The Cost-Effectiveness of Cholesterol-Lowering Therapy with Simvastatin in the Primary Prevention of Coronary Heart Disease in the Netherlands

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De kosten-effectiviteit van verlaging van het serumcholesterol middels simvastatine in de preventie van coronaire hartziekten

PROEFSCHRIFT

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To my parents
and Patricia

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1 INTRODUCTION

Cardiovascular disease is the leading cause of mortality in most industrialized countries.[1] In the Netherlands, cardiovascular disease accounts for one-half of all deaths. One-half of cardiovascular mortality, and thus one-quarter of total mortality, is due to coronary heart disease.[2] Coronary heart disease morbidity and mortality and their associated loss in longevity and quality of life represent a substantial burden to society. The health care costs and productivity losses that are caused by coronary heart disease also pose a financial burden on society.[3-5]

The leading cause of coronary heart disease is atherosclerosis of the coronary arteries. Autopsy studies of soldiers killed in action have revealed that the process of atherosclerosis starts at an early age.[6,7] Biochemical studies have shown that cholesterol is the principal ingredient of atherosclerotic lesions.[8] The role of serum cholesterol in atherosclerosis has been confirmed by animal experiments in which the feeding of excessive amounts of cholesterol led to the development of atherosclerotic lesions.[9] The observation that coronary heart disease patients have higher serum cholesterol levels than those free of such disease is more than 50 years old.[10] Epidemiologic studies such as the Framingham Study have provided convincing evidence of the relation between serum cholesterol and the incidence of coronary heart disease.[11] Finally, clinical trials such as the Lipid Research Clinics Coronary Primary Prevention Trial and the Helsinki Heart Study have demonstrated that lowering serum cholesterol levels does reduce the incidence of coronary heart disease.[12,13]

The overwhelming evidence of the role of cholesterol in the development of coronary heart disease and the efficacy of lowering

serum cholesterol levels in the prevention of coronary heart disease has led to the organization of many cholesterol consensus conferences, which have provided physicians with guidelines for the detection and treatment of elevated serum cholesterol levels.[14-16] The most widely used lipid lowering agents at the time of these consensus conferences were bile acid sequestrants (e.g., cholestyramine, colestipol), fibrates (gemfibrozil, bezafibrate, fenofibrate, clofibrate) and nicotinic acid. Many consensus conferences, including the 1987 Dutch Cholesterol Consensus Conference, recommended bile acid sequestrants as drugs of first choice.[15] At that time, however, an entirely new class of cholesterol-lowering agents was being developed. Hydroxy-methylglutaryl-coenzyme A reductase inhibitors (lovastatin, simvastatin, pravastatin, fluvastatin, and dalvastatin) are pharmacologic agents that lower serum cholesterol levels through inhibition of hydroxy-methylglutaryl-coenzyme A reductase, the rate-limiting enzyme of cholesterol synthesis. Clinical studies show that these agents are more effective in lowering serum cholesterol levels and are also associated with fewer side effects than are older medications.[17,18] Simvastatin was the first hydroxy-methylglutaryl-coenzyme A reductase inhibitor to be registered in the Netherlands, and has been marketed since January 1989.

The introduction of simvastatin was expected to increase the number of patients on cholesterol-lowering therapy dramatically because of the high effectiveness and favorable side effect profile of this medication. Prior to the introduction of simvastatin in the Netherlands, approximately 15,000 persons were being treated with cholestyramine at an estimated annual cost of close to 30 million guilders.[19] There have been estimates that the annual cost of treatment with simvastatin of all persons that would be eligible for therapy under the guidelines of the Dutch Cholesterol Consensus Conference would be well in excess of a

billion guilders. The latter implies that the introduction of simvastatin alone would increase health care expenditures in the Netherlands by approximately 3%, which is more than the average annual rate of growth between 1982 and 1987.[20]

The research described in this dissertation was initiated and largely funded by Merck Sharp & Dohme, the manufacturer of simvastatin. As early as 1986, well in advance of registration and marketing of simvastatin in the Netherlands, Merck Sharp & Dohme realized that, given the increase in the number of patients on cholesterol-lowering therapy and the accompanying increase in health care expenditures, the price of simvastatin would require economic justification. Therefore, this study was designed to answer the question: how does the cost-effectiveness of therapy with simvastatin compare with that of current cholesterol-lowering therapy and that of other generally accepted medical practices in the Netherlands? Because of the nature of the available data, the research had to be limited to the primary prevention of coronary heart disease, i.e., among persons free of symptomatic coronary heart disease.

Chapter 2 reviews the evidence of the role of cholesterol in the development of coronary heart disease and the efficacy of cholesterol lowering in reducing the incidence of such disease. Chapter 3 reviews a number of publications that describe economic evaluations of cholesterol-lowering therapy. Chapter 4 describes the model for the incidence and prevalence of coronary heart disease that was used to estimate costs and effects of cholesterol-lowering therapy in the Netherlands. Chapter 5 describes the effect of cholesterol lowering on outcomes such as lifetime coronary risk, life expectancy, and resource utilization in health care. Chapter 6 analyzes the cost-effectiveness of cholesterol lowering therapy with simvastatin and cholestyramine and

evaluates the guidelines of the Dutch Cholesterol Consensus Conference. In chapter 7, tests are made of the sensitivity of these results to changes in the key parameters of the disease history model. Chapter 8 contains a general summary and conclusions.

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2 SERUM CHOLESTEROL AND CORONARY HEART DISEASE

2.1 Introduction

In a publication adapted from the lecture delivered when they received the Nobel Prize in Physiology or Medicine, Brown and Goldstein describe cholesterol as the most highly decorated small molecule in biology, since thirteen Nobel Prizes have been awarded to scientists who devoted major parts of their careers to cholesterol.[1]

Cholesterol is a lipid molecule that plays an essential function in membranes of animal cells, where it modulates fluidity and maintains the barrier between cell and environment. Furthermore, it is the raw material for the manufacture of steroid hormones and bile acids. Because cholesterol is insoluble in water, it can circulate only through the bloodstream bound to proteins in complexes that are called lipoproteins. In the 1950's and 1960's, these lipoproteins were classified in four major classes: very low density lipoprotein (VLDL), low density lipoprotein (LDL), intermediate density lipoprotein (IDL), and high density lipoprotein (HDL). Elevations in the total serum cholesterol are generally due to an elevation in LDL-cholesterol, which is considered to play a key role in the development of atherosclerosis. High levels of HDL-cholesterol on the other hand have been found to have a protective effect. VLDL-particles are also referred to as serum triglycerides. The role of hypertriglyceridemia as an independent risk factor for coronary heart disease is not certain.

Since serum cholesterol has been found to be a major constituent of atherosclerotic lesions,[2] it is to be expected that elevated serum cholesterol levels cause those cardiovascular diseases that are

predominantly due to atherosclerosis: coronary heart disease, stroke, and peripheral vascular disease. However, the role of serum cholesterol as an independent risk factor for cardiovascular disease has only been demonstrated convincingly for the case of coronary heart disease.

Stroke, i.e., brain damage caused by insufficient blood flow to the brain, can be caused by atherosclerosis through one of three mechanisms: 1) atherosclerotic deposits obstruct the arteries that supply the brain with blood, 2) fragments of atherosclerotic lesions in major arteries (e.g., aorta, coronary arteries) dislodge and obstruct smaller arteries, thus causing cerebral infarction, or 3) atherosclerotic deposits in small vessels of the brain cause cerebral bleeding.

Most of the epidemiologic studies that have reported a statistically significant relationship between serum cholesterol and stroke incidence were carried out as univariate analyses.[3-5] Until recently, case control studies[6,7] and multivariate, longitudinal studies[5,8-11] have failed to establish an independent association between serum cholesterol and stroke incidence, except in the case of 65-74 year old women in the Framingham Study.[12] It has therefore been suggested that the relationship between serum cholesterol and stroke is likely to be caused by a relationship between serum cholesterol and variables that have been shown to be independently associated with stroke, such as smoking and hypertension.[13]

The six-year follow-up of 350,977 middle-aged men (35 to 57 years) from the original screening cohort of the Multiple Risk Factor Intervention Trial, however, revealed that after proportional hazards regression to control for age, cigarette smoking, diastolic blood pressure, and race or ethnic group, there was an inverse relationship between six-year mortality from intracranial hemorrhage and serum cholesterol level,

as well as a positive association between six-year mortality from nonhemorrhagic stroke and serum cholesterol level.[13]

The increased risk of death from intracranial hemorrhage was confined to men with a diastolic blood pressure higher than 90 mm Hg and serum cholesterol levels below 160 mg/dl. This suggests that there is an interaction between high blood pressure and very low serum cholesterol causing an increased risk of intracranial hemorrhage. The authors suggested several biologically plausible mechanisms for this interaction.

The association between serum cholesterol and mortality from nonhemorrhagic stroke resulted in a positive relationship between serum cholesterol and all stroke mortality. This relation however, is weaker than the relationship between serum cholesterol and cardiac mortality. The age-adjusted relative risk ratios for those with cholesterol levels over 300 mg/dl compared to those with cholesterol levels between 180 and 200 mg/dl for instance, were 2.4 and 4.4 for six-year mortality from all strokes and coronary heart disease respectively. The absolute risk of cardiac death in these middle-aged men was an order of magnitude greater than the risk of stroke death: age-adjusted death rates in the entire cohort were 6.6 and 60.5 per 10,000 for stroke death and coronary heart disease death respectively.

The authors concluded that the public health impact of the inverse relationship between the serum cholesterol level and the risk of death from hemorrhagic stroke in middle-aged American men is overwhelmed by the positive association of higher serum cholesterol levels with death from non-hemorrhagic stroke and total cardiovascular disease.

Although the follow-up of the screening cohort of the Multiple Risk Factor Intervention Trial demonstrates that there is a positive association between serum cholesterol levels and the risk of non-hemorrhagic stroke

in middle-aged men, there are no clinical trials that demonstrate the efficacy of cholesterol lowering in preventing such stroke. The latter is also the case for 65- to 74-year-old women, among whom, according to multivariate analysis in the Framingham study, serum cholesterol is a statistically significant, independent risk factor in the two-year risk of stroke and transient ischemic attack.[12]

Peripheral vascular disease refers to atherosclerotic narrowing of the arteries supplying blood to the extremities, in particular the legs. The independent role of peripheral vascular disease on mortality is not clear since most patients have concomitant diabetes and/or coronary artery disease. As in the case of stroke, there are some studies that have confirmed a relationship between cholesterol and the incidence of peripheral vascular disease in univariate analysis.[4,10,14] A recent report on cholesterol screening in the elderly was unable to locate any study that assessed the association between serum cholesterol and peripheral vascular disease independent of confounding variables such as cigarette smoking and blood pressure.[15]

The major manifestations of ***coronary heart disease***, also referred to as ischemic heart disease because its symptoms result from myocardial ischemia, are: 1) myocardial infarction, irreversible damage of the heart muscle caused by a thrombotic obstruction of a coronary artery; 2) angina pectoris, a characteristic syndrome of chest pain incurred by physical effort or severe emotion that disappears after relaxation or discontinuation of physical activity; 3) unstable angina, a syndrome of prolonged chest pain at rest accompanied by electrocardiographic abnormalities, but lacking the enzymatic and electrocardiographic changes typical for myocardial infarction; and 4) sudden death, the unexpected death of an apparently well person within one hour of the

onset of symptoms, usually caused by either severe arrhythmias or massive myocardial infarction.

The evidence for the association between serum cholesterol levels and coronary heart disease incidence and the efficacy of cholesterol lowering in preventing such disease will be reviewed in the remainder of this chapter.

2.2 Pathophysiology of coronary heart disease

The principal cause of coronary heart disease is atherosclerosis, a process of thickening and hardening of the arterial walls.[16] The arterial wall consists of the endothelium and three subsequent layers called the intima, media, and adventitia. Endothelial cells form a one-cell layer, through which transportation of macromolecules, such as lipoproteins, takes place. The normal intima and media of the coronary arteries consist of mainly smooth muscle cells, and some connective tissue cells.

The earliest manifestation of atherosclerosis is the so-called fatty streak, which is a grossly flat lipid-rich lesion.[17] Macrophages penetrate into the subendothelial space and, through interaction with lipoproteins, are transformed into foam cells. At this stage, the endothelium appears to be normal and intact. The transformation of a fatty streak into a fibrous plaque is marked by an increase in lipid-laden smooth muscle cells and the development of a fibromuscular cap.[18-20] Beneath this fibromuscular cap is a basal pool, which is rich in smooth muscle cells, macrophages, and connective tissue cells, and also contains extracellular lipid, necrotic debris, and fibrinogen.[21] The basal pool beneath the fibromuscular cap raises the lesion and starts the process of narrowing the artery. The narrowing of the artery results in a diminished blood flow to the myocardial tissue that does not necessarily cause any clinical

symptoms. In a situation, however, where physical exercise or intense emotion require an increased effort of the heart, the blood flow may become insufficient resulting in angina pectoris, a chest discomfort, sometimes radiating to the left arm, that disappears after relaxation or discontinuation of physical activity. The fibrous plaque may develop into a complicated plaque when the basal pool continues to grow and the fibromuscular cap ruptures, which causes platelet adhesion and aggregation and will result in thrombus formation. The thrombus may propagate into an occlusive thrombus, either at the site of the plaque, or by becoming segregated from the plaque and causing occlusion at some other location in the coronary arteries. Either way, myocardial infarction or sudden death due to severe ventricular dysrhythmia will occur.

