted. Furthermore, the model estimated about 10,300 avoided or postponed fatal CVD events (mostly fatal CHD) and around 7,000 avoided revascularisation interventions.

overall: in 600,000 statin takers minus 28,000 fewer CVD cases, minus 10,300 avoided/postponed fatal CVDs

In other words, 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.

NNT: 21, 59 and 86 to avoid 1 CVD case, fatal event or revascularisation respectively

Although the results suggest that quite a few patients need to be treated in order to gain benefits in one, the prescription of statins from 1996 to 2006 nevertheless should have resulted in some observable population health gains compared to the alternative of not taking statins. This is particularly the case for avoided non fatal MIs and reduced CHD mortality. Further effects in regards to stroke (for those with a history of CHD), cerebrovascular mortality and revascularisation interventions exist but are significantly smaller. To what extent model outcomes are observable in Austrian CVD epidemiology will be addressed in the following chapter.

health gains should be observable in CVD epidemiology

6 Epidemiological Trends in Cardiovascular Morbidity and Mortality in Austria

6.1 Morbidity

hospital data for morbidity trend

As a proxy for morbidity trends in cardiovascular diseases in Austria, administrative hospital data that document the angina, MI and stroke cases as well as revascularisation interventions (PCI, CABG) will be presented in this chapter. When evaluating the trends, we viewed the discharge figures (absolute cases) recorded in the form of ICD codes for the time period between 1995 and 2005 (see chapter 3.3).

every eights case of hospital discharge because CVD

Overall, in 2005 every eighth hospital discharge was due to cardiovascular disease. For men this was the primary cause for hospitalisation and for women the third leading cause. From the age of 50 and over, discharge rates for those who were hospitalised for CVD rose steadily [36].

discharges after MI rose

As Figure 6.1-1 illustrates, the number of patients who were discharged after an MI constantly rose in the 10 year period. While in 1995, there were 21,218 MI patients, in 2005 there were 37,064 (+75 %) patients. The number of annual 'MI discharges' was 10 % higher for men than for women.

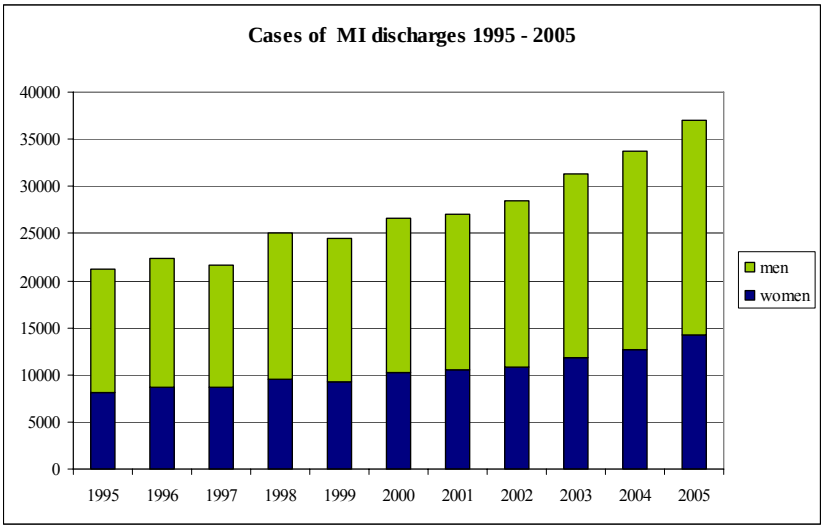

Figure 6.1-1: Absolute cases of MI discharges 1995-2005

Source: hospital discharge data (LKF-Statistics); MI: myocardial infarction

hospitalised females are older than males

Age-specific data show that the number of discharges has continuously risen since 1995 for all age groups in both male and female patients. However, the highest number of discharges in female patients was in the 76 to 84 year old age group. Men were most often discharged after an MI between the ages of 66 and 75 and almost just as often between the ages of 56 and 65. A higher number of females than males above the age of 85 were hospitalised for an MI. This may be due to the longer life-expectancy of and the later occurrence of CVD in women (Figure 6.1-2).

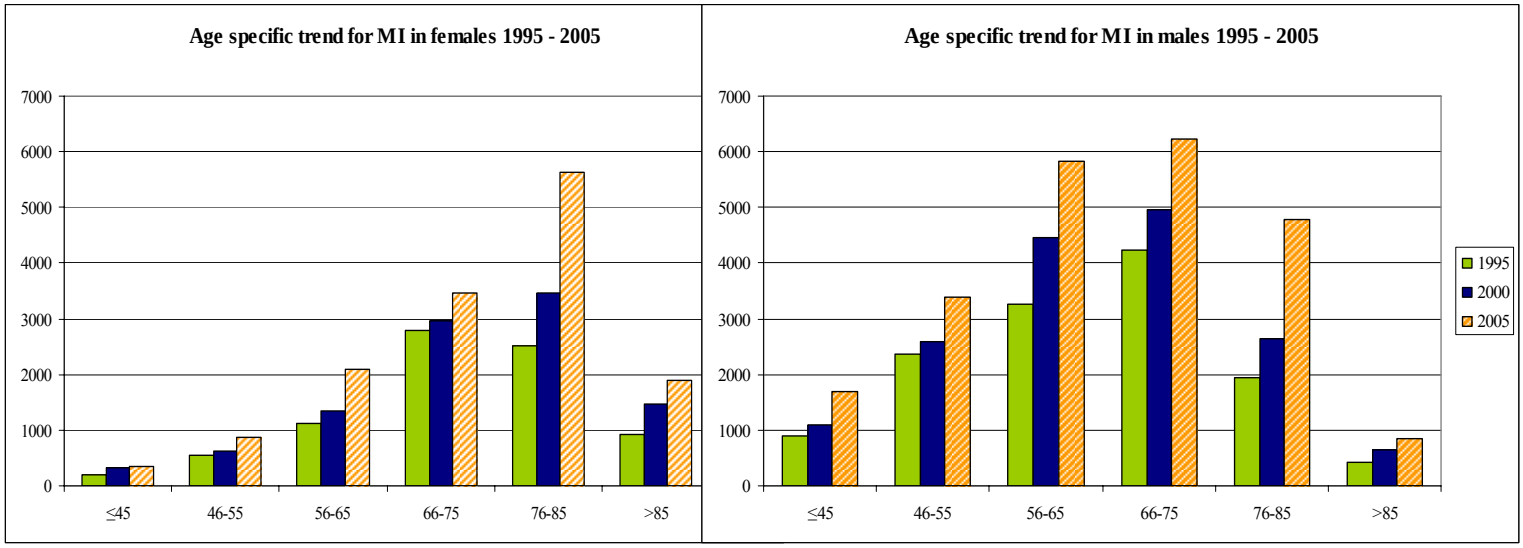

Figure 6.1-2: Absolute age and gender specific trend for MI discharges 1995-2005

Source: hospital discharge data (LKF-Statistics); MI: myocardial infarction

angina: slightly rising trend

A similar although slightly less continuous trend can be observed in discharges with the diagnosis of stable or unstable angina (Figure 6.1-3). In 1995, 26,204 cases were documented. In 2005, the figure rose to 39,051 cases with women accounting for slightly more than 40 %.

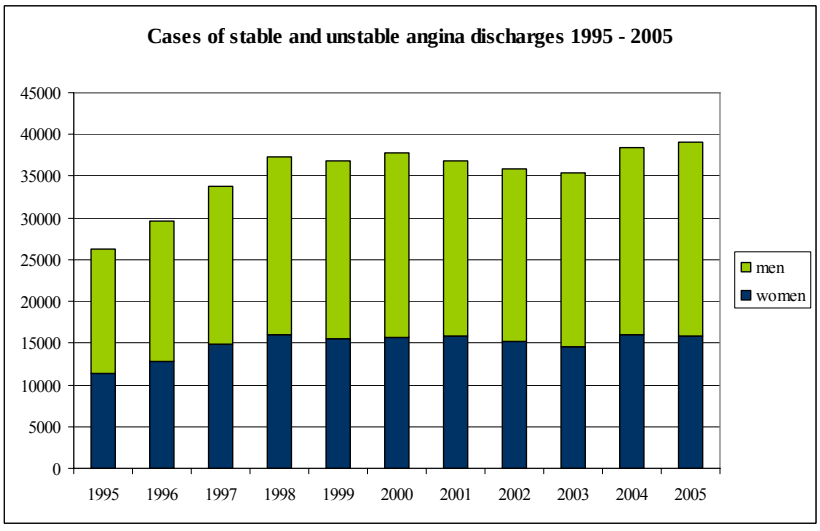

Figure 6.1-3: Absolute cases of stable and unstable angina 1995-2005

Source: hospital discharge data (LKF-Statistics)

stroke data unclear

The case of stroke is unclear. Figure 6.1-4 demonstrates that there is a substantial drop of discharges in 2001 (from 62,700 to about 41,000 cases overall) after which discharges remain at the lower level. This is surprising for two reasons: Firstly, there is no disease-related explanation for the sharp drop in 2001 and secondly, it seems implausible that between 1995 and 2000

the number of stroke-related discharges was considerably higher than discharges with a diagnosis of MI.

change in coding of data may cause inconsistency…

…data was not used further

This indicates substantial uncertainty with respect to data quality and accuracy. The true reason behind the inconsistency may be a change in the payment scheme linked to changes in coding of data which resulted in different classification of diagnoses in patients. For that reason, stroke data are not used for further analysis in the report. However, since the statin analysis is restricted to stroke outcomes for those patients with a history of CHD only and the previous report has shown little health impact from statins for those patients omission of stroke data will not influence the following results and the conclusion to a great extent.

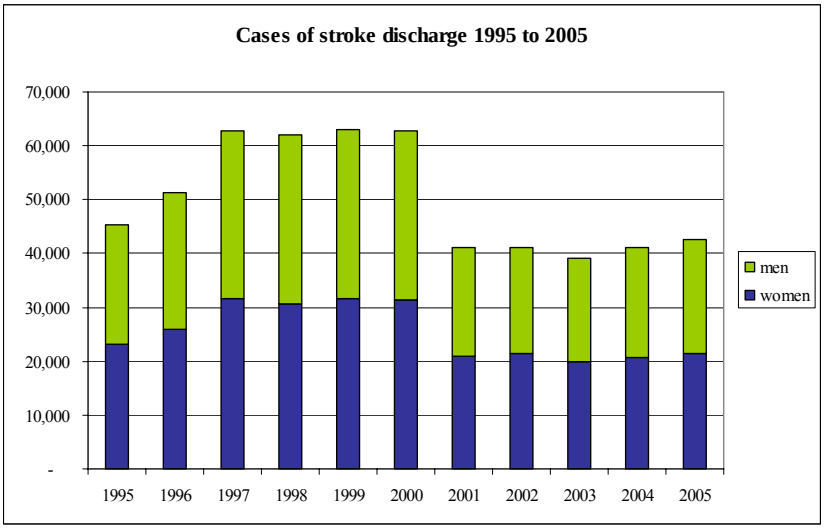

Figure 6.1-4: Absolute cases of stroke discharge 1995-2005

Source: hospital discharge data (LKF-Statistics)

rising number of PCIs

Furthermore revascularisation procedures have been analysed. Corresponding to MI, administrative data on percutaneous coronary intervention (PCI) show that the number of PCIs has risen progressively since 1995. While in 1995, 5,506 interventions were registered, the amount of cases rose almost three times to 16,153 administered interventions in 2005. Females received below a third of all the interventions (Figure 6.1-5).

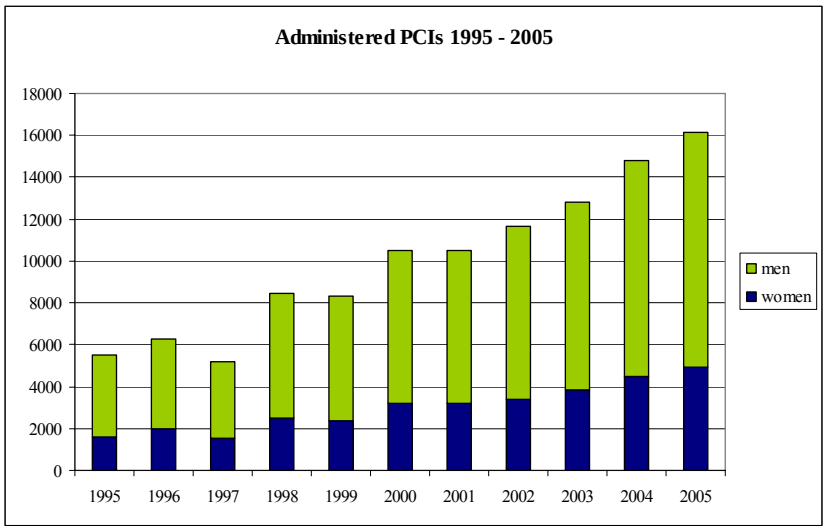

Figure 6.1-5: Absolute cases of administered PCIs 1995-2005

Source: hospital discharge data (LKF-Statistics): PCI: percutaneous coronary intervention

PCIs rose in every age-group

Similar to the age-specific picture for MI, PCIs have also risen in every age group in both male and female patients (Figure 6.1-6). However, while in male patients the number of PCIs per age group seems to roughly correspond with the number of MIs, this is not the case for female patients. For females, the age group with the highest number of MIs (76 to 85 years) shows a comparably low number of PCIs. The number is even lower than for males in the same age group despite a higher number of MIs in women than in men in this age group.

corresponds with number of MIs in males…

…but not in females

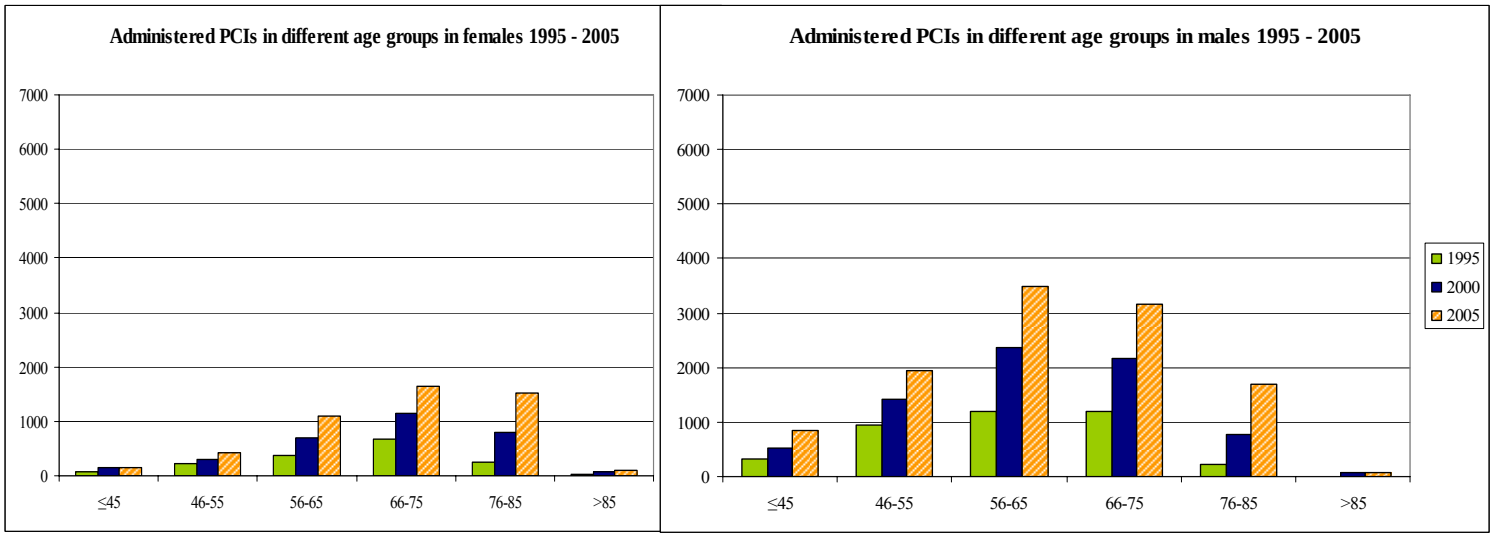

Figure 6.1-6: Absolute cases of administered PCIs gender and age specific 1995-2005