Based on observations made through fiberoptic angioscopy, Forrester et al. proposed a model in which they presented acute and chronic coronary heart disease as a single pathophysiologic entity.[22] Their model departs from the stable atheroma, which, depending on the degree of arterial occlusion, may cause clinical symptoms of stable angina pectoris. The development of stable coronary heart disease into acute coronary heart disease is marked by endothelial ulceration of the atheroma, which may cause an increase of the frequency of angina attacks (accelerated angina). Forrester et al. postulate that there are two histopathologic cycles at the endothelial surface that determine the specific symptoms of acute coronary heart disease. In the first cycle, embolization of platelet aggregates at the site of the ulceration may cause either sudden death or ischemic cardiomyopathy. In case of survival, the ulcer will heal with increase of the coronary stenosis. The patient's clinical state will return to more severe stable angina. In the second cycle, endothelial ulceration is followed by partial thrombosis. When a partially occlusive thrombus develops, the patient will experience unstable angina. If the thrombosis

develops into a complete occlusion of the coronary artery, acute myocardial infarction results. A return to more severe stable angina pectoris may take place through either of two mechanisms: lysis of the thrombus, either by endogenous lysis or through thrombolytic therapy, or incorporation of the thrombus in the vessel wall. Despite the fact that the angioscopic observations by Forrester et al. are limited to patients sufficiently ill that they required by-pass surgery, their paradigm is substantiated by a number of autopsy studies.

2.3 Epidemiology of cholesterol and coronary heart disease

A large number of epidemiologic studies have provided evidence of the relationship between serum cholesterol levels and the incidence of coronary heart disease.[23-29] The best-known of these is the Framingham Study, which started in the late 1940s and is on-going.[30]

Since 1948, the Framingham Study has followed an initial cohort of 5209 men and women. At the onset of the study, the participants, who were all residents of the city of Framingham, Massachusetts, were between 30 and 59 years of age and free of cardiovascular disease. During standardized clinical examinations that took place at two-year intervals, cardiovascular risk factors were measured and cardiovascular disease morbidity and mortality were monitored. Additional information on morbidity and mortality were obtained from a number of other sources such as hospital files, physicians' records, and death registers.[31] The cardiovascular risk factors under consideration in the Framingham Study included serum cholesterol, blood pressure, cigarette smoking, glucose intolerance, left ventricular hypertrophy as detected by EKG, and metropolitan relative weight. The cardiovascular diseases whose onset

was monitored included coronary heart disease, stroke, transient ischemic attack, intermittent claudication, and congestive heart failure.

The association between coronary heart disease incidence and serum cholesterol that emerged from the Framingham Study is one of slowly rising risk at lower cholesterol levels and a rapidly increasing risk at higher levels (250 mg/dl and above).[32] A similar pattern emerged after pooling the Framingham Study data with those of a number of other U.S. based studies (The Pooling Project).[33] The interaction of cholesterol with other coronary risk factors such as smoking and hypertension appears to be synergistic; that is, a combination of risk factors produces a larger coronary heart disease risk than would be expected on the basis of each risk factor alone.[34,35]

The Framingham Study investigators originally reported that total cholesterol was a strong coronary risk factor for middle-aged persons, but that it was not significantly associated with coronary heart disease incidence in persons age 65 years and older.[36] Multivariate logistic regression analysis and Cox proportional hazards analysis of the 30-year follow-up suggest that strongly elevated cholesterol levels are associated with an increase in coronary heart disease risk in elderly women, but not in elderly men.[37,38]

The 30-year follow-up of participants in the Framingham study showed a direct association between serum cholesterol level and both cardiovascular and all-cause mortality in men and women younger than 50 years of age.[39] The relationship between all-cause mortality and serum cholesterol was statistically significant in men, but only suggestive in women. The relationship between cardiovascular mortality and serum cholesterol level was much stronger and was statistically significant for both men and women. The authors suggested that the association of serum cholesterol levels with coronary heart disease may be confounded

by people whose cholesterol levels are falling, perhaps due to diseases predisposing to death such as cancer.

Although the *Multiple Risk Factor Intervention Study* was a multifactorial intervention trial, the data of the 361,662 men aged 35-57 years that were originally screened during a two-year period beginning in 1973 have been used to examine the relationship between 6-year mortality from coronary heart disease and cholesterol levels.[41] The data showed that the risk of coronary heart disease mortality rises at an ever-increasing rate beginning at about the 20th percentile of serum cholesterol levels (181 mg/dl; 4.68 mmol/l). In an analysis by quintiles, there was a significantly higher risk of coronary heart disease death for each quintile above the first. Persons in the top 15% of serum cholesterol levels had a probability of dying from coronary heart disease that was 3.8 times greater than that of those with cholesterol levels below 181 mg/dl. The investigators defined the risk of coronary death in the lowest quintile as baseline risk, and showed that half of the observed mortality from coronary heart disease was attributable to cholesterol levels higher than 181 mg/dl. The excess deaths from coronary heart disease were evenly distributed between those with cholesterol levels above the 85th percentile (253 mg/dl; 6.54 mmol/l) and those with cholesterol levels between the 20th and 85th percentile. These findings call for a population-wide approach to lower serum cholesterol levels through dietary changes in combination with an individual approach toward patients with serum cholesterol levels in the higher deciles of the cholesterol distribution.

The relationship between serum cholesterol and all-cause mortality showed a J-shaped relationship. Men with serum cholesterol levels below the 10th quintile may have the lowest risk of dying from coronary heart disease, but their overall mortality is increased due to death from

other causes, primarily cancer. This phenomenon could suggest a causal relationship between very low serum cholesterol levels and the incidence of cancer, but it is believed that the causal relationship is actually inverse: early stages of certain cancers cause a strong decrease in serum cholesterol.[42,43] This explanation is supported by the finding that the association between low serum cholesterol and mortality from cancer does not persist when the period of follow-up is extended.[44]

The follow-up of the original screening cohort of the Multiple Risk Factor Intervention Trial revealed that, for middle aged men, there is a strong association between serum cholesterol level and six-year mortality from both coronary heart disease mortality and all-cause mortality.

2.4 Clinical trials of cholesterol lowering

The relationship between serum cholesterol levels and coronary heart disease incidence that emerged from epidemiologic studies is not prima facie evidence of a causal relationship. Even if this relationship were causal, randomized clinical trials would be needed to demonstrate that lowering serum cholesterol levels does indeed lower the incidence of coronary heart disease. In the following section, a number of clinical trials of cholesterol lowering in the prevention of coronary heart disease will be discussed. Although the focus will be on the primary prevention of coronary heart disease, some attention will be given to secondary prevention trials as well as the so-called regression studies: trials of cholesterol lowering that do not study the effect of intervention on clinical manifestations of coronary heart disease, but use coronary angiography to assess the effect of cholesterol lowering on the progression of atherosclerotic lesions in the coronary arteries.

2.4.1 Primary prevention trials

In his review of primary prevention trials of coronary heart disease, Stammler points out a number of limitations and methodological problems of these studies.[45] One of the major limitations of these studies is that they lack statistical power to detect positive outcomes. This lack of power is principally due to a combination of small sample size and a limited duration of follow-up, although many studies also revealed that assumptions used in the design of the trial overestimated the differences in risk factor reduction between intervention group and control group. In several studies, the reduction in risk factor levels was lower than expected due to a number of reasons such as simultaneous improvements in risk factor levels in the control group and a lower-than-foreseen adherence to therapy. Several trials found that the incidence of atherosclerotic events in the control group was lower than expected, probably due to a bias towards selecting healthier persons during enrollment. The lack of statistical power of these primary prevention trials results in a high probability of false-negative outcomes, which makes the interpretation of their findings very difficult. Many studies have shown significant decreases in morbidity and mortality from coronary heart disease, but no study has been able to demonstrate that the reduction in coronary mortality results in a statistically significant decrease in all-cause mortality.

Trials of diet counseling

The *Los Angeles Veterans Administration Domiciliary Facility Study* was a double-blind randomized clinical trial which assessed the effect of cholesterol lowering on the incidence of severe atherosclerotic events, i.e., major manifestations of coronary heart disease, cerebrovascular

disease, and peripheral vascular disease.[46] In the intervention group, serum cholesterol reduction was accomplished by means of a fat-modified diet, low in cholesterol and saturated fat, and high in polyunsaturated and total fat. Serum cholesterol levels in the intervention group decreased by 20% compared to baseline levels, and by 12.7% compared to cholesterol levels in the control group. During the 8.5 years of follow-up, both the incidence of severe atherosclerotic events and the mortality from atherosclerotic disease were significantly lower in the intervention group, both 31%. All-cause mortality in both groups barely differed, due to a larger number of deaths from cancer in the intervention group. The Los Angeles Veterans Administration Study conclusively demonstrated that lowering serum cholesterol levels through dietary modification resulted in a substantial reduction in morbidity and mortality from atherosclerotic disease.

One of the few trials to examine cholesterol lowering among women was the *Finnish Mental Hospital Study*.[47] This trial was carried out in two mental hospitals in the years 1959-1971 using a cross-over design. In the intervention group, the dairy fats originally present in the normal diet were almost totally replaced by vegetable oils. Because of a substantial loss to follow-up (about 12% per year), average length of follow-up was only slightly over 4 years. Mean serum cholesterol reductions ranged from 12% to 18%, depending on gender and hospital under consideration. Among men, coronary heart disease mortality decreased considerably during each of the diet-periods, coronary mortality was at least one-half of that during the control-period. This result was highly significant for one hospital and the pooled material, and on the borderline of significance for the other hospital. For women, the reduction in coronary heart disease mortality in one hospital was highly significant. In the pooled population as well as in the other hospital, the

differences did not reach statistical significance, probably because there had been major changes in the female population of the latter hospital, which resulted in exceptionally low mortality rates during the control-period. No significant differences in mortality from other causes than coronary heart disease and all-cause mortality were observed. The findings of the Finnish Mental Hospital Study justified the conclusion that, among men, a cholesterol-lowering diet considerably reduces mortality from coronary heart disease, but did not permit definite conclusions for women.

The objective of the *Multiple Risk Factor Intervention Trial* was to assess the ability to prevent primary coronary heart disease events through simultaneous intervention on all three major risk factors: serum cholesterol, diastolic blood pressure, and cigarette smoking.[48] Half of the almost 13,000 male participants, enrolled between 1973 and 1976, were randomly assigned to the Special Intervention group and received counselling for cessation of smoking and modification of eating habits to lower serum cholesterol. When diet failed to control hypertension, a stepped care drug regimen would be initiated. The other half of the participants formed the Usual Care group that received regular community health care. The trial lost considerable statistical power because of marked improvements in cholesterol levels, blood pressure, and smoking behavior in the Usual Care group. After 7 years of follow-up, small but statistically insignificant reductions in coronary heart disease mortality and cardiovascular mortality were observed. All-cause mortality in the Special Intervention group was slightly, but not significantly, higher than in the Usual Care group. Subgroup analysis, however, showed that the risk of coronary heart disease death was inversely related to changes in serum cholesterol and the number of cigarettes smoked.

Trials of drug therapy

The *WHO Cooperative Trial of clofibrate* was a randomized, double blind, controlled study designed to assess the effect of serum cholesterol reductions on coronary heart disease morbidity and mortality.[49,50] The trial was carried out in Edinburgh, Budapest, and Prague, and 10,627 men were randomized to clofibrate or placebo. After an average of 5.3 years of follow-up, non-fatal myocardial infarction rates in the clofibrate group showed a significant 25% reduction; coronary heart disease mortality showed a slight, nonsignificant increase. The finding that all-cause mortality in the clofibrate group showed a significant 27% increase caused considerable concern. After an average of 9.6 years of follow-up, i.e., years after drug treatment had been discontinued, all-cause mortality in the clofibrate group was still significantly higher. These results suggest that clofibrate has long-term toxic effects. Although the WHO Cooperative Trial of clofibrate demonstrated that lowering serum cholesterol levels with clofibrate reduces the incidence of non-fatal myocardial infarction, its major conclusion was that long-term toxic effects of clofibrate caused an increase in all-cause mortality that outweighed possible decreases in coronary mortality. It thus focused the attention on the possibility of long-term adverse effects of cholesterol-lowering drugs.

The *Lipid Research Clinics Coronary Primary Prevention Trial* was a multi-center, randomized, double blind study that was carried out in Canada and the U.S.A. between 1973 and 1983.[51,52] Thirty-eight hundred men aged 39-59 years with plasma cholesterol levels of 265 mg/dl and greater and with an LDL-cholesterol level of at least 190 mg/dl were randomized to the bile acid sequestrant cholestyramine resin (six packets of 4 grams each per day, divided into two or four equal doses) or an equivalent amount of placebo. At entry, all men were free

of symptomatic coronary heart disease. Participants in the cholestyramine group had a daily intake of approximately four packets, which slightly decreased during the trial from 4.2 to 3.8 packets in the first and seventh year of the trial respectively. Adherence in the placebo group was higher (4.9 and 4.6 packets in the first and seventh year). Participants treated with cholestyramine experienced a decrease in cholesterol levels of 13.4% over placebo in the first year and 7.3% in the seventh year of the trial. Averaged over the entire duration of the trial, the reduction in cholesterol levels in the cholestyramine group was 8.5% relative to the placebo group. After an average period of follow-up of 7.4 years, cholesterol reductions in the treatment group were associated with a significant 19% reduction in coronary heart disease incidence (defined as definite coronary heart disease death and/or definite non-fatal myocardial infarction). The number of definite coronary heart disease deaths in the cholestyramine treated group was 24 percent lower than in the placebo group, but this difference was not statistically significant. Because there were a greater number of violent and accidental deaths in the cholestyramine group, all-cause mortality showed a slight but nonsignificant decrease. Subgroup analysis of the cholestyramine treated group by adherence to medication showed that the reductions in coronary heart disease incidence were positively related to the decrease in plasma lipids. These results indicated that every percent cholesterol reduction resulted in a two percent decrease in coronary heart disease incidence, a finding that has become known as the 1:2 rule of thumb. The Lipid Research Clinics Coronary Primary Prevention Trial demonstrated that it was possible to lower cholesterol levels safely by drug therapy and achieve substantial reductions in coronary heart disease incidence. The study, however, was not able to demonstrate that the

reduction in coronary heart disease incidence would lead to a reduction in all-cause mortality.