Source: hospital discharge data (LKF-Statistics): PCI: percutaneous coronary intervention

CABG: slight decrease…

Finally, data on the number of coronary artery bypass grafting (CABG) were analysed (Figure 6.1-7). In contrast to PCI, the number of CABGs has slightly decreased since 2000 in both men and women. In total, 4,126 CABGs were documented in 1995 while in 2005, the number decreased to 4,114. Women received around a quarter of those interventions.

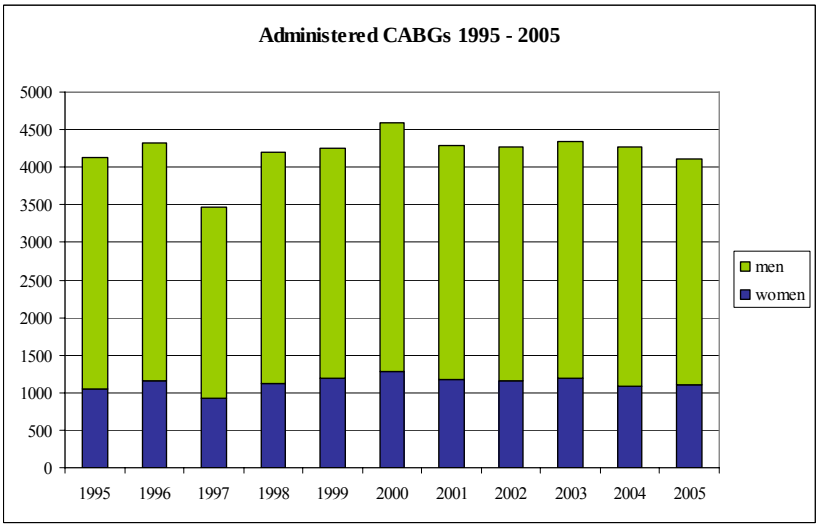

Figure 6.1-7: Absolute cases of administered CABGs 1995-2005

Source: hospital discharge data (LKF-Statistics): CABG: coronary artery bypass grafting

…except for patients aged 76-85

In both, male and female patients, CABGs decreased in all age groups except in the 76 to 85 year olds, in which the number has constantly increased. However, in the 66 to 75 year olds, the decrease was slightly greater in female than in male patients (Figure 6.1-8).

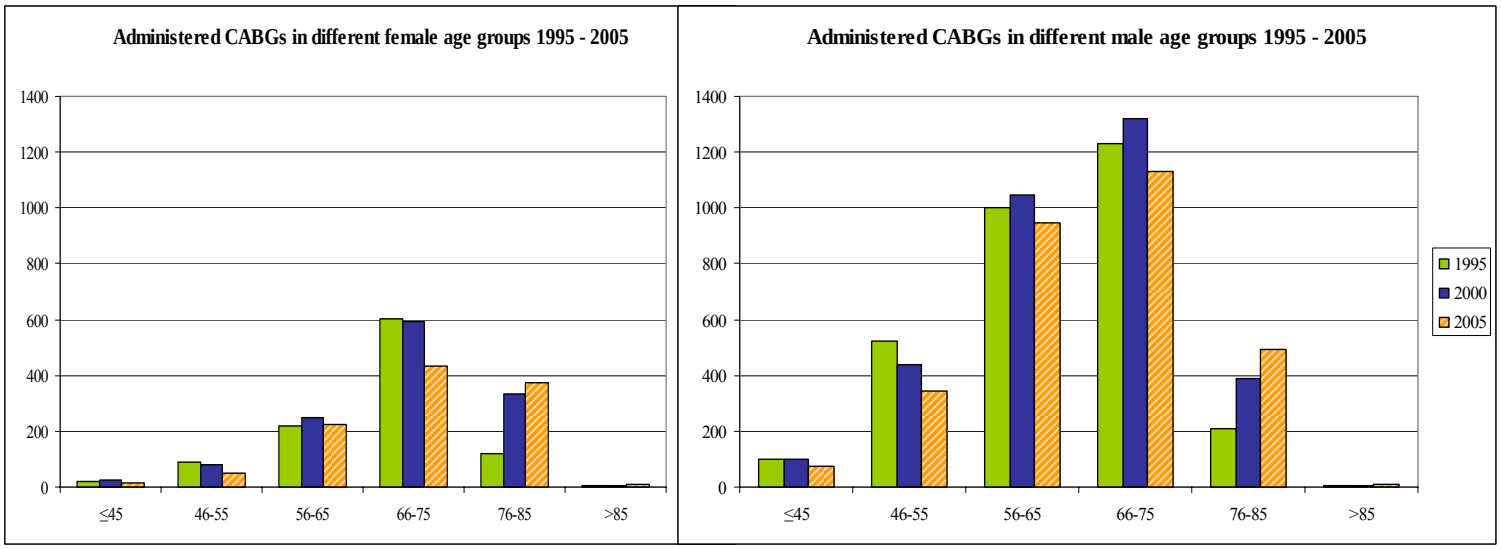

Figure 6.1-8: Absolute cases of administered CABGs gender and age specific 1995-2005

Source: hospital discharge data (LKF-Statistics): CABG: coronary artery bypass grafting

fewer people die from CVD in hospital…

…results in increasing morbidity rates

reinforced by aging of population

In contrast to absolute numbers of discharges in cardiovascular diseases, Leitner (2007) [36] shows that the level of age standardised discharge rates per 100,000 continuously rose from 1989 to 1998 but has stagnated since 1998. Furthermore, she demonstrates that the age-standardised discharge rate of persons who died during hospitalisation has fallen over the last ten years, thus indicating an increase in those who survive a CVD event. Consequently this factor has resulted in an increase in CVD morbidity. This is reinforced even further by demographic changes with larger cohorts moving into higher age-groups.

6.2 Mortality

standardised mortality rates fell by 50% since 1970

For the Austrian population, total age standardised mortality rate has declined sharply by 51 % since 1970. The decrease is similar for men (-51 %) and for women (-52 %). The decrease is linear in shape since the 1970ies exhibiting no specific dynamics such as accelerations. This is true for both males and females [4].

CVD mortality rate fell by 59%

Cardiovascular disease is one of the most important causes of mortality. In 2005, 32,636 people died from cardiovascular disease accounting for almost half of all deaths [36]. Age standardized mortality rate fell by 59 % between 1970 and 2005. This trend has been particularly noticeable during the 1980s and since the beginning of the 21st century. The decline is similar for men and women. However, to what extent these figures are a result of true health gains or a consequence of the change from ICD-9 to ICD-10, the introduction of new death certificates and improved data quality is unclear [4].

change from ICD-9 to ICD-10 may have influenced data

4 of 10 CVD deaths are due to CHD

Twenty percent of all deaths and forty percent of all cardiovascular deaths are due to CHD. Mortality caused by CHD has been reduced by 14 % since the period of 1988-94 and by 26 % since the period of 1978-84 [4].

more than 7,000 fatal MIs annually

mortality rates decreased, decline stronger in men

Myocardial infarction is the most significant cause of death among all deaths from CHD. More than 7,000 people die every year from an MI accounting for almost half of all CHD deaths (53 % in men and 40 % in women). The standardised death rate is more than twice as high in men as in women. Again, mortality has decreased since 1970. Within the last ten years the decline was 28 % and greater in men (-30 %) than in women (-27 %) [4].

cerebrovascular deaths declined but still 11% of all deaths

Similarly, fatal cerebrovascular diseases have decreased. They fell by one third compared to the period of 1988-94 and by 57 % compared to 1978-84. Nevertheless, cerebrovascular diseases account for 11 % of all deaths in Austria (8 % in men and 13 % in women) which equals more than 8,000 deaths per year. The death rate for men is 20 % higher than for women [4].

Figure 6.2-1 demonstrates the decline in the gender specific and age-standardised mortality rates for CVD overall, as well as for CHD, MI and cerebrovascular diseases.

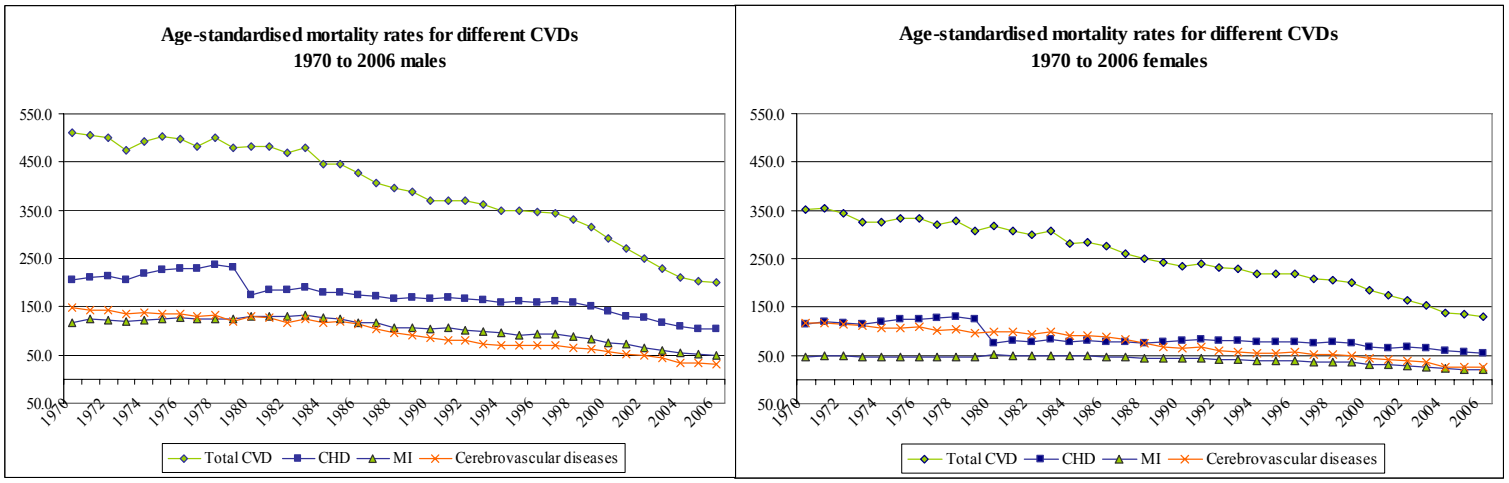

Figure 6.2-1: Age-standardized mortality rates for different CVDs 1970-2006; males and females

Source: Statistik Austria [37]

Most of the mortality cases in cardiovascular disease occur above the age of 65. The average age of CVD death was 81.9 years in 2005. Women die on average at the age of 84.9 from CVD while the average age of CVD death for men is 77.5. The average age of death has increased by 5.3 years and 3.7 years for women and men respectively over the last 20 years [36].

average age of CVD death: 82 years

7 Contrasting the Results: Expected and Observed Health Gains

contrasting predicted health gains with observed epidemiology…

In this chapter, expected population health gains from taking statins as forecast by the model and described in chapter 5.2 are contrasted with the observed changes in cardiovascular epidemiology in Austria (from chapter 6) for the period between 1995 and 2006. The aim is to analyse whether the model results are reflected in real-life population health. At the same time, the issue of model validity is addressed. In particular, this relates to the external validity of clinical statin studies, since the model results are strongly based on the efficacy of statins in randomised controlled trials. As repeatedly stressed, efficacy may depart from effectiveness in routine practice, particularly due to reduced compliance of patients or other influential factors (e.g. co-morbidity).

…addresses issues of model validity

Following, model outcomes and observational data in terms of cardiovascular morbidity as well as mortality are compared based on the method described in chapter 3.3.

7.1 Morbidity

contrasting morbidity is limited

Contrasting morbidity results from the model and observed morbidity is limited to a summary of both observed data and model results.

expected health gains:

decrease in non fatal MI

people remain longer in less severe health state

Changes in the absolute number of persons in the health states under evaluation as well as differences between taking statins and not taking statins have been presented earlier. Overall, statin treatment is expected to result in a considerable decrease in non fatal MIs and a slight decrease in revascularisation interventions. On the other hand, the number of persons with stable angina is expected to increase in the statin group as people remain longer in the less life-threatening health state of stable angina. Furthermore, the number of non-fatal strokes is not likely to be affected to a great extent when the two alternatives are compared. Figure 7.1-1 summarises the outcomes.

hospital data:

increasing numbers of MI and PCI diagnoses

On the other hand, hospital discharge data have shown that aside from CABG, all the parameters evaluated indicate an increase in the ten year observational period from 1995 to 2005. This is particularly the case for the diagnoses of MI and PCI as highlighted in Figure 7.1-2.

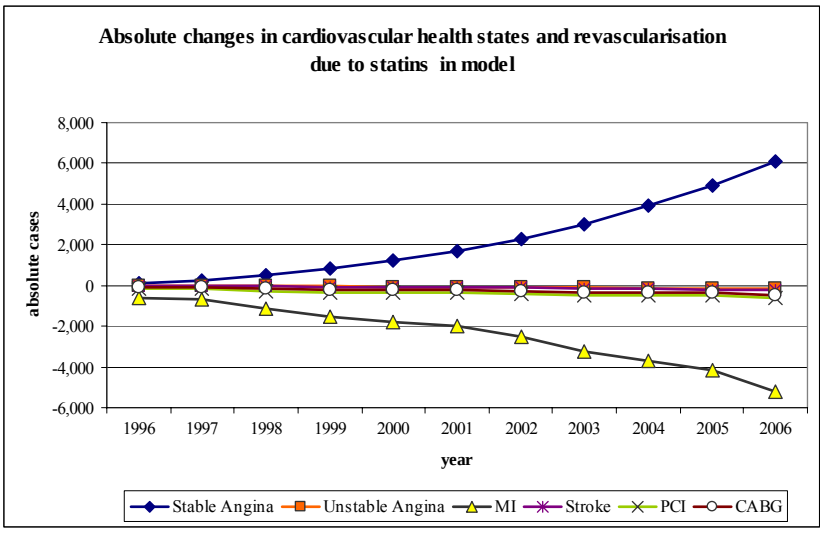

Figure 7.1-1: Absolute changes in cardiovascular health states and revascularisation in model

CABG: coronary artery bypass grafting; MI: myocardial infarction; PCI: percutaneous coronary intervention