The *Helsinki Heart Study* was a randomized, double-blind, controlled trial that was carried out among 4,081 Finnish men aged 40-55 years.[53] The participants, who had non-HDL cholesterol levels (i.e., total cholesterol minus HDL cholesterol) exceeding 5.2 mmol/l, were randomly allocated to treatment with either gemfibrozil 600 mg b.i.d. or a similar regimen of placebo. The overall reduction in total serum cholesterol levels over the entire duration of the study was 10%. Fatal and non-fatal myocardial infarction and coronary heart disease death were the primary endpoints of the study. After 5 years of follow-up, there was a significant 34% reduction in five-year incidence rates in the gemfibrozil-treated group. All-cause mortality showed a slight, but not significant, increase in the treatment group. In light of the 1:2 rule of thumb that emerged from the Lipid Research Clinics Coronary Primary Prevention Trial, the 34% reduction in coronary heart disease incidence seems much higher than one would expect from an 10% cholesterol reduction. Based on preliminary data analysis, the investigators from the Helsinki Heart Study have suggested that the 11% increase in HDL-cholesterol levels that resulted from gemfibrozil therapy may have made a significant contribution to the observed reduction in coronary heart disease incidence. The Helsinki Heart Study gave conclusive evidence that drug treatment of elevated cholesterol levels can result in a substantial reduction in coronary heart disease incidence, and focused attention on the potential clinical benefits of raising HDL-cholesterol levels.

2.4.2 Secondary prevention trials

The aim of secondary prevention is to prevent recurrent events in persons who have already experienced a manifestation of coronary heart disease. Since the underlying disease is the same, i.e. coronary atherosclerosis, one would expect that primary and secondary prevention trials would give similar results.

Dietary trials of secondary prevention generally consist of many fewer participants than dietary trials of primary prevention. As a result, these studies often lack power to show statistically significant decreases in either coronary heart disease mortality or events. Yusuf et al. published a meta-analysis of dietary trials of cholesterol lowering in the secondary prevention of coronary heart disease and concluded that these trials demonstrated only a marginally significant reduction in coronary heart disease incidence, no change in cardiac mortality and a non-significant increase in non-cardiac mortality in the intervention group.[54]

By far the largest of the *drug trials* of secondary prevention is the Coronary Drug Project. Started in 1966, this trial recruited 8,000 men between the ages of 30 and 64 years who had experienced a myocardial infarction, irrespective of cholesterol level. The participants were randomly assigned to placebo treatment or one of five arms of drug treatment: niacin, clofibrate, D-thyroxine, and two dose regimens of estrogen. Treatment with D-thyroxine and both estrogen regimens were discontinued before the end of follow-up because of an excess of non-fatal coronary heart disease events or excessive all-cause mortality in comparison with the placebo group.[55,56] After 6.2 years of follow-up, neither the clofibrate nor the niacin treated group showed significant changes in either cardiac or all-cause mortality.[57] A remarkable finding of the Coronary Drug Project was that after a mean follow-up of 15

years, i.e., many years after therapy had been discontinued, both coronary and all-cause mortality in the niacin treated group were significantly lower than in the placebo group.[58] These findings raise the possibility that lipid lowering is beneficial only to those survivors of a myocardial infarction whose coronary disease and left ventricular damage are sufficiently mild to allow them to survive for a long time.[59]

A recent meta-analysis confirmed that there is conclusive evidence that cholesterol-lowering therapy in the secondary prevention of coronary heart disease decreases cardiovascular mortality and the number of both nonfatal and fatal myocardial infarctions.[60] The trend for all cause mortality was favorable, but did not reach statistical significance.

In addition to trials using clinical end points there have been a number of coronary *angiographic studies* that examined the effect of cholesterol lowering on the progression of atherosclerotic lesions.[61-64] These studies show that reducing cholesterol levels can not only slow the progression of atherosclerosis, but can even lead to regression of atherosclerotic lesions.

2.5 Discussion

Epidemiological studies, notably the Framingham Heart Study and the follow-up of the original screening cohort of the Multiple Intervention Risk Factor Trial, have provided convincing evidence that, at least for men and women at younger ages, there is a relationship between serum cholesterol levels and the incidence of coronary heart disease, mortality from coronary heart disease, and mortality from all causes. In the primary prevention of coronary heart disease, clinical studies have been able to demonstrate that the reduction of serum cholesterol levels lowers the morbidity and mortality from coronary heart disease, but have not

demonstrated a beneficial effect on total mortality. In the secondary prevention of coronary heart disease, there are more grounds for optimism in regard to all-cause mortality. However, the evidence from clinical trials is even more limited than that from epidemiological studies: most of these trials have been conducted in middle-aged men only. The only study that examined the effect of cholesterol-lowering therapy in women was unable to demonstrate a statistically significant effect.

An important issue in the discussion whether to treat hyperlipidemic patients is the fact that clinical trials have been unable to demonstrate that lowering serum cholesterol levels lowers all-cause mortality and thus increases life expectancy. Stammler has pointed out that the lack of effect on mortality in primary prevention trials is probably due to a lack of statistical power.[45] There is, however, also considerable concern that the lack of effect on all-cause mortality could result from an adverse effect of cholesterol lowering on non-cardiovascular mortality. Such an adverse effect may be due to the cholesterol-lowering medication, but it is also possible that lower cholesterol levels per se are associated with an increased mortality from a number of conditions.

Muldoon et al. recently reported a meta analysis of the mortality observed in primary prevention trials of cholesterol lowering which showed a slight but insignificant increase in all-cause mortality in the intervention group and was thus unable to demonstrate a beneficial effect of cholesterol lowering on all-cause mortality.[65] Mortality from cancer was significantly increased only when the results of the WHO clofibrate trial were included in the analysis. Muldoon et al. reported that there was a statistically significant increase in the number of violent deaths (i.e., suicides, accidents, and violence) in the treatment group.

The fact that the meta-analysis by Muldoon et al. did not show a significant effect of cholesterol lowering on all-cause mortality is very

likely to be due to a lack of statistical power. The clinical trials included in their analysis were not designed to demonstrate differences in all-cause mortality, but in outcomes on which cholesterol lowering would have a much larger effect, such as fatal and nonfatal myocardial infarction. For instance, if one out of every four deaths is due to coronary heart disease, a 20% reduction in the mortality from coronary heart disease will result in a reduction in all-cause mortality of only 5%. Meta-analysis can be valuable in aggregating studies that each lack the statistical power to detect differences between treatment and control group when they have the same clinical endpoint. However, a meta-analysis that simply aggregates all available studies cannot be expected to compensate for the lack of statistical power that is due to the fact that the studies were designed around an endpoint that required a considerably lower sample sizes than the one studied in the meta-analysis.

Muldoon et al.'s observation that the relationship between cholesterol lowering and cancer mortality becomes insignificant after excluding the clofibrate trial reflects the experience in the WHO Cooperative Trial of clofibrate, that showed a statistically significant increase in all-cause mortality, which has generally been interpreted as the result of a toxic effect of clofibrate. After excluding the clofibrate trial, Muldoon et al.'s analysis shows that the relative risk of cancer mortality, that is, the risk in the intervention group relative to the risk in the control group, is lower in the drug intervention studies than in the diet intervention studies. Although this difference is not statistically significant, it certainly does not suggest that cholesterol-lowering medication is more likely to cause cancer than a cholesterol-lowering diet. The evidence suggesting that reduced cholesterol levels are causally related to cancer remains equivocal: the relationship disappears with

inclusion of extended follow-up data and has not been observed in secondary prevention trials.[66]

The apparent increase in mortality from violent causes remains one of the most intriguing observations of the primary prevention trials of cholesterol lowering. Muldoon et al. report a similar increase in the risk of mortality not related to illness in the treatment groups in diet intervention studies as in those in the drug intervention studies. However, this increase reaches statistical significance in the drug intervention studies only. Although these findings have been interpreted as suggestive of a relationship between violent death and either low cholesterol levels or cholesterol-lowering interventions, they are not entirely consistent with such a relationship since the diet intervention studies were conducted among persons with lower cholesterol levels and resulted in larger reductions in cholesterol level than the drug intervention studies. Furthermore, Wysoski and Gross conducted a case-by-case analysis of the violent deaths in the Lipid Research Clinics Coronary Primary Prevention Trial and the Helsinki Heart Study.[67] Exclusion of drop-outs and noncompliers revealed that almost all violent deaths occurred among persons with known risk factors for such death, such as a history of psychiatric dysfunction or alcoholisme. Although it is possible that cholesterol lowering increases the risk of violent death in persons with alcoholisme or a history of psychiatric disease, since mortality unrelated to illness is only a small fraction of total mortality and randomization was not stratified with respect to risk factors for violent death, it is more likely that the observed effect is due to a chance fluctuation in the randomization process.

Smith and Pekkanen recently revived the discussion about the benefits and risks of cholesterol lowering by adding a number of other studies to the previous meta-analysis by Muldoon et al.[68] Their analysis,

however, is poorly conceived as illustrated by their finding that inclusion of the Finnish Mental Hospital Study lowers the relative risk of violent death in diet intervention studies to a level considerably below that in drug intervention studies. Patients are admitted to a psychiatric hospital not only for treatment, but also to prevent them from doing harm to themselves or to others. A study in such an institutional setting is therefore heavily biased toward the null hypothesis, that is, that there is no difference in violent death rates between treatment and control group. The finding by Smith and Pekkanen reflects the particular design of the Finnish study rather than the relationship between cholesterol lowering and mortality from causes unrelated to illness.

The main conclusion by Smith and Pekkanen is that "dietary lowering of cholesterol may be safe, whereas lowering of cholesterol with drugs may not be", although "the apparent difference between diet and drug interventions studies may not be definitive". This statement is largely based on the observation that total mortality is increased in the intervention group in drug trials and that the difference in odds ratio for total mortality between drug and diet trials approaches significance. Contrary to Muldoon et al., however, Smith and Pekkanen do not exclude clofibrate from their analysis even though it is known to have adverse effects on all-cause mortality. Since, in addition to the WHO study of clofibrate, their analysis is based on a number of drug trials that use different drugs, it is not clear whether each of these drugs has an adverse effect on mortality from causes other than coronary heart disease.

It is important to realize that whatever the explanation for the difference in non-cardiac mortality observed in some of the studies of older drugs, there is no evidence that HMG-CoA reductase inhibitors are associated with an increase in non-cardiac mortality.[69] In a five-year study of lovastatin in 745 patients and a one-year study of simvastatin in

2361 patients–roughly 12,000 patient years of vigorous lipid-lowering therapy–only one death due to an accident occurred and none due to homicide or suicide.[70] The incidence of cancer in the five-year lovastatin study was well below that expected on an actuarial basis.[70] Clinical trials of HMG-CoA reductase inhibitors with sufficient numbers of patients to help clarify questions concerning total mortality are now under way in the United Kingdom and the United States.[71]

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3 ECONOMIC EVALUATION OF CHOLESTEROL LOWERING

3.1 Introduction

Economic evaluation has two basic characteristics. First, it considers both the inputs and the outputs of medical interventions. Second, it is concerned with alternative ways of allocating scarce health care resources and will, therefore, always consider alternative medical strategies. On the basis of these characteristics, Drummond et al. defined economic evaluation as "the comparative analysis of alternative courses of action in terms of both their costs and consequences".[1] Table 3.1, which was taken from Drummond et al., employs these two characteristics to

Table 3.1 Distinguishing characteristics of health care evaluations

Is there comparison of two or more alternatives?	Are both costs and consequences of the alternatives examined?		
	No		Yes
No	Examines only consequences	Examines only costs	
	PARTIAL EVALUATION		PARTIAL EVALUATION
	Outcome description	Cost description	Cost-outcome description
Yes	PARTIAL EVALUATION		FULL EVALUATION
	Efficacy or effectiveness evaluation	Cost analysis	Cost-minimization analysis Cost-effectiveness analysis Cost-utility analysis Cost-benefit analysis

distinguish six forms of evaluation. The table shows that only evaluations that meet both the criterion of comparing two or more alternative strategies, and the criterion of simultaneously assessing both costs and effects of the alternatives, are considered to be full economic evaluations. Randomized clinical studies typically assess the outcomes of two or more clinical strategies, and would be categorized as efficacy or effectiveness evaluations.

In economic evaluation, the concept of an alternative strategy should be seen more broadly than simply as another way of treating the same disease. The priority that a certain therapy has in the allocation of scarce health care resources may not only be determined by the costs and effects of alternative ways to treat the same disease, but also by the cost-effectiveness of ways to treat other diseases. For example, in the case of an impairment for which there is only one known therapy, a study that would report on the cost-effectiveness of that therapy versus the alternative of no therapy can only obtain relevance by comparing the cost-effectiveness of therapy with that of other accepted medical practices.

In comparing costs and consequences of alternative strategies, there are four basic types of analysis: cost-minimization analysis, cost-effectiveness analysis, cost-utility analysis, and cost-benefit analysis.

When the alternative treatment programs have the same outcome, the analysis can be confined to comparing the costs of both programs. *Cost-minimization analysis* aims at identifying the program with the lowest resource use out of two or more programs with the same outcome.

It is possible that two programs have the same outcome of interest, but that one program is more successful in achieving this outcome than the other. Unless the more successful program is also the least costly one, one would rather compare these programs based on their cost per

unit of effect. Such analysis is usually referred to as *cost-effectiveness analysis*. The unit of effect depends on the programs that are being compared, and may take the form of a cost per case detected in a screening program,[2] a cost per mm Hg decrease in diastolic blood pressure,[3] a cost per life saved,[4] or a cost per year of life saved.[5] In comparing two programs, one does not necessarily have to choose the program with the lowest cost per unit of effect. When the more expensive program achieves more units of effect, the question is rather whether the extra cost of that program is justified by the extra effect that will be achieved. One might simply ask persons how much they are willing to pay for the additional benefits of one program over the other, which Jönsson et al. did in the comparison of transdermal nitroglycerine patches and oral slow-release nitrates for the treatment of angina pectoris.[6] In general, however, one will compare the cost-effectiveness of a program with that of other generally accepted health care interventions.[7]

Using the cost-effectiveness of other accepted health care interventions as an estimate of societal willingness-to-pay, however, requires that the outcomes of different programs are expressed in the same unit of effect. Since the ultimate aim of health care programs is to prevent morbidity and its associated mortality, years of life gained are typically used as the unit of effect. Recently, economists have started to base their analysis on the utility, that is the value or worth, that individuals or society attach to changes in health status. The result of a *cost-utility analysis* is usually a cost per quality-adjusted life-year gained.

In *cost-benefit analysis*, all costs and benefits, including the gains in health, are valued in monetary terms and the results are usually reported as a net cost or net benefit. Although this type of analysis has the advantage of combining the effects that programs can have on different

outcomes by valuing the change in each outcome, the analyst is faced with the task of putting a monetary value on human life and suffering.

In the following, a number of publications on the costs and effects of cholesterol lowering will be reviewed. These studies were selected on the criterion that they assessed changes in economic outcomes such as gains in life expectancy, savings in medical treatment costs, and averted productivity losses as opposed to the intermediate outcomes that are usually reported in clinical and epidemiologic studies, such as morbidity and mortality rates. It should be noted that all of these studies are limited to the role of cholesterol lowering in the primary prevention of coronary heart disease.

3.2 Partial evaluations

Oster and Epstein estimated the economic benefits of lowering serum cholesterol levels among adult men.[8] They conceptualized an individual's risk of developing coronary heart disease as a series of annual risks. The economic cost associated with the occurrence of a coronary event at a certain age consists of the expenditures for medical care (direct costs) and the losses in productivity due to morbidity and mortality (indirect costs) that would be incurred over a lifetime should a person develop coronary heart disease at that age. Using a discount rate, these annual economic costs were summed to a present value representing the lifetime economic cost of coronary heart disease for a given individual of a certain age and serum cholesterol level. The economic benefits of cholesterol lowering were defined as the reductions in lifetime economic cost caused by the changes in coronary heart disease risk. The relationship between serum cholesterol and coronary heart disease risk was modeled using a multivariate logistic risk function from

the Framingham Heart Study. The benefits of cholesterol lowering were estimated by assuming that, after lowering the cholesterol level, the coronary risk could not be lower than that of persons with the naturally occurring lower cholesterol level, and that the reduction in coronary risk actually achieved would be 80 percent of the difference in coronary risk between pre- and posttreatment cholesterol level.

Oster and Epstein limited their analysis to adult men with serum cholesterol levels above 260 mg/dl (6.7 mmol/l), because the evidence of benefit from such an intervention is most firmly established for this group, notably by the Lipid Research Clinics Coronary Primary Prevention Trial. Their results indicate that both direct and indirect benefits vary substantially depending on baseline cholesterol level and age at initiation of therapy. Direct and indirect benefits decrease with increasing age, becoming insignificant for older patients. Although both direct and indirect benefits increase as cholesterol reduction increases, they do so at a decreasing rate. Until roughly the age of 60 years, indirect benefits are considerably higher than direct benefits. Oster and Epstein concluded that "cholesterol-lowering interventions, no matter what their cost, are unlikely to result in important direct savings to the health care system; while the human toll of coronary heart disease is high, the present value of total health care dollars saved is probably no more than a few hundred dollars, even among those for whom the benefits of intervention are highest. In this respect, cholesterol lowering appears to be much like other forms of medical intervention directed at the prevention of disease -- the benefits of treatment are reflected principally in terms of reduced mortality and improved quality of life".

In accordance with the economic concept of the consumer as a rational decision-maker, ***Taylor et al.*** assumed that, in deciding whether to undertake a dietary program to reduce serum cholesterol levels, a

person must consider how much benefit to expect.[9] They therefore developed a model that estimates gains in life expectancy resulting from a 6.7 percent reduction in serum cholesterol, which is the mean reduction achieved by an intensive program of dietary intervention in the Multiple Risk Factor Intervention Trial.

Taylor et al. modeled life expectancy by generating life tables that showed an individual's risk of death in successive years. This annual probability of dying was estimated as the sum of the probability of dying from coronary heart disease and of dying from all other causes. To obtain coronary heart disease mortality rates as a function of cholesterol level, blood pressure, and smoking habit, average age- and sex-specific mortality rates due to coronary heart disease from United States vital statistics data were multiplied by a factor that adjusted these rates for the difference between cholesterol level, blood pressure, and smoking behavior of the individual and the average values of these risk variables in the age- and sex-matched U.S. population. The latter adjustment was done using univariate logistic regression coefficients from the Framingham Heart Study. In a similar way, a risk function for mortality from all causes was constructed, but only as a function of blood pressure and smoking behavior. The probability of dying from non-cardiac causes was calculated as the difference between all-cause mortality and coronary heart disease mortality. The model estimates gains in life expectancy as a decrease in all-cause mortality set forth by a decrease in coronary mortality. Persons with additional risk factors (e.g., hypertension) will experience larger reductions in coronary risk from a given cholesterol reduction than normotensive persons will. However, the model also takes into account that hypertensive persons will have larger non-cardiac mortality rates than normotensive persons because of their increased risk of other life-threatening diseases, such as stroke.

Taylor et al. presented model results for men and women at the age of 20, 40, and 60 years, and at low- and high-risk of coronary heart disease. Persons at high risk were defined as the 90th percentile of the age-and sex-stratified population distribution for smoking habit and systolic blood pressure and the 10th percentile for HDL cholesterol level. Low risk was defined by persons at the 10th percentile of the age-and sex-stratified population distribution for smoking habit and systolic blood pressure and the 90th percentile for HDL cholesterol level. The gains in life expectancy vary between 3 days and 3 months for persons at low risk, and between 18 days and 12 months for persons at high risk, depending on age, sex, and initial cholesterol level. A remarkable and counter-intuitive result was that the estimates of the gain in life expectancy for women are higher than for men. For example, among 40-year-old persons at high risk, a 6.7 percent reduction in serum cholesterol level increases life expectancy by 9 months among women and 7 months among men. This difference is caused by the fact that the model does not assign benefits to cholesterol lowering after the age of 64 years in men, since serum cholesterol level and risk of death from coronary heart disease are not associated in men over the age of 64 years in the Framingham Study.

Taylor et al. also examined the effect on life expectancy of smoking cessation and blood pressure lowering. Using the reductions in smoking rates and levels of systolic blood pressure observed in the Multiple Risk Factor Intervention Trial, they estimated that months and even years of life could be gained from reductions in these two risk factors. Cholesterol reduction through dietary counseling, however, results in increased life expectancy of only weeks to months. For example, a 40-year-old man at high risk of coronary heart disease can achieve a gain in life expectancy of 7 months from a cholesterol reduction of 6.7 percent,

or even 18 months from a cholesterol reduction of 20 percent, compared to 63 months from quitting smoking, and 34 months from a 13.4 percent reduction in systolic blood pressure. There are two reasons for the difference in additional life expectancy between cholesterol lowering through dietary counseling and smoking cessation and blood pressure control. First, smoking and blood pressure have a greater impact on the level of risk than the dietary regimen for cholesterol lowering. Second, smoking cessation and blood pressure control also reduce the risk of dying from causes other than coronary heart disease.

The analytic model by Taylor et al. was developed to provide health professionals with a tool to assist patients in making their own choice about cholesterol reduction: "For each person - of any age, either sex, with any cholesterol level, and any combination of risk factors for ischemic heart disease - our model provides an estimate of that person's increase in life expectancy from a program of cholesterol reduction. Having been provided with this individualized estimate of benefit, each person can apply his or her own values and determine whether the estimated benefit is worth a lifelong program of dietary change".[9] Unfortunately, however, the model by Taylor et al. does not consider non-fatal coronary events; survival is the sole outcome of interest. The postponement of non-fatal myocardial infarction and angina pectoris may be a more relevant benefit to some patients than the gain in overall life expectancy, especially since the latter will occur at a later time in life.

Weinstein et al. developed a computer simulation model that projects the future morbidity, mortality, and costs of coronary heart disease in the population of 35- to 85-year-old persons in the United States.[10] The Coronary Heart Disease Policy Model consists of three submodels: the Demographic-Epidemiologic Model, the Bridge Model, and the Disease History Model.

The Demographic-Epidemiologic Model uses U.S. Bureau of Census data to project the size of the cohort of 35-year-old persons that enters the model in each year from 1981 through 2015. This submodel also allocates persons free of coronary heart disease into three groups: deaths from non-cardiac causes, incident cases of coronary heart disease, and those who remain free of coronary heart disease. Persons who experience coronary heart disease transit into the Bridge Model; persons who reach the age of 85 years without developing coronary heart disease leave the Coronary Heart Disease Policy Model. The population in the Demographic-Epidemiologic Model is stratified into 540 strata by sex, five 10-year age groups, two smoking statuses (cigarette smoker and nonsmoker), and three ranges each for diastolic blood pressure (<95 mm Hg, 95-104 mm Hg, and ≥ 105 mm Hg), serum cholesterol (<250 mg/dl, 250-299 mg/dl, and ≥ 300 mg/dl), and relative weight ($<110\%$ of norm, 110-129% of norm, and $\geq 130\%$ of norm). Age- and sex-specific estimates of overall coronary heart disease incidence are based on the Framingham Heart Study and adjusted according to the risk variables of each stratum using univariate coefficients from the same study. Similar risk functions were developed for all-cause mortality and coronary heart disease mortality as a function of diastolic blood pressure and cigarette smoking. The risk of dying from causes other than coronary heart disease was calculated by subtracting the risk function for coronary heart disease mortality from the risk function for all-cause mortality.

The Bridge Model covers the first thirty days following the initial coronary heart disease event. This submodel distributes the incident cases over four diagnostic categories (angina pectoris, myocardial infarction, and cardiac arrest with or without accompanying myocardial

infarction), estimates treatment costs and survival in the thirty-day period, and transits the survivors into the Disease History Model.

The Disease History Model is stratified by age, sex, and coronary heart disease state. There are 12 states, four of which are reserved for persons in the 11 months that immediately follow the initial coronary heart disease event. Persons who have survived the first year after the initial event can be in any of the remaining eight states that are characterized, in addition to the presence of angina, by the presence of one or more myocardial infarctions, cardiac arrests, coronary artery by-pass surgeries, or a combination of these events. At the beginning of any given year, coronary heart disease patients can experience coronary heart disease events (i.e., myocardial infarction, cardiac arrest, or by-pass surgery), and during the remainder of that year they may die because of that event, from non-cardiac causes, or from chronic coronary heart disease or old myocardial infarction. At the end of the year, persons are reassigned to states that reflect their updated coronary heart disease history. Treatment costs are assigned to every combination of coronary heart disease state and coronary heart disease event during the year.

The Coronary Heart Disease Policy Model is a scenario model; i.e., it yields not only estimates of future numbers and rates of coronary heart disease incidence, prevalence, and mortality and the associated treatment costs, but also offers the opportunity to simulate the costs and effects of preventive interventions or changes in therapeutic strategies. The Coronary Heart Disease Policy Model predicts that the future incidence rates of coronary heart disease in the United States will decline because of the more favorable risk factor status in newer cohorts. The annual number of persons experiencing their first cardiac event, however, will increase by 38 percent between 1980 and 2010 due to the increase in the

population of 35- to 85-year-old persons. The costs of treating coronary heart disease will increase about 50 percent from $32 billion in 1980 to $47 billion in 2010. According to Weinstein et al., the passage of the post-war baby-boom generation into older age ranges will have an even more dramatic effect on costs in the 20 years following 2010. To maintain in 2010 the same estimated annual incidence of about 210,000 new cases of coronary heart disease in men aged 45-64 year that was found in 1980 would require: "that all men in the baby-boom generation have normal cholesterol levels (with a mean cholesterol level of 200 mg/dl) and normal diastolic blood pressures (with a mean diastolic blood pressure of about 81 mm Hg), and that their cigarette smoking be only one-half that of current males age 45-64."

The *Office of Technology Assessment* released a report on the costs and effectiveness of cholesterol screening in the elderly.[11] The objective of this study was to assess costs and health effects of implementation of the recommendations for cholesterol screening and treatment of the National Heart, Lung, and Blood Institute's National Cholesterol Education Program in the elderly (i.e., age 65 or older).[12] Since all trials of cholesterol lowering have been performed in middle aged men, the authors had to infer evidence for the beneficial effects of cholesterol lowering in the elderly from epidemiologic studies. They found that there was no evidence of an association between cholesterol level and coronary heart disease incidence or mortality in elderly men, but that serum cholesterol was found to predict coronary heart disease incidence or mortality in elderly women. The authors concluded that they could not perform a full cost-effectiveness analysis since, based on the available literature on epidemiologic studies and clinical trials, "there is no firm evidence to suggest that cholesterol screening and subsequent treatment

would prolong the lives of elderly individuals who have no evidence of heart disease".

The health effects of cholesterol lowering are at least smaller in the elderly than in younger persons. The case for cholesterol lowering in the elderly is further weakened by the observation that medications often have more severe and frequent side-effects in the elderly. The elderly may have a slower metabolism than younger persons; they may take other medications with the possibility of adverse drug interactions; and they often suffer from multiple health impairments that decrease their tolerance for drugs.