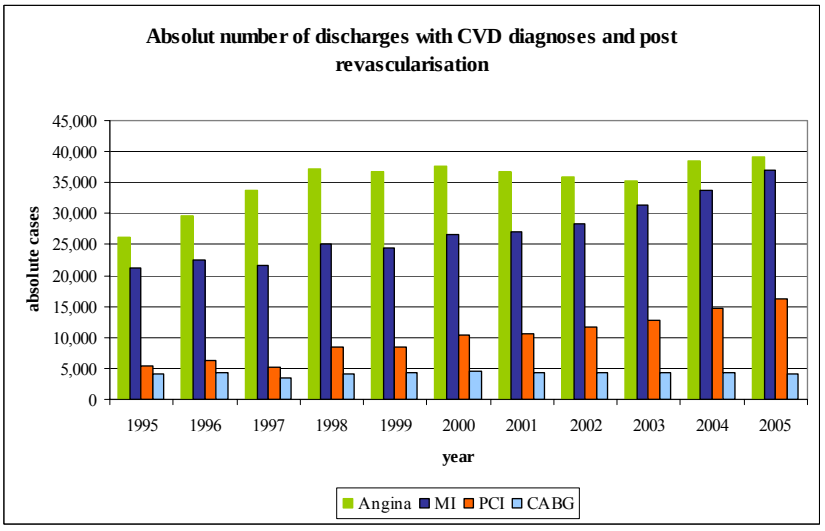

Figure 7.1-2: Absolute number of discharges with CVD diagnoses and post revascularisation

CABG: coronary artery bypass grafting; MI: myocardial infarction; PCI: percutaneous coronary intervention

7.2 Mortality

changes in mortality rates with reference year 1995 calculated

To compare mortality outcomes in the model with observed mortality, changes in overall CVD mortality rates and changes in mortality rates for specific CVD-subgroups (CHD mortality rates, MI mortality rates and cerebrovascular mortality rates) in cases per 100,000 person years based on the reference year of 1995 have been calculated.

CVD mortality rates decreased in model as and in epidemiological data…

…but greater in observational data

Figure 7.2-1 presents the results of the comparison in overall CVD mortality rates. Based on the reference year of 1995, mortality rates (cases per 100,000 person years) decreased in the model as well as in observational data. However, the decrease is considerably greater in observed CVD mortality than in the model results. While the former decreased by more than 100 per 100,000 between 1996 and 2006 the latter fell by 40 per 100,000 in the same time period.

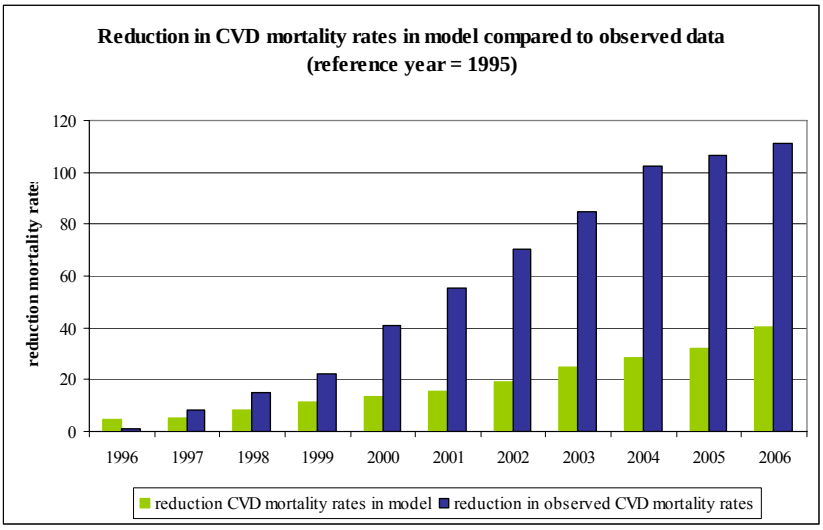

Figure 7.2-1: Reduction in CVD mortality rates in model and observed data (cases per 100,000 person years)

CVD: cardiovascular disease

high consistency in CHD subgroup

The results are different, when focusing on selected subgroups of CVD individually. As demonstrated in Figure 7.2-2 changes in CHD mortality rates between 1995 and 2006 are more or less consistent between model outputs and observed mortality. In both cases mortality rates decreased by around 40 fatal events per 100,000.

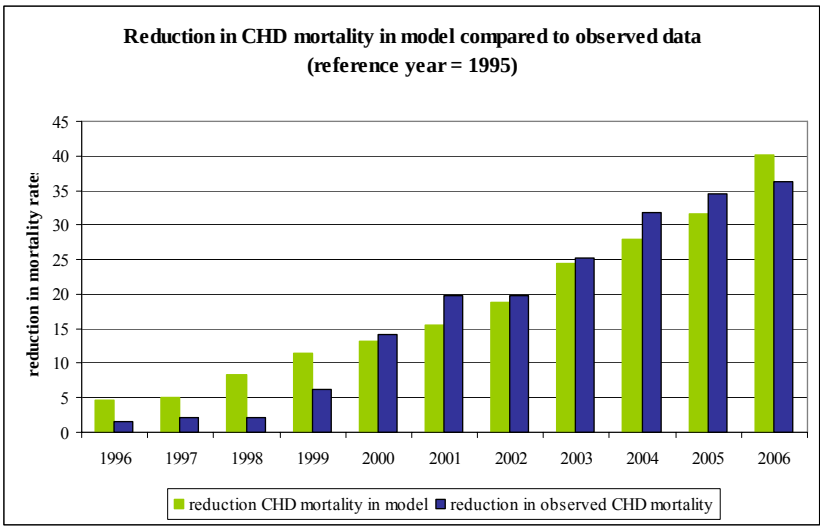

Figure 7.2-2: Reduction in CHD mortality rates in model and observed data (cases per 100,000 person years)

CHD: coronary heart disease

MI: reduction in observed mortality rate greater than in model

For MI as a subgroup of CHD, reduction in mortality rate is slightly greater in observed MI mortality than in the model outcomes. While observed MI mortality rates fell by roughly 25 per 100,000 between 1995 and 2006, MI mortality rates in the model outcomes dropped by around 20 cases per 100,000 person years during the same time period (Figure 7.2-3).

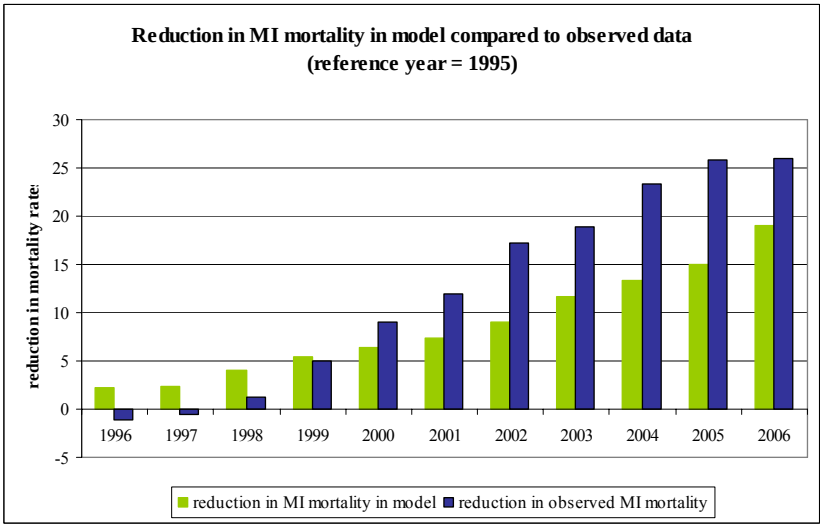

Figure 7.2-3: Reduction in MI mortality rates in model and observed data (cases per 100,000 person years)

MI: myocardial infarction

large differences in cerebrovascular mortality rates

On the contrary, cerebrovascular mortality rate reductions were almost negligible with respect to model outcomes while observed cerebrovascular mortality showed a considerable decrease of minus 30 cases per 100,000 in 2006 compared to 1995 (Figure 7.2-4).