Therefore, the Office of Technology Assessment's report is limited to an analysis of the costs that would be incurred if the recommendations of the National Cholesterol Education Program would be fully implemented in the elderly population. The National Cholesterol Education Program protocol specifies periodic cholesterol screening (every 5 years beginning at age 20 years) as well as diagnostic follow-up and treatment regimens for individuals with elevated serum cholesterol levels. The treatment regimens and cut-off levels for initiation of therapy are dependent on additional coronary risk factors such as hypertension, diabetes, smoking, and family history of premature coronary heart disease (i.e., before the age of 55). The circumstance that there are no data available on the distribution of these risk factors in the elderly U.S. population introduces an uncertainty that, as in the case with several other variables in the model, was resolved by generating probable upper and lower boundaries. In general, the model tends to underestimate the costs of the National Cholesterol Education Program. Dietary intervention, for instance, is assumed to lower LDL-cholesterol levels by 10 percent, without incurring any costs such as dietary counseling or additional physician visits. The high effectiveness of diet will lead to an

underestimation of the number of elderly persons among whom drug therapy will be initiated, with drug therapy being the most expensive part of the protocol. The authors conclude that the costs of screening and follow-up testing are a very small part of the total cost of screening and treatment: "In 1995, the cost of screening and follow-up testing would be about $57 million, while total national health care expenditures associated with screening and treatment would range from at least $2.9 billion to $14.2 billion". The latter figures assume 100 percent compliance of the elderly to the National Cholesterol Education Program.

Given the lack of evidence for beneficial effects of cholesterol lowering in the elderly, it is remarkable that the Office of Technology Assessment's report finishes with the rather mild conclusion: "If studies demonstrate that cholesterol lowering interventions reduce coronary heart disease and all cause mortality among the elderly, the rationale for screening could become more persuasive".

3.3 Full economic evaluations

Berwick et al. used multivariate risk functions from the Framingham Study to assess the cost-effectiveness of pediatric screening and dietary intervention programs for hypercholesterolemia.[13] They estimated the cost per year of life saved for universal screening of 10-year-olds to be $10,700 for boys and $9,300 for girls. Limiting the screening to boys and girls with a family history of coronary heart disease would improve the cost per year of life saved to $6,700 and $7,700 respectively.

Weinstein and Stason used the reduction in coronary heart disease mortality achieved in the Lipid Research Clinics Coronary Primary Prevention Trial and coronary heart disease death rates from the Framingham Heart Study to estimate the cost-effectiveness of

pharmacologic treatment with cholestyramine.[14] This analysis takes into account only drug costs and the gains in life expectancy due to averted fatal coronary heart disease events. Therapy among 45- to 50-year-old men with serum cholesterol levels higher than 265 mg/dl (6.85 mmol/l) increases life expectancy at a cost per year of life saved of $126,000. The economic benefits of preventing non-fatal coronary heart disease events were not included in the base case analysis, but the authors report that cost-effectiveness is not appreciably altered by incorporating these benefits. The authors suggest that the cost-effectiveness of therapy would certainly improve if treatment were limited to men with serum cholesterol levels above 300 mg/dl (7.75 mmol/l), but the available data from the Lipid Research Clinics Coronary Primary Prevention Trial did not allow an analysis for this extremely high-risk group. Weinstein and Stason concluded: "Clearly, pharmacologic intervention cannot be recommended as a cost-effective intervention at this time, at least for men with only moderately elevated serum cholesterol levels."

Oster and Epstein followed-up on their outcome analysis of cholesterol lowering with a publication on the cost-effectiveness of cholesterol-lowering therapy with cholestyramine in the primary prevention of coronary heart disease among men between the ages of 35 and 75 years.[15] Costs and effects that were taken into account in this study were 1) the lifetime cost of drug therapy, i.e., drug costs, physician's fees for routine office visits, and cholesterol testing; 2) the cost of treating side effects of cholestyramine therapy, such as gastrointestinal complaints; 3) savings in medical care costs due to prevented cases of both fatal and non-fatal coronary heart disease; 4) gains in life expectancy due to lifelong cholesterol-lowering therapy; and 5) the cost of medical care for individuals during those additional years of life that result from cholesterol-lowering therapy.

The study by Oster and Epstein considered a cholestyramine regimen of 16 grams per day and estimated the associated cholesterol reduction to be 8.8 percent, based on the dose-response relationship reported by the Lipid Research Clinics Coronary Primary Prevention Trial. The total annual cost of therapy, including drug costs, office visits, cholesterol testing, and treatment of side effects, was estimated at $843.36. The resulting cost-effectiveness ratios ranged from $36,000 to more than $1,000,000 per year of life saved, depending on pretreatment cholesterol level and age at initiation of therapy. Oster and Epstein concluded that their results suggest that "pharmacologic therapy may not be cost-effective for all patients with elevated cholesterol levels, especially those over 65 years of age. For many younger patients, however--those with additional coronary risk factors and more severe elevations in cholesterol levels--the cost-effectiveness of therapy may be comparable with other accepted medical practices".

Kinosian and Eisenberg published an analysis in which they compared the cost-effectiveness of treatment with three alternative agents: cholestyramine, colestipol, and oat bran.[16] This study is actually an economic evaluation of the LRC-CPPT with an additional analysis of the cost-effectiveness of colestipol and oat bran in dose regimens that are assumed to achieve the same cholesterol lowering as cholestyramine did in the first year of the LRC-CPPT. The costs and effects under consideration for a period equal to the actual follow-up in the LRC-CPPT were 1) the cost of cholesterol-lowering therapy; that is, the costs of office visits, cholesterol testing, and dietary counseling according to the actual protocol of the trial, as well as the cost of the cholesterol-lowering agent; 2) savings in direct medical care costs, which were calculated from the actual number of non-fatal coronary heart disease events that were averted in the LRC-CPPT's treatment group as

incremental cost-effectiveness ratios that only compare well with those of other generally accepted health care interventions in men with cholesterol levels above 250 mg/dl (6.47 mmol/l). Primary prevention had favorable cost-effectiveness ratios only in subgroups of men who, in addition to elevated serum cholesterol levels, also had additional coronary risk factors. Among women, primary prevention was rarely projected to have a favorable cost-effectiveness ratio. Goldman et al. conclude that "current national recommendations regarding medication for secondary prevention are not as aggressive as our projections would suggest, while recommendations regarding the use of medications for primary prevention should consider the cost of medication as well as the risk factor profile of the individual patient."

Hay et al. developed a model comparable to that of Oster and Epstein[8,15] that uses multivariate risk functions from the Framingham Study to estimate the cost-effectiveness of cholesterol-lowering therapy with lovastatin.[19] Although the cost per life-year saved with lovastatin among low-risk men compares unfavorably with the cost-effectiveness ratios of other health care interventions, Hay et al. suggest that at least 10 percent of the 8 million U.S. men aged 35 to 55 years are at sufficiently high risk of coronary heart disease so that the net cost of therapy would be less than $35,000 per year of life saved. Among women, the benefits of intervention are not as great. Hay et al. conclude: "Nevertheless, there are a large number of high-risk persons in the U.S. for whom the net cost of cholesterol reduction could be favorably compared to either losses in expected wage earnings or to other widely used medical interventions.

3.4 Discussion

The relevance of partial economic evaluations is limited, given the fact that they examine either the costs or the effects of therapy. The study by Oster and Epstein shows that cholesterol lowering is unlikely to result in substantial savings in health care costs and that the trade-off for the cost of therapy has to be found in increases in life expectancy or improvement in quality of life.[8] The study by Taylor et al. is revealing in situations where the patient bears no or insignificant financial costs, for instance in the case of dietary therapy. The relatively small gains in life expectancy are unlikely to provide an incentive for most patients to adhere to a diet.

Only cost-effectiveness analysis can provide information about the relationship between the amount of resources that are consumed by initiating and maintaining therapy and the effect of therapy on health status and medical care costs. If one is concerned with identifying the pharmacological agent that is least costly in achieving a certain effect, the analysis can be limited to the cost per unit change in intermediate outcomes, for instance serum cholesterol levels in the study by Schulman et al.[17] From an economic point of view, however, the relevance of such an analysis is limited in the case of cholesterol-lowering therapy. From a clinical point of view, it is rational to lower cholesterol levels in the entire population since the relationship between serum cholesterol and coronary heart disease mortality is continuous and graded.[20] Since the costs per year of life saved increase rapidly with decreasing pretreatment cholesterol level,[15,16,18,19] only a comparison with the cost-effectiveness of other generally accepted health care interventions can establish the cholesterol level above which therapy is desirable, given society's willingness to pay.

In the studies that estimate the cost per year of life saved, the relationship between lowering serum cholesterol levels and the resulting reduction in coronary heart disease incidence and/or mortality has been modeled in two ways. Weinstein and Stason[14] and Kinosian and Eisenberg[16] used the actual cholesterol reduction and the decrease in fatal and non-fatal coronary heart disease events that were observed in the Lipid Research Clinics Coronary Primary Prevention Trial. A number of other researchers used logistic regression coefficients from the Framingham Heart Study to assign a coronary risk to pre- and posttreatment cholesterol levels and assumed that, either with or without a time lag in which no benefits occur, the coronary risk of those whose cholesterol has been lowered becomes equal to that of those with the naturally occurring lower cholesterol level. In this group, one should distinguish between the models by Oster and Epstein[15] and by Hay et al.[19] that are based on a multivariate logistic risk function that calculates coronary heart disease risk as a function of age, serum cholesterol, smoking, blood pressure, glucose intolerance, and left ventricular hypertrophy, and the model by Weinstein et al.[10,18] that uses univariate logistic regression coefficients to construct a risk function that adjusts the average coronary risk in the population to reflect the coronary risk of a specific person based on the differences between the coronary risk factors of that individual and the population means.

The study by Oster and Epstein, which is based on data from the Framingham Study, reports cost-effectiveness ratios for cholestyramine that are comparable to those reported by Kinosian and Eisenberg, who use data from the Lipid Research Clinics Coronary Primary Prevention Trial. Although there are other methodological differences between these two studies, the fact that they report similar cost-effectiveness ratios for

cholestyramine provides support for the use of epidemiologic data from the Framingham Study in modeling the effect of cholesterol reductions.

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4 THE CORONARY HEART DISEASE MODEL

4.1 Introduction

The coronary heart disease model was designed to assess costs and effects of cholesterol lowering in the primary prevention of coronary heart disease, i.e., among persons free of clinically manifest coronary heart disease. The model estimates the effect of serum cholesterol lowering on clinical outcomes such as lifetime coronary heart disease risk, survival free of coronary heart disease, and life expectancy, as well as the effect on economic outcomes such as resource utilization in health care. Combining changes in clinical and economic outcomes allows the calculation of cost-effectiveness ratios.

The coronary heart disease model simulates the annual follow-up of a cohort of persons who are between the ages of 35 and 75 years and free of coronary heart disease at the start of the simulation. The model calculates the future incidence and prevalence of coronary heart disease as well as its associated morbidity, mortality, and treatment costs, for men and women of given age, total serum cholesterol level, and other coronary risk factors, i.e., diastolic blood pressure, cigarette smoking, glucose intolerance, and left ventricular hypertrophy.

The incidence of coronary heart disease has been estimated using multivariate logistic risk functions from the Framingham Heart Study and data on coronary risk factors in the Netherlands. Mortality rates after the onset of coronary heart disease were taken from Dutch data sources, with the exception of long-term mortality after myocardial infarction, which has been modeled using the results of the Minnesota Heart Survey.

Costs of treating coronary heart disease are based on the cost of treating the initial event, i.e., myocardial infarction, angina pectoris, and unstable angina pectoris, as well as recurrent myocardial infarction. A panel of 6 cardiologists determined typical patterns of care for patients with coronary heart disease in the Netherlands. Estimation of the costs associated with these treatment patterns provided treatment costs for each coronary heart disease event.

4.2 General model

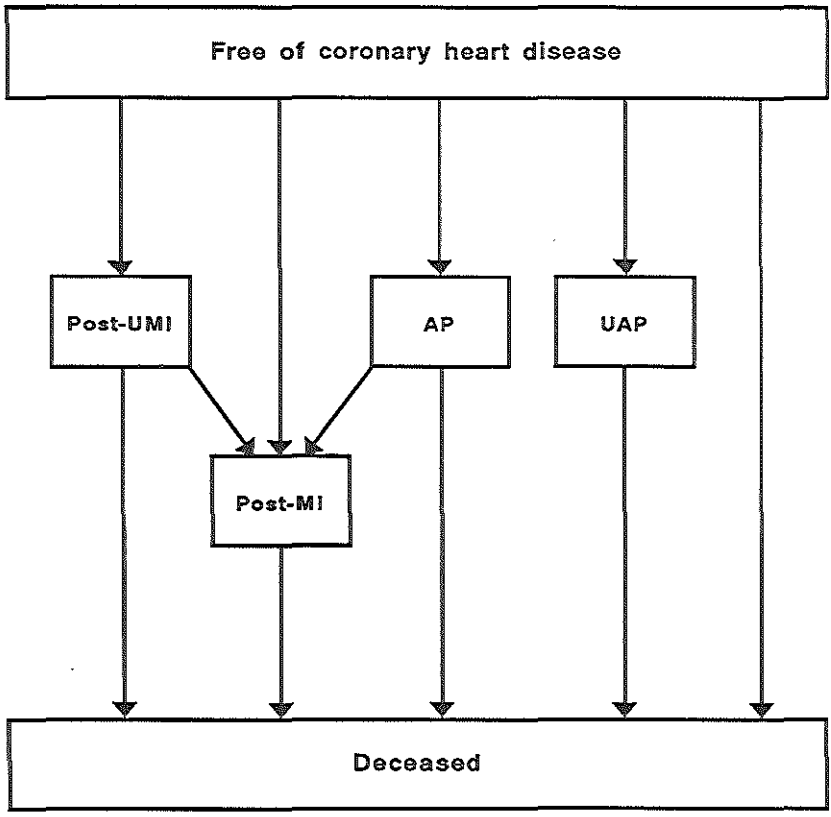
The coronary heart disease model is a Markov model with a cycle time of one year which uses death as an absorbing state.[1] At the start of the cycle count, all individuals in the cohort are free of symptomatic coronary heart disease. Thereafter, at any given moment in time, an individual can be in one of six states:

1. alive and free of symptomatic coronary heart disease;
2. suffering from angina pectoris without a prior myocardial infarction ("AP");
3. suffering from unstable angina pectoris without a prior myocardial infarction ("UAP");
4. survivor of a myocardial infarction ("post-MI");
5. survivor of an unrecognized myocardial infarction ("post-UMI"); or
6. dead.