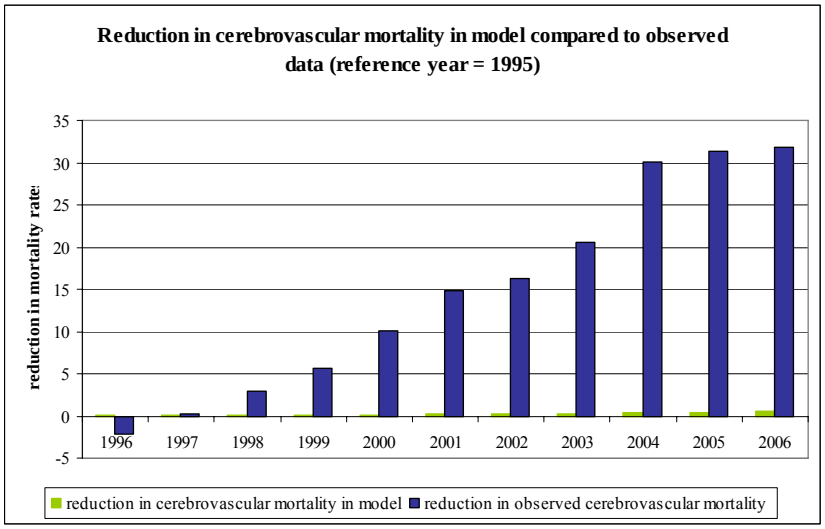

Figure 7.2-4: Reduction in cerebrovascular mortality rates in model and observed data (cases per 100,000 person years)

different time periods – different trends?

In order to further explore the possible influence of statins on cardiovascular mortality trends, a statistical analysis was conducted to discover if the trend in the decline from 1998 onwards (when statins are expected to clearly have an impact on population health) was significantly different from the trend between 1970 and 1998.

all cause deaths

Table 7.2-1 demonstrates the outcomes of the analysis: First, for comparative reasons, changes in total age-standardised mortality rates for all causes of death in Austria are analysed. In the first period of observation, age-standardised mortality rates annually decreased on average by 14.4 per 100,000 (standard deviation/sd= 12.6) while in the second period, the average difference is minus 12.8 per 100,000 (sd= 8.9). Relative changes per year are minus 1.96 % (sd= 1.6) for the first period and minus 2.6 % (sd= 1.8 %) in the second period. Both, the average changes in mortality rates and relative changes between the two periods do not differ statistically significant (t-test: p= 0.74 and 0.69 respectively). The same is true for gender-specific analyses.

no statistically significant difference between different periods

CHD mortality

greater decline after 1998 than before

With respect to CHD, from 1970 to 1998 age-standardised mortality rates decreased each year on average by 1.6 per 100,000 (sd= 10.8). From 1998 to 2006 the average decrease per 100,000 per year was 3.79 (sd= 2.9). In terms of relative changes, the average decrease was 0.9 % (sd= 6.7 %) in the first period and 4.0 % (sd= 2.9 %) in the second period. Both, the average changes in mortality rates as well as the relative changes differ significantly between the two periods (Wilcoxon-test: p= 0.011 and 0.004 respectively).

similar in gender specific analysis

Gender specific results show a similar pattern. Concerning CHD deaths in men, age standardized death rates per 100,000 as well as relative changes fell

on average statistically significantly more (Wilcoxon-test: p = 0.012 and 0.002 respectively) from 1998 onwards than between 1970 and 1998.

In women the decline in death rates per 100,000 was also greater from 1998 onwards than between 1970 and 1998, although this is not statistically significant (Wilcoxon-test: p = 0.067). Yet, the relative decrease in death rates from CHD in women were on average significantly greater after 1998 than before 1998 (Wilcoxon-test: p = 0.026).

MI mortality declined stronger after 1998 than before

In the case of myocardial infarction, age-standardised death rates per 100,000 dropped on average by 0.5 (sd= 2.5) in the first period of observation while from 1998 onwards the average decline is 2.9 per 100,000 (sd= 1.6). The relative differences per year were on average minus 0.7 % (sd= 3.4 %) for the first period and minus 6.2 % (sd= 3.5 %) for the second period. Both variables show that the average decline was statistical significantly greater after 1998 than before (t-test: p = 0.011 and < 0.001 for absolute and relative changes respectively).

same pattern in gender specific analysis

The same pattern appears in the gender specific analysis. In males the average decrease in myocardial infarction death rates per 100,000 and the average relative decline are significantly greater in the second period than in the first one (t-test: p = 0.009 and < 0.001). Respectively, in women the average decline in death rates per 100,000 and the average relative decline are also statistical significantly stronger in the period from 1998 onwards than from 1970 to 1998 (t-test: p= 0.040 and 0.003 respectively).

cerebrovascular death decline: difference between periods not so obvious

The results differ slightly for cerebrovascular diseases. For the overall population, death rates per 100,000 decreased each year on average by 2.6 (sd= 3.7) for the first period and by 3.5 (sd= 2.7) for the second period. Relative changes were on average minus 2.8 % (sd= 3.8 %) and minus 7.8 % (sd= 6.9 %) for the two periods respectively. While the difference between the two periods is statistically significant when relative changes are compared (t-test: p= 0.009) this is not the case for the differences in death rates per 100,000 (t-test: p= 0.513).

similar in gender specific analysis

A gender specific analysis shows similar outcomes. In men, the average changes in death rates per 100,000 do not statistically differ between the two periods observed (t-test p= 0.396), however the relative changes declined significantly more in the latter period than in the former (t-test: p= 0.009). The same is true for women. Both variables seem to decline to a greater extent in the latter than in the former period. However, the difference in the reduction in death rates per 100,000 is not statistically significant (t-test: p= 0.626) while the difference in the relative reduction is statistically significant (t-test: p= 0.031).

Table 7.2-1: Mortality differences between periods 1970-1998 and 1998-2006

	Average annual changes in mortality rates per 100,000 person years					**Average relative changes in mortality rates**				
	1970-1998		**1998-2006**			**1970-1998**		**1998-2006**		
	Rate/ 100,000 (p.a.)	**sd**	**Rate/ 100,000 (p.a.)**	**sd**	**p-value**	**Relative changes (%)**	**sd**	**Relative changes (%)**	**sd**	**p-value**
Overall mortality	-14.4	12.6	-12.8	8.9	0.740	-1.96	1.6	-2.6	1.8	0.690
CHD mortality	-1.6	10.8	-3.79	2.9	0.011	-0.9	6.7	-4.0	2.9	0.004
MI	-0.5	2.5	-2.9	1.6	0.011	-0.7	3.4	-6.2	3.5	0.001
Cerebrov. disease	-2.6	3.7	-3.5	2.7	0.513	-2.8	3.8	-7.8	6.9	0.009

CHD: coronary heart disease; Cerebrov. disease: cerebrovascular disease; MI: myocardial infarction; sd.: standard deviation; p.a.: per annum

8 Sensitivity Analysis

previous report: uncertainty in model outcomes

In the preceding report [3] sensitivity analysis demonstrated that potential population health gains from taking statins are subject to considerable uncertainty when age and gender distribution of the statin takers was varied. This is especially the case for non-fatal MI and fatal CHD where more cases were avoided in sensitivity analysis than in the base case [3].

sensitivity analysis here:

Consequently, sensitivity analyses with the same variation in gender and age distribution were also conducted to compare mortality rate reductions in cases per 100,000 person years (reference year 1995) between model results and observational data. Figures 8.2-1 to 8.2-4 illustrate these outcomes.

different gender and age distribution -> greater CVD mortality rate reduction due to…

Compared to the base case, differences between observed mortality rate reduction and model results are lower with respect to overall CVD mortality when a different gender and age distribution of Austrian statin taker is assumed. In other words, model results in sensitivity analysis illustrate higher reductions in overall CVD mortality rates than it was shown in the base case (Figure 8.2-1).