Figure 4.1 shows the model states and the allowed transitions between them. Patients who are initially free of coronary heart disease may, over the course of any given year, either remain free of coronary heart disease, develop symptomatic coronary heart disease, or die from causes unrelated to coronary heart disease. A person who develops coronary heart disease will either survive the first year and transfer to

one of the coronary heart disease states (i.e., "AP", "UAP", "post-MI', or "post-UMI") or die. Coronary heart disease patients may, over the course of any given year, remain in their present state, die, or, as is the case in "AP", "UAP", and "UMI" patients, transit to the "post-MI" population after surviving the first year after a myocardial infarction.

Figure 4.1 Model states and allowed transitions in the coronary heart disease model.



The coronary heart disease model generates estimates of the fraction of the cohort that is still alive at any given point in time. Using standard life table techniques, these survival probabilities are recalculated into the expected value of the life expectancy of a man or woman with specific coronary risk variables.

Treatment costs for symptomatic coronary heart disease consist of the cost of treating acute manifestations and the cost of routine care in patients who have a diagnosis of coronary heart disease. The model generates probabilities over time of the onset and recurrence of distinct manifestations of coronary heart disease, as well as probabilities of being in one of the coronary heart disease states. Treatment costs are allocated to each of these probabilities. Using a discount rate, these costs and the probability that they will occur can be recalculated into a present value of the lifetime coronary heart disease treatment costs.

4.3 Model specifications

4.3.1 Coronary heart disease incidence

Multivariate logistic risk functions from the 24-year follow-up of participants in the Framingham Heart Study were used to estimate the future incidence of coronary heart disease.[2] These risk functions estimate the eight-year probability of a first manifestation of coronary heart disease as a function of age, total serum cholesterol, blood pressure, cigarette smoking, left ventricular hypertrophy, and glucose intolerance. Table 4.1 shows the sex- and age-specific mean values of these coronary risk factors in the Netherlands.

The serum cholesterol and blood pressure data in Table 4.1 were obtained from the Epidemiologic Preventative Study Zoetermeer

(Epidemiologisch Preventief Onderzoek Zoetermeer - EPOZ).[3] The EPOZ studied the prevalence of several chronic diseases: rheumatic disease, urinary tract infection, chronic aspecific respiratory disease and cardiovascular disease. The study involved the measurement of cardiovascular risk factors among a cohort of more than 10,000 inhabitants above five years of age of Zoetermeer, a city in the west of the Netherlands.[4] A review of 29 studies of serum cholesterol distributions in the Netherlands, among which is the EPOZ, concluded that although

Table 4.1 Mean Values of Cardiovascular Risk Factors Among Dutch Men and Women

	Age	Serum Cholesterol (mmol/l)	Diastolic Blood Pressure (mm Hg)	Cigarette Smoking	Glucose Intolerance	Left Ventricular Hypertrophy
Reference:		3	3	6,7	9,10	8
Men	35-39	5.75	82.0	.36	.0039	.0042
	40-44	5.91	83.8	.36	.0267	.0090
	45-49	6.14	86.5	.37	.0267	.0132
	50-54	6.09	87.2	.35	.0545	.0129
	55-59	6.14	87.8	.32	.0545	.0139
	60-64	6.07	85.5	.32	.0739	.0182
	65-69	5.93	85.6	.26	.1491	.0238
	70-74	5.87	86.8	.26	.1491	.0295
Women	35-39	5.38	79.8	.33	.0084	.0054
	40-44	5.55	82.2	.33	.0308	.0049
	45-49	5.78	86.7	.34	.0308	.0047
	50-54	6.19	87.7	.25	.0530	.0114
	55-59	6.47	88.5	.25	.0530	.0176
	60-64	6.64	88.3	.25	.0998	.0202
	65-69	6.53	88.4	.11	.1407	.0259
	70-74	6.50	88.3	.11	.1407	.0317

these studies were quite different in purpose, design, and location, both geographically and in time, the results were fairly consistent.[5] This suggests that the serum cholesterol distributions in the EPOZ can be considered representative for the Netherlands as a whole.

Data on the combined prevalence of cigarette, cigar, and pipe smoking from a 1988 survey were adjusted to reflect the prevalence of cigarette smoking in 1988 using a 1983 survey that reported the prevalence of each habit seperately.[6,7] Since there are no data available on the prevalence of left ventricular hypertrophy in the Netherlands, age- and sex-specific data from the Framingham study were used.[8] The prevalence of glucose intolerance is assumed to be twice the prevalence of diagnosed diabetes mellitus. Age- and sex-specific data on the prevalence of diabetes mellitus in a number of general practices in the Nijmegen area were adjusted for regional variation using a national survey.[9,10]

Cross-sectional epidemiologic studies of serum cholesterol levels reveal that there is an increase of serum cholesterol with age, followed by a subsequent decrease after age 50 years. Lipid experts agree that this is rather a longitudinal effect related to, among others, changes in endocrine function with age, than a cohort effect.[11] To adjust estimates of the future incidence of coronary heart disease for the increase and subsequent decrease of cholesterol levels with age, the assumption was made that individual cholesterol levels would show perfect tracking along a line parallel to the line that represents the 80th percentile. Separate algorithms for men and women were estimated by polynomial regression of age- and sex-specific 80th percentiles in the EPOZ study.[3]

Serum cholesterol levels are measured with a substantial error due to intra-individual biological variation in serum cholesterol as well as the analytical error in the laboratory determination. For this reason the risk

functions from the Framingham Heart Study underestimate the relationship between serum cholesterol and the incidence of coronary heart disease. This is a concern since current cholesterol testing methods provide a much better estimate of individual cholesterol levels than those existent at the time that the cholesterol data were collected in the Framingham Heart Study (between 1950 and 1970). Accuracy and precision of the laboratory determination have improved considerably since the introduction of standardization programs by the World Health Organization in the early 70s. Furthermore, some cholesterol consensus conferences such as the one organized in the Netherlands, advise physicians to base the decision to initiate cholesterol-lowering therapy on the average of three measurements because of the combined effect of biological variation and laboratory variation. Appendix 1 describes the algorithm that was used to correct the risk functions from the Framingham Heart Study for biological and analytical variation in cholesterol measurement.

The 24-year follow-up of participants in the Framingham Heart Study provides logistic functions for the eight-year probabilities of coronary heart disease, myocardial infarction, and coronary heart disease death (both sudden and non-sudden).[2] Eight-year probabilities P_8 were converted into annual probabilities by assigning the average annual incidence in the eight-year interval, i.e., $1-(1-P_8)^{1/8}$, to the midpoint within the eight-year interval. The incidence of angina pectoris and unstable angina pectoris were estimated by first subtracting the incidence of myocardial infarction and coronary heart disease death from total coronary heart disease incidence, and apportioning the remainder to angina pectoris and unstable angina pectoris using the actual breakdown by type of event as observed in the Framingham Heart Study.[12]

In the Framingham Study, 28 percent of all myocardial infarctions were not recognized as such, but appeared on biannual routine electrocardiographic examination.[13] Only one half of these unrecognized myocardial infarctions were silent infarctions, and the other half had atypical symptoms. It was assumed that currently 85 percent of myocardial infarctions are recognized. In the Framingham Study, persons with an unrecognized myocardial infarction survived the first year after the event by definition.

Based on Dutch hospital and mortality statistics, it was estimated that 28 percent of those experiencing coronary heart disease death (i.e. sudden death and non-sudden death) or recognized myocardial infarction die before they are hospitalized.[14,15] Age-specific one-year survival rates were calculated from van Rees.[16]

For patients with angina pectoris, both in the first year after the onset of angina pectoris as well as in later years, it was assumed that their probability of dying from causes unrelated to coronary heart disease would be the same as that of the general population, and that their excess mortality would be due to their increased risk of myocardial infarction and coronary heart disease death. Using results from the German Prospective Cardiovascular Study Münster (PROCAM), it was estimated that the probability of myocardial infarction or coronary heart disease death in AP patients would be 3.9 times that in the sex- and age-matched population free of coronary heart disease.[17] Only 94 percent of persons experiencing UAP will be alive one year after the initial attack.[16]

4.3.2 Mortality from causes other than coronary heart disease

The probability of dying from causes other than coronary heart disease is assumed to be independent of whether a person has symptomatic

coronary heart disease. Therefore, the age- and sex-specific probability of dying from causes other than coronary heart disease of the general population in the Netherlands has been assigned to the coronary heart disease free population.

Life tables that pool mortality statistics from the Netherlands over the period 1979-1983 provide sex- and age-specific mortality rates from all causes for one-year age intervals.[18,19] The age- and sex-specific proportion of mortality that was not caused by coronary heart disease, i.e., all causes excluding ICD 410-414, was calculated from mortality statistics for the period 1979 through 1983.[20-24]

Since the multivariate logistic functions from the Framingham Heart Study are valid only for persons between 35 and 74 years of age, coronary heart disease has been modeled between these ages only. At later ages, persons in the "free of symptomatic coronary heart disease" state either remain in that state or die. The corresponding transition probability was set equal to the age- and sex-specific mortality rate from all causes as reported in life tables from the Netherlands.[20-24]

4.3.3 Morbidity and mortality after the first year of coronary heart disease

Persons who have survived the first year after a myocardial infarction and transferred to the "post-MI" population may, over the course of any given year, either remain in that state or die. Based on results from the Minnesota Heart Survey, the annual mortality rate in the "post-MI" population was assumed to be 4.25 percent for men and 4.95 percent for women.[25] The reinfarction rate was assumed to equal that in the first year after myocardial infarction: 3.5 percent per year.[16]

Persons in the "post-UMI" population may over the course of any given year either 1) remain in that state, 2) die, or 3) transfer to the "post-MI" population because they survived the first year after a myocardial infarction. Results from the Framingham Heart Study show that among both men and women, mortality rates after unrecognized myocardial infarction do not differ significantly from those after recognized infarction.[13] Mortality rates in the "post-UMI" population are therefore assumed to be equal to those in the "post-MI" population: 4.25 percent for men and 4.95 percent for women. Results from the Framingham study also indicate that the reinfarction rate in men with unrecognized myocardial infarction is the same as in men with recognized MI. Among women, however, the rate of reinfarction after unrecognized MI is only half that after recognized MI. As in the case of the "post-MI" population, it was therefore assumed that 3.5 percent of men and 1.75 percent of women who survive until the end of a given year have experienced a reinfarction that has been recognized and that they will transfer to the "post-MI" population.

For persons in the "AP" population it was assumed that their probability of dying from causes unrelated to coronary heart disease would be the same as that of the general population, and that their excess mortality would be due to their increased risk of myocardial infarction and coronary heart disease death. Using results from the PROCAM study, the latter risk was estimated to be 3.9 times that in the sex- and age-matched population free of coronary heart disease.[17]

Persons in the "UAP" population may over the course of any year either 1) remain in that state, 2) die, or 3) transfer to the post-MI population because of a myocardial infarction. The assumption that the mortality rate among persons in the UAP-population equals that of post-MI patients was adopted from Hartunian et al., as was the assumption

that the infarction rate among UAP patients is the same as the reinfarction rate among post-MI patients.[26]

4.3.4 The costs of treating coronary heart disease

The costs associated with the treatment of symptomatic coronary heart disease were estimated by costing out typical patterns of care which were obtained from a panel of six cardiologists representing several different hospitals in the Netherlands (two university hospitals, two large training hospitals, and two peripheral hospitals). The panel determined typical patterns of care, including rates of inpatient and outpatient care, diagnostic procedures (e.g., coronary angiography), surgical procedures (coronary artery bypass surgery, coronary angioplasty), and pharmacologic therapy for each of the different manifestations of coronary heart disease. Wherever possible, the costs associated with these treatment patterns were estimated using published and unpublished data on the actual costs of medical and surgical procedures. In other cases, reimbursement rates were used. Appendix 2 contains a detailed description of the treatment patterns that were developed by the panel of cardiologists, as well as the way in which the associated health care costs were estimated.

4.4 Simulation of a cholesterol-lowering intervention

The coronary heart disease model simulates a cholesterol-lowering intervention by lowering the value of the cholesterol risk variable in the multivariate logistic risk function. Both the Lipid Research Clinics Coronary Primary Prevention Trial and the Helsinki Heart Study showed no difference in coronary heart disease incidence between placebo group

and treatment group during the first two years of these trials.[27,28] The model therefore assumes that there will be no benefits from cholesterol lowering during the first two years after the intervention, and that after this two-year lag time the coronary heart disease risk equals that of persons with the naturally occurring lower cholesterol level.

4.5 Discussion

This chapter describes a model of life expectancy and coronary heart disease treatment costs that can be used to estimate the cost-effectiveness of cholesterol-lowering interventions in the Netherlands. This model is based on a variety of data sources, both from the Netherlands and the United States. Multivariate logistic risk functions from the Framingham Study and data on coronary risk variables from the Netherlands were used to model the incidence of coronary heart disease. Clinical and epidemiologic data from the Netherlands were used to estimate the one-year survival after the onset of disease, and the results of a U.S. study were used to model the long-term survival after myocardial infarction.