…greater CHD mortality rate reduction

This is mainly due to greater reductions in CHD mortality in the sensitivity analysis which is demonstrated in Figure 8.2-2. In contrast to the base case, the model's calculation regarding CHD mortality rate reduction correspond less to the observed mortality in sensitivity analysis. The latter demonstrates a greater reduction in CHD mortality rates in the model than in observed epidemiology. Yet, with respect to MI mortality, results between model outcomes and observed mortality are more or less consistent (Figure 8.2-3).

cerebrovascular mortality: no difference

In terms of cerebrovascular mortality rate reduction, sensitivity analysis did not have a noteworthy impact on the results (Figure 8.2-4).

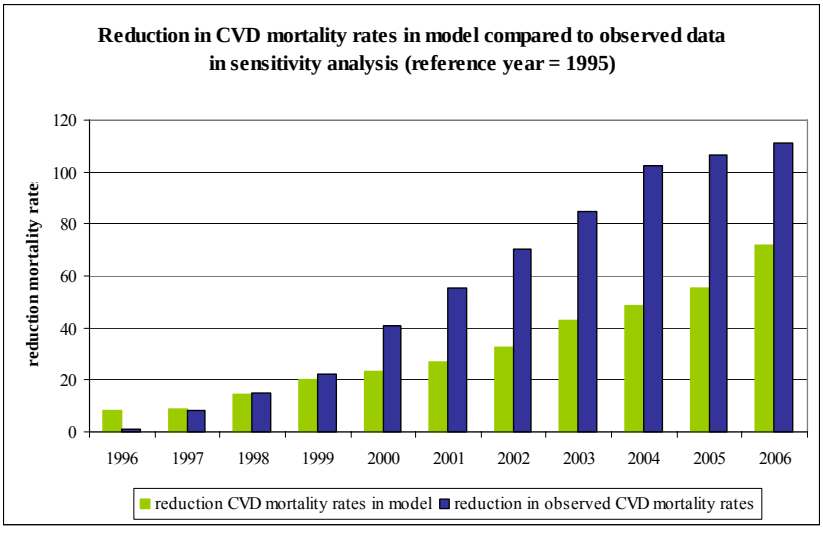

Figure 8.2-1: Reduction in CVD mortality rates in model and observed data (cases per 100,000 person years); sensitivity analysis

CVD: cardiovascular disease

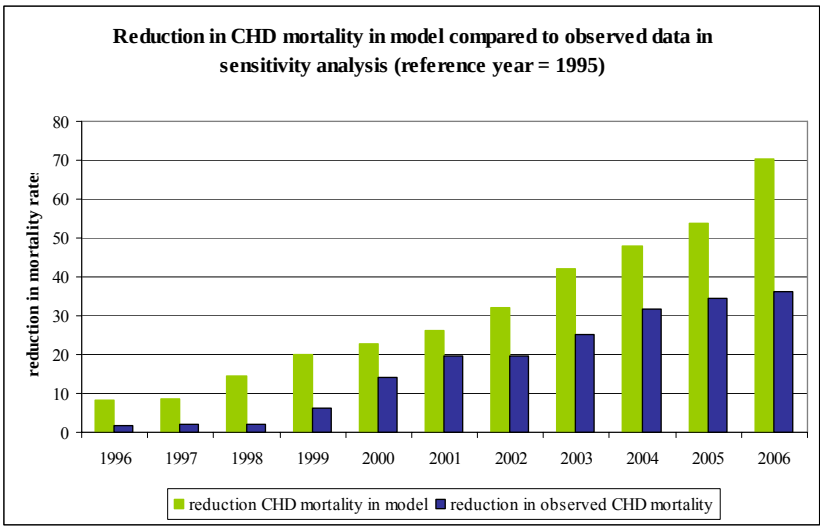

Figure 8.2-2: Reduction in CHD mortality in model and observed data (cases per 100,000 person years); sensitivity analysis

CHD: coronary heart disease

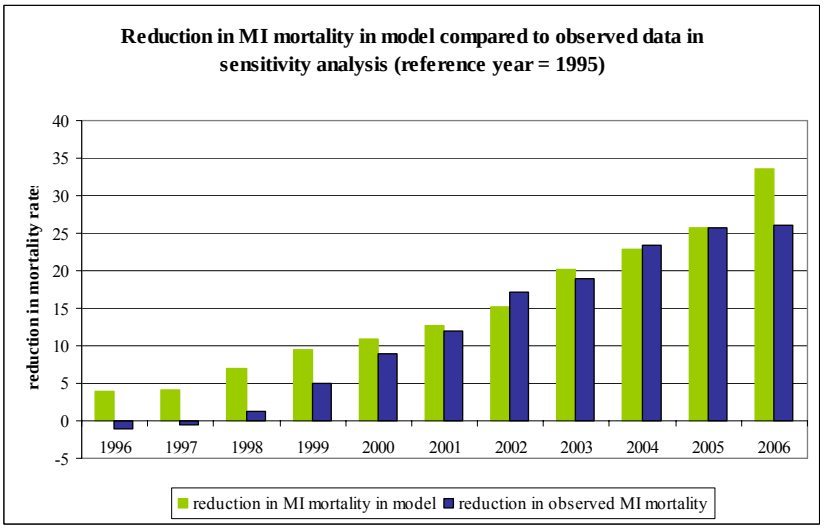

Figure 8.2-3: Reduction in MI mortality in model and observed data (cases per 100,000 person years); sensitivity analysis

MI: myocardial infarction

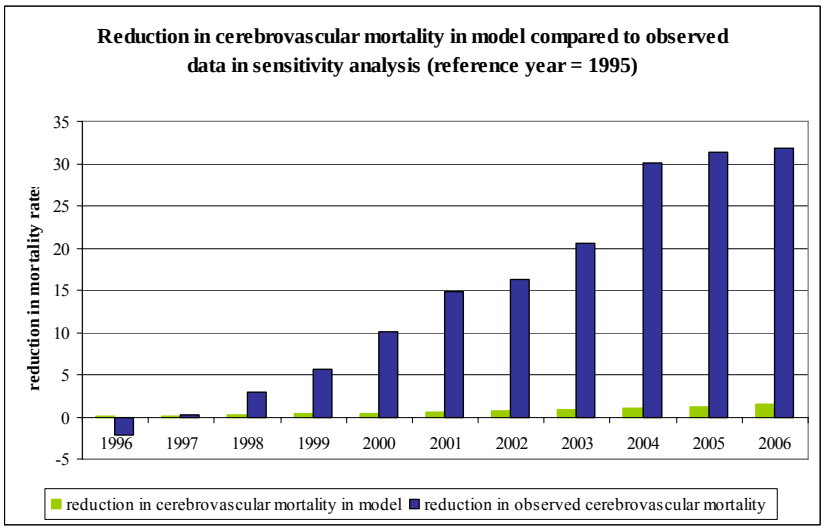

Figure 8.2-4: Reduction in cerebrovascular mortality in model and observed data (cases per 100,000 person years); sensitivity analysis

9 Discussion

comparison of model and observed data

The aim of this study was to analyse whether expected health gains from eleven years of statin treatment in Austria (based on the evidence from clinical studies) can at the same time be observed in Austrian cardiovascular disease epidemiology. To achieve this, the expected health gains in cardiovascular morbidity and mortality forecast by a model that compared persons undergoing statin treatment to those with no medical treatment, were measured against observed cardiovascular epidemiology in Austria.

in model: statins reduce non fatal MI, less severe health states increase

In terms of morbidity, potential health gains in the model have been shown for non fatal MI in particular. The population model demonstrated that the statins prescribed led to an estimated reduction of up to 26,600 non-fatal MIs by 2007. Additionally, some revascularisation interventions seem to have been avoided due to statins although the reduction is small probably due to an increase in other CHD health states that offsets the effect.