Because of the use of multivariate risk functions from the Framingham Study to estimate coronary heart disease incidence, the cost-effectiveness model shows a strong resemblance to the models that were developed by Oster and Epstein and by Hay et al.[30,31] There are, however, a number of differences. For instance, the cost-effectiveness model described in this dissertation adjusts serum cholesterol levels for the upward drift in cholesterol level with age. The only other economic evaluation that contains such an adjustment is the outcome evaluation by Taylor et al.[32] Furthermore, Oster and Epstein and Hay et al. model survival after the onset of coronary heart disease by adjusting survival data from the Framingham Study for the improvement in survival due to

medical progress in the last few decades. This study uses more recent data to model survival once coronary heart disease has become clinically manifest. The study described in this dissertation distinguishes itself from other economic evaluations of cholesterol lowering in that it is the only study that accounts for the effect of intra-individual biological variation and analytical variation in cholesterol measurement. Appendix 1 contains a detailed description of the algorithm that was used and shows that cost-effectiveness studies that fail to adjust for biological and analytical variation can overestimate the cost per year of life saved by cholesterol lowering by as much as 50 percent.

The cost-effectiveness model presented in this dissertation is based on a variety of assumptions. The effect of changes in these assumptions on the model results will be examined in the sensitivity analysis in Chapter 7.

There are a number of limitations to this study. First, epidemiologic data from the United States may not be applicable to patients in the Netherlands. This concern particularly pertains to the generalizability of the risk functions from the Framingham Study to the Dutch population. Furthermore, the model estimates the effect of cholesterol lowering on life expectancy and coronary heart disease treatment costs based on the difference in coronary heart disease risk between the two cholesterol levels observed in an epidemiologic study rather than based on the observed effect in an intervention study. Both issues will be addressed in the following.

The multivariate risk functions from the Framingham Study estimate the eight-year probability of a first manifestation of coronary heart disease as a function of sex, age, total serum cholesterol, blood pressure, cigarette smoking, left ventricular hypertrophy, and glucose intolerance. These risk functions may not be applicable to the Dutch population

because the relationship between coronary heart disease incidence and these risk variables may differ between the Framingham population and the Dutch population. There are no studies that compare risk estimates from the Framingham Study with the actual incidence of coronary heart disease in the Netherlands. Schulte and Assmann, however, recently compared the coronary heart disease risk predicted by the Framingham risk functions with the observed incidence of coronary events in the PROCAM study. The PROCAM study is a prospective study of coronary risk factors and coronary heart disease incidence in the German state Westphalia. The four-year follow-up of 40- to 64-year-old men observed sufficient coronary events to enable this comparison. After making adjustments for differences in disease classification and length of follow-up, they concluded that the Framingham risk functions are fairly accurate predictors of the coronary risk of 40- to 64-year-old men in the PROCAM study. Since the populations of West Germany and the Netherlands have comparable serum cholesterol levels and coronary heart disease mortality rates, these findings support the use of Framingham logistic risk functions in modeling coronary heart disease incidence in the Netherlands.

The cost-effectiveness model does not estimate the benefits of cholesterol-lowering therapy using the results of clinical trials of cholesterol lowering, but models these benefits using the results of an epidemiologic study, i.e., the Framingham Study. Based on the Lipid Research Clinics Coronary Primary Prevention Trial and the Helsinki Heart Study, the model assumes that lowering serum cholesterol will not change coronary risk during the first two years after the intervention. During later years, coronary risk is assumed to equal the risk that has been observed at the naturally occurring lower cholesterol level. The latter assumption may well overestimate the benefits of cholesterol-

lowering therapy. In order to assess the validity of this assumption, the cost-effectiveness model was used to simulate the results of the Lipid Research Clinics Coronary Primary Prevention Trial.

The Lipid Research Clinics Coronary Primary Prevention Trial was a multi-center, randomized, double blind study in which 3,800 men aged 39-59 years with cholesterol levels of 265 mg/dl and greater were randomized to the bile acid sequestrant cholestyramine resin (six packets of 4 grams each per day, divided into two or four equal doses) or an equivalent amount of placebo.[27,29] At entry, all men were free of symptomatic coronary heart disease. After an average follow-up of 7.4 years, an average reduction in total cholesterol of 7.5 percent in the cholestyramine-treated group was accompanied by a 19 percent reduction in the cumulative incidence of coronary heart disease, which was defined as definite coronary heart disease death and/or definite non-fatal myocardial infarction.[27] Using a Cox proportional hazards model, the investigators estimated that a 7.5 percent cholesterol reduction would cause a 17.1 percent decrease in the cumulative incidence of coronary heart disease.[29]

The reduction in the cumulative incidence of coronary heart disease due to a 7.5 percent cholesterol lowering was predicted by entering the post-entry characteristics of the placebo group in the Lipid Research Clinics Coronary Primary Prevention Trial into the cost-effectiveness model. The placebo group consisted of 1,900 men with an average age of 47.8 years, a mean plasma cholesterol level of 275.4 mg/dl, which corresponds with a serum cholesterol of 7.37 mmol/l (285.3 mg/dl) and a mean diastolic blood pressure of 79 mm Hg. At the start of the trial, 35 percent of these men were cigarette smokers. Men with glucose intolerance or left ventricular hypertrophy were excluded from the trial. Using the definition of coronary heart disease in the Framingham study

(i.e., including angina pectoris and coronary insufficiency), the model estimated the reduction in coronary heart disease risk at the end of the seventh and eighth year at 17.1 and 17.4 percent respectively. This result is slightly higher than that of the Cox proportional hazards model (17.1 percent). Limiting the endpoints in the coronary heart disease model to those used in the Lipid Research Clinics Coronary Primary Prevention Trial, i.e., definite coronary heart disease death and/or definite non-fatal myocardial infarction, resulted in predicted risk reductions of 15.6 percent and 15.9 percent at the end of the seventh and eighth years respectively. This result is lower than the proportional hazards model predicts, which may reflect a too conservative assumption that there is no change in coronary risk during the first two years after cholesterol lowering. Nevertheless, the coronary heart disease model does not seem to overestimate the benefits of cholesterol-lowering interventions.

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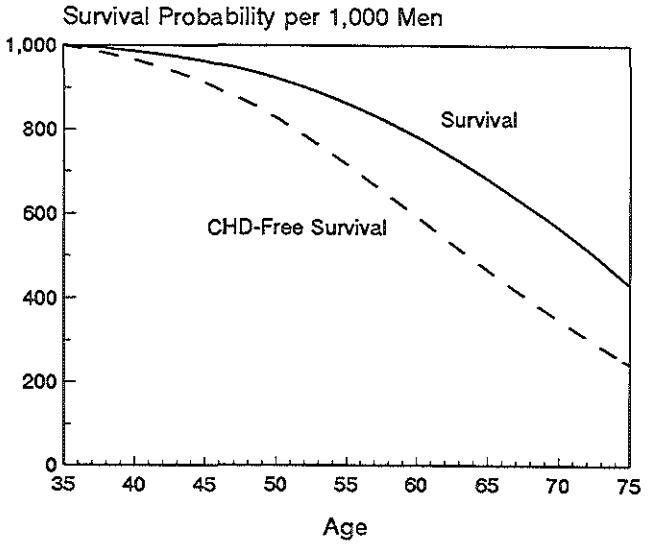
5 EFFECTS OF CHOLESTEROL-LOWERING

5.1 Introduction

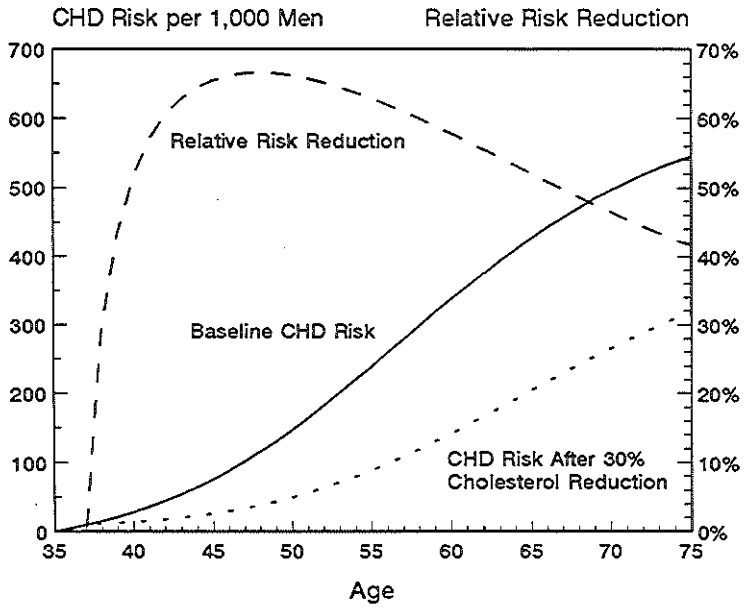
The coronary heart disease model described in Chapter 4 estimates the future distribution of a cohort of men and women who are initially free of coronary heart disease over the different states that have been defined in the model. As an example, Figure 5.1 shows the survival and prevalence of coronary heart disease in a cohort of 1,000 men who, at

Figure 5.1 Survival and coronary heart disease free survival among men with a serum cholesterol of 8 mmol/l at age 35 years.



35 years, were free of coronary heart disease and had a total serum cholesterol level of 8 mmol/l and an otherwise average coronary risk profile. The area under the survival curve represents life expectancy; the area under the curve depicting survival free of coronary heart disease represents the time until onset of coronary heart disease. According to the model, men who have a serum cholesterol of 8 mmol/l at age 35 years and no pre-existing coronary heart disease have a life expectancy of approximately 36 years. On the average, they will experience their first manifestation of coronary heart disease at age 63 years. The

Figure 5.2 The effect of a 30% cholesterol reduction at age 35 on the coronary heart disease risk in men with a serum cholesterol of 8 mmol/l.



initiation of therapy with 20 mg simvastatin per day at age 35 years will lower their serum cholesterol by 27 percent, which will postpone their first coronary heart disease event on the average by almost 5 years, which results in a gain in life expectancy of 2.5 years.

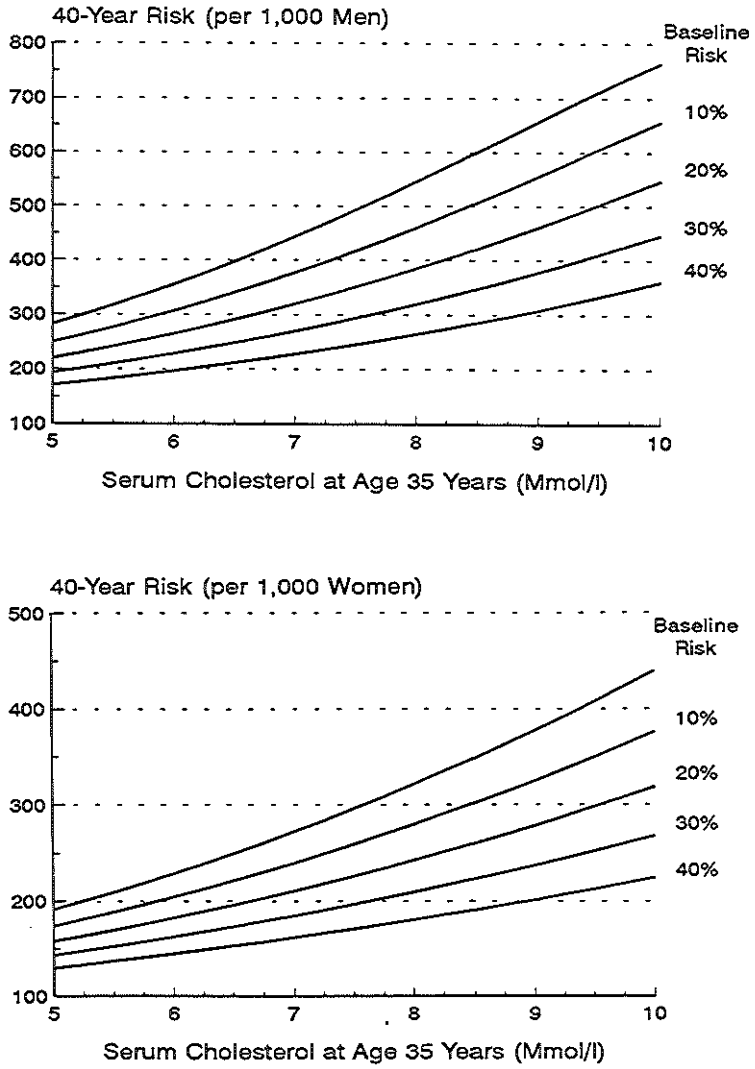
This chapter will review the effect of cholesterol lowering on outcomes such as coronary heart disease risk, life expectancy, and coronary heart disease treatment costs. The effect of reductions in serum cholesterol level on the incidence of coronary heart disease is generally assumed to be independent of the method by which cholesterol levels have been lowered. Therefore, rather than presenting results for the two medications which are the subject of this dissertation, e.g., simvastatin and cholestyramine, estimates will be presented of the effects of 10, 20, 30, and 40 percent reductions in total serum cholesterol level on selected outcomes.

5.2 Reduction in coronary heart disease risk

Figure 5.2 shows the cumulative risk of developing coronary heart disease by age for men with a serum cholesterol level of 8 mmol/l at age 35 years and no pre-existing coronary heart disease. Shown are the cumulative risk per 1,000 men with and without a 30 percent cholesterol reduction at age 35 years, as well as the risk reduction in percent. In the absence of any cholesterol-lowering intervention, 543 of 1,000 men would develop coronary heart disease between the ages of 35 and 75 years. A 30 percent cholesterol reduction at age 35 would prevent the onset of coronary heart disease in 225 of these men.