in reality: rising hospital MI-discharges and revascularistions

However, in contrast to model results, hospital discharge data have shown an increase in the diseases under evaluation, most significantly in MI discharges. This was particularly the case for older age groups. Furthermore, the number of administered PCIs has risen. Only the number of CABGs fell slightly in the period observed.

comparing results is limited

Thus, there seems to be no correspondence in morbidity trends between model results and observed cardiovascular morbidity. However, comparison of these two types of results is extremely limited:

other factors may affect CVD epidemiology:

overweight, obesity, smoking…

…may counterbalance positive effects of statins

First of all, as has been demonstrated in chapter 4.2.2, many other factors exist that can affect the epidemiology of cardiovascular diseases. Thus, health gains with respect to avoided MIs due to statins may be counterbalanced by other determinants of cardiovascular diseases. For example, the model does not take into account aging of the population. While cardiovascular morbidity may well be reduced in younger age groups, this is likely to be compensated by the aging of the population with rising morbidity in older age groups. Additionally, recent health survey data indicate a trend towards an increasing number of people who are overweight or obese, higher rates of smoking among women and lowering physical activity [38, 39]. Similar to the example of England and Wales in chapter 4.2, this may counteract the positive effect from lowering cholesterol.

economic factors influence hospital admissions

Secondly, hospital admissions are influenced by incentives which may not necessarily be disease related but induced by economic factors (a built bed is a filled bed). This is particularly the case for revascularisation interventions where capacity for PCIs has increased considerably over the last years [40, 41].

technology was improved, guidelines for state of the art changed over time

Thirdly, rising numbers of cardiovascular discharges may be caused by improved diagnosis and reduced out-of-hospital case-fatalities resulting in an increase in admission rates. Moreover, guidelines for state of the art management of cardiovascular disease have been revised over the years [42] which particularly influences the number of revascularisation interventions.

discharge data not always valid

Furthermore, as the case of stroke has shown, morbidity data need further investigation. It may be that discharge data is not a very valid source for factual epidemiology, hence under- or overestimation of the true number of cases in cardiovascular diseases seems likely.

overestimation of statin effect possible

Finally, however, it could also be the case that the model overestimates the true benefit. In other words, with respect to morbidity and revascularisation interventions, the benefit of statins in routine clinical practice could be lower than demonstrated in clinical studies under ideal conditions. Since we do not know how hospital discharges would have been affected without the existence of statins, this question cannot be definitely answered for the time being.

international results similar

Other countries have shown similar results. For instance, Majeed et al. (2004) [43] demonstrated that the great increase in cost and volume for prescribed lipid regulating drugs in England has been associated with only a modest reduction in admission rates for MI between 1996 and 2002. Changing diagnostic criteria such as the use of cardiac troponin measurement have been mentioned as possible explanatory factors.

CHD mortality results in model and observed data similar, CVD results differ

In terms of mortality, base case model results correspond well with observed epidemiology in regards to CHD mortality rate reduction, while the results differ considerably with respect to cerebrovascular and overall CVD mortality rate reduction.

reason: model included only patients with CHD history

The differences can be explained by the fact that the model only considered fatal stroke with a history of CHD while epidemiological data include all types of CVD mortality. Consequently, overall CVD mortality rates are expected to be lower in the model results than in observed mortality. Yet, as sensitivity analysis has shown, some uncertainty also exists for CHD mortality rate reduction.

CHD mortality decreased stronger after 1998 than before, but…

On the other hand, the comparison of observed CHD mortality between the period of 1970 to 1998 and from 1998 onwards has shown that mortality rate has decreased significantly faster in the later period than in the earlier one in both males and females. The difference for cerebrovascular mortality rate changes between the two periods observed was less clear.

several factors influence cardiovascular mortality

These results are consistent with the model outcomes and indicate that statins may well have had an influence on decreasing CHD mortality. However, no evidence seems to indicate an impact on cerebrovascular mortality. Nevertheless, similar to the case of morbidity described earlier, results are not enough to substantiate a causal relationship between the utilisation of statins and observed changes in cardiovascular mortality. This is again because several other factors may have influenced cardiovascular mortality between 1996 and 2007:

greatest effect from reduced smoking

In chapter 4.2.2, international studies were presented which showed that CHD deaths avoided or postponed in secondary prevention were mostly related to changes in smoking behaviour, only a quarter of prevented deaths were attributed to statins. Furthermore, improved treatment in acute MI has shown a greater influence on CHD mortality changes than statins.

Norway and Denmark: different statin utilisation… …no obvious mortality differences

Moreover, an international study by Folino-Gallo et al. (2005) [2] concluded that statin use might not be a major factor in the reduction of CHD mortality. The authors had selected two countries with high variability in statin utilisation (Norway and Denmark) and compared their trends in CHD mortality. They demonstrated that despite a two- to five-fold greater utilisation of statins in Norway, no obvious difference in country-specific mortality trends could be observed. Failed targeting resulting in underuse, overuse or misuse of the medication as well as discrepancies between efficacy and real world effectiveness were mentioned as the factors most likely explaining the result.

other study: positive impact of new drug launch on mortality

On the other hand, an econometric study by Lichtenberg [6] that analysed the launch of new drugs' impact on longevity between 1982 and 2001 has shown that – after controlling for other factors such as nutrition, environment, lifestyle, income etc. – new drug launches had a positive impact on the probability of survival in a sample of the 52 countries analysed. Yet, the study addressed drugs for several types of diseases which limits the interpretation for cardiovascular diseases.

study limitations

limited data, few demographic characteristics

comparison difficult

Overall, the study has several limitations: First of all, the data used provide only a narrow range of information. Most importantly, hospital discharge data are of limited use for analysing morbidity. Furthermore, aggregated data on statin prescription without more precise information on demographic or clinical characteristics of statin patients leaves room for considerable uncertainty in the analysis of potential population health gains, thus making a comparison between model outcomes and observational data difficult.

many questions left unanswered

valid control group needed

Generally, the results can only very tentatively be interpreted and leave many questions unanswered. More precise information could be generated with patient-level data on statin utilisation, linked with information on their individual risk, compliance/continuance and outcome. Yet, without a valid control group, the determination of a causal relationship between addressing a single risk factor, such as elevated blood cholesterol, and cardiovascular disease outcome parameters will remain difficult.

IMPACT model may be applied for Austria

Future research may consider applying the IMPACT model mentioned in the literature to evaluate the numerous determinants of CVD mortality trends in Austria in more detail.

10 Conclusion

tentative answer to research question:

Results indicate that the question regarding whether statin treatment has achieved the expected impact on population health can only be answered vaguely.

statins seem to reduce mortality, morbidity gains and cost savings less clear

Tentative evidence exists that statins seem to have contributed to decreasing CHD mortality in Austria while the expected benefits with respect to CHD morbidity and related revascularisation interventions are less explicit. Hence, repeatedly mentioned cost saving potentials in economic evaluations need to be treated with caution.

funding justified by health gains…

…less on economic ground

On the basis of this study, further funding of statins may be justified by a certain likelihood of mortality health gains, but less on economic grounds. Yet, even if results on mortality gains are robust, several hundred thousand patients needed to be treated life-long in order to achieve this benefit. Whether this is acceptable, is subject to political and public discussion.

further studies needed

improving data top-priority

Overall, the study highlights very clearly that much needs to be done to obtain a better understanding of population benefits of a widely used and accepted pharmaceutical intervention. The methodological challenges of this are more than obvious. For extended research, the approach chosen requires further development. Improving morbidity data quality and gathering detailed patient-level data have been identified as top-priorities and preconditions for obtaining more definite results.

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