During the first two years after the cholesterol-lowering intervention has been started, the model assumes that there is no reduction in coronary risk. After those two years, the percentage

Figure 5.3 Forty-year risk of coronary heart disease as a function of the serum cholesterol at age 35 years. Shown is, for both men and women, the 40 year risk at baseline and after 10-40% cholesterol reductions.



reduction in coronary heart disease risk increases rapidly to almost 67 percent at age 47 and slowly declines to 41 percent at age 75. Based on the results of the Lipid Research Clinics Coronary Primary Prevention Trial (LRC-CPPT), it is generally assumed that a one percent reduction in serum cholesterol will cause a two percent reduction in coronary heart disease risk. The model results presented in Figure 5.2 indicate that this rule of thumb is valid only for the particular follow-up period of the LRC-CPPT, which was seven to ten years. After that time period, the relative risk reduction steadily declines.

Estimates of the 40-year risk of coronary heart disease as a function of total serum cholesterol at age 35 years are presented in Figure 5.3 both for men and women. Shown is the 40-year risk of coronary heart disease risk at baseline and after 10-40 percent cholesterol reductions at age 35 years. The figure shows that men have a substantially higher coronary risk than women with the same serum cholesterol level. For instance, of 1,000 men with a serum cholesterol level of 8 mmol/l at age 35 years, 543 will have a manifestation of coronary heart disease before the age of 75 years, as opposed to 319 of 1,000 women of similar cholesterol level and age. After a 30 percent cholesterol reduction at age 35 years, the 40-year risk of coronary heart disease among men is comparable to that of women who have the same initial cholesterol level but have not received cholesterol-lowering therapy.

The average serum cholesterol level of 35-year-old men in the Netherlands is approximately 5.7 mmol/l. The results in figure 5.3 suggest that almost one of every three 35-year-old Dutch men will experience some manifestation of coronary heart disease. The average serum cholesterol among 35-year-old women in the Netherlands is 5.3 mmol/l, which corresponds with a probability of one in five chance of developing coronary heart disease before the age of 75 years.

Table 5.1 Undiscounted gains in life expectancy, by cholesterol level and age at initiation of therapy for selected cholesterol reductions.

Cholesterol reduction (%)	*Age at initiation of therapy (Years)*	*Gain in life expectancy for men/women (Years)*		
		7 mmol/l	8 mmol/l	9 mmol/l
10	35 - 39	0.69 / 0.32	1.03 / 0.48	1.46 / 0.71
	40 - 44	0.55 / 0.28	0.80 / 0.40	1.11 / 0.58
	45 - 49	0.42 / 0.24	0.58 / 0.34	0.78 / 0.47
	50 - 54	0.28 / 0.19	0.38 / 0.27	0.50 / 0.36
	55 - 59	0.18 / 0.15	0.24 / 0.20	0.30 / 0.26
	60 - 64	0.10 / 0.11	0.13 / 0.14	0.16 / 0.18
	65 - 69	0.05 / 0.07	0.07 / 0.09	0.08 / 0.11
	70 - 74	0.02 / 0.03	0.02 / 0.04	0.03 / 0.05
20	35 - 39	1.25 / 0.59	1.85 / 0.86	2.64 / 1.26
	40 - 44	1.01 / 0.51	1.46 / 0.73	2.02 / 1.04
	45 - 49	0.77 / 0.44	1.07 / 0.61	1.44 / 0.85
	50 - 54	0.53 / 0.36	0.71 / 0.49	0.93 / 0.66
	55 - 59	0.34 / 0.28	0.44 / 0.37	0.57 / 0.48
	60 - 64	0.19 / 0.20	0.25 / 0.27	0.31 / 0.34
	65 - 69	0.10 / 0.13	0.12 / 0.17	0.16 / 0.21
	70 - 74	0.03 / 0.06	0.04 / 0.08	0.06 / 0.09
30	35 - 39	1.69 / 0.81	2.50 / 1.17	3.55 / 1.69
	40 - 44	1.38 / 0.70	1.98 / 1.00	2.75 / 1.40
	45 - 49	1.06 / 0.61	1.47 / 0.85	1.98 / 1.17
	50 - 54	0.74 / 0.50	0.99 / 0.69	1.29 / 0.92
	55 - 59	0.48 / 0.40	0.62 / 0.52	0.80 / 0.67
	60 - 64	0.27 / 0.29	0.35 / 0.38	0.44 / 0.48
	65 - 69	0.14 / 0.19	0.18 / 0.24	0.22 / 0.29
	70 - 74	0.05 / 0.09	0.06 / 0.11	0.08 / 0.13
40	35 - 39	2.05 / 1.00	3.00 / 1.42	4.25 / 2.03
	40 - 44	1.68 / 0.87	2.40 / 1.22	3.32 / 1.70
	45 - 49	1.30 / 0.76	1.80 / 1.04	2.41 / 1.42
	50 - 54	0.92 / 0.63	1.22 / 0.85	1.59 / 1.13
	55 - 59	0.60 / 0.50	0.78 / 0.65	0.99 / 0.84
	60 - 64	0.34 / 0.37	0.44 / 0.48	0.55 / 0.60
	65 - 69	0.17 / 0.24	0.22 / 0.30	0.28 / 0.37
	70 - 74	0.06 / 0.11	0.08 / 0.14	0.10 / 0.17

Figure 5.3 shows that for men as well as for women the benefits of cholesterol-lowering therapy increase, both in an absolute and a relative sense, as pretreatment levels increase. However, cholesterol-lowering therapy has greater benefits among men than among women. For instance, a reduction in serum cholesterol levels of 30 percent at age 35 years will prevent the onset of coronary heart disease in the following 40 years for 225 men per 1,000. Among 1,000 women of similar age and cholesterol level, coronary heart disease would be prevented in 110 women.

5.3 Increase in life expectancy

Table 5.1 lists undiscounted estimates of the increase in life expectancy resulting from 10-40 percent cholesterol reductions by cholesterol level and age at initiation of therapy. At all ages among both men and women, the gains in life expectancy increase with increasing reduction in cholesterol level. However, they do so at a decreasing rate. For instance, a 10 percent cholesterol reduction in 35- to 39-year-old men with a pretreatment cholesterol level of 8 mmol/l increases life expectancy by 1.03 years. An additional 10 percent reduction in serum cholesterol levels results in a further increase in life expectancy of 0.82 years. Increasing the cholesterol reduction by another 10 percent will gain only 0.65 additional years of life. The fourth 10 percent increment in cholesterol reduction will add only 0.50 years to life expectancy. These diminishing returns occur for both men and women and at all pretreatment cholesterol levels and ages at initiation of therapy.

For both men and women and at all levels of cholesterol reduction, the gains in life expectancy increase with increasing pretreatment cholesterol level. For example, when a 30 percent cholesterol reduction

Table 5.2 Undiscounted gains in life years free of coronary heart disease, by cholesterol level and age at initiation of therapy for selected cholesterol reductions.

Cholesterol reduction (%)	*Age at initiation of therapy (Years)*	*Gain in life years free of coronary heart disease for men/women (Years)*		
		7 mmol/l	8 mmol/l	9 mmol/l
10	35 - 39	1.41 / 0.56	2.01 / 0.75	2.69 / 0.98
	40 - 44	1.18 / 0.49	1.64 / 0.66	2.15 / 0.85
	45 - 49	0.92 / 0.43	1.25 / 0.56	1.60 / 0.73
	50 - 54	0.66 / 0.35	0.86 / 0.45	1.08 / 0.58
	55 - 59	0.42 / 0.26	0.55 / 0.33	0.68 / 0.41
	60 - 64	0.23 / 0.17	0.29 / 0.22	0.35 / 0.27
	65 - 69	0.10 / 0.09	0.12 / 0.11	0.15 / 0.14
	70 - 74	0.03 / 0.03	0.03 / 0.04	0.04 / 0.05
20	35 - 39	2.56 / 1.04	3.64 / 1.39	4.91 / 1.81
	40 - 44	2.15 / 0.93	2.99 / 1.22	3.95 / 1.58
	45 - 49	1.70 / 0.81	2.29 / 1.06	2.96 / 1.35
	50 - 54	1.22 / 0.66	1.60 / 0.85	2.02 / 1.08
	55 - 59	0.79 / 0.49	1.02 / 0.62	1.27 / 0.78
	60 - 64	0.43 / 0.33	0.55 / 0.41	0.67 / 0.51
	65 - 69	0.19 / 0.17	0.23 / 0.22	0.28 / 0.26
	70 - 74	0.05 / 0.06	0.06 / 0.08	0.07 / 0.09
30	35 - 39	3.48 / 1.47	4.93 / 1.94	6.67 / 2.51
	40 - 44	2.94 / 1.31	4.08 / 1.71	5.40 / 2.20
	45 - 49	2.34 / 1.14	3.16 / 1.48	4.08 / 1.89
	50 - 54	1.71 / 0.93	2.23 / 1.20	2.81 / 1.51
	55 - 59	1.12 / 0.70	1.44 / 0.88	1.79 / 1.09
	60 - 64	0.62 / 0.47	0.77 / 0.59	0.95 / 0.73
	65 - 69	0.27 / 0.25	0.33 / 0.31	0.40 / 0.38
	70 - 74	0.08 / 0.09	0.09 / 0.11	0.11 / 0.13
40	35 - 39	4.22 / 1.84	5.94 / 2.41	8.02 / 3.11
	40 - 44	3.59 / 1.63	4.94 / 2.13	6.54 / 2.73
	45 - 49	2.88 / 1.43	3.86 / 1.85	4.99 / 2.35
	50 - 54	2.11 / 1.17	2.75 / 1.50	3.46 / 1.88
	55 - 59	1.40 / 0.88	1.79 / 1.11	2.22 / 1.37
	60 - 64	0.78 / 0.59	0.98 / 0.74	1.19 / 0.91
	65 - 69	0.35 / 0.32	0.42 / 0.39	0.50 / 0.47
	70 - 74	0.10 / 0.11	0.12 / 0.14	0.14 / 0.10

is started among 35- to 39-year-old men, the gain in life expectancy among men with a pretreatment cholesterol level of 9 mmol/l is more than twice that among men with pretreatment cholesterol levels of 7 mmol/l (3.55 vs 1.69 years).

Among both men and women and for all pretreatment cholesterol levels, the gains in life expectancy decrease as age at initiation of therapy increases. For instance, a 30 percent cholesterol reduction among 55- to 59-year-old men with pretreatment cholesterol levels of 8 mmol/l gains only one fourth of the increase in life expectancy that would be achieved by starting therapy in 35- to 39-year-old men with similar cholesterol levels (0.62 vs 2.50 years).

Finally, the gains in life expectancy for women are substantially lower than those among men for all pretreatment cholesterol levels and for all ages at initiation of therapy up to approximately 60 years. For example, a 30 percent cholesterol reduction among 35- to 39-year-old individuals with serum cholesterol levels of 8 mmol/l results in an increase in life expectancy of 1.17 years for women compared to 2.50 years for men. Therapy started between the ages of 60-64 years, however, yields similar gains in life expectancy among men and women. The gain in life expectancy from a 40 percent cholesterol reduction among 35-year-old individuals with average serum cholesterol levels is 1.3 years among men and and 0.5 years among women.

5.4 Increase in expected years of life free of coronary heart disease

Table 5.2 reports undiscounted estimates of the increase in the number of years of life free of coronary heart disease caused by 10-40 percent cholesterol reductions by cholesterol level and age at onset of therapy. At all ages among both men and women, the gains in years of life free

of coronary heart disease increase with increasing reduction in cholesterol level. However, they do so at a decreasing rate. For instance, a 10 percent cholesterol reduction in 35- to 39-year-old men with a pretreatment cholesterol level of 8 mmol/l increases the expected number of life years free of coronary heart disease by 2.01 years. An additional 10 percent reduction in serum cholesterol levels results in a further increase of 1.63 years of life free of coronary heart disease. Increasing the cholesterol reduction by another 10 percent will gain only 1.29 additional years. The fourth 10 percent increment in cholesterol reduction will add only 1.01 years of life free of coronary heart disease. These diminishing returns occur for both men and women and at all ages at initiation of therapy.

The gains in expected years of life free of coronary heart disease increase with increasing pretreatment cholesterol levels. For example, for a 30 percent cholesterol reduction among 35- to 39-year-old men, the gain in the number of years of life free of coronary heart disease for those with pretreatment cholesterol levels of 9 mmol/l is almost twice that for those with pretreatment cholesterol levels of 7 mmol/l (6.67 vs 3.48 years).

Among both men and women and for all pretreatment cholesterol levels, the gains in years of life free of coronary heart disease decrease as age at initiation of therapy increases. For instance, a 30 percent cholesterol reduction among 55- to 59-year-old men with pretreatment cholesterol levels of 8 mmol/l achieves just over one fourth of the number of years of life free of coronary heart disease that would be achieved by starting therapy in 35- to 39-year-old men at the same pretreatment cholesterol level (1.44 vs 4.93 years).

The estimated gains in years of life free of coronary heart disease for women are substantially lower than those among men, for all

pretreatment cholesterol levels and for therapy begun prior to 70 years. For example, a 30 percent cholesterol reduction among 35- to 39-year-old individuals with serum cholesterol levels of 8 mmol/l results in an increase the number of life years free of coronary heart disease of 1.94 years for women compared to 4.93 years for men. Therapy started between the ages of 65-69 years, however, yields similar gains in years of life free of coronary heart disease among men and women.

The increase in the expected number of years of life free of coronary heart disease is 1.5 to 2.4 times greater than the gain in life expectancy, depending on sex, pretreatment cholesterol level, and age at initiation of therapy. Among men the gain in the number of years of life free of coronary heart disease is relatively larger than among women. For instance, when a 30 percent cholesterol reduction is initiated among 35- to 39-year-old men with cholesterol levels of 8 mmol/l, the gain in years of life free of coronary heart disease is almost twice as high as the gain in life expectancy: 4.93 vs 2.50 years. Among women of similar age and cholesterol level, the gain in years of life free of coronary heart disease is 1.5 times as high as the gain in life expectancy: 1.94 vs 1.17 years.

5.5 Savings in coronary heart disease treatment costs

Estimates of the direct economic benefits (i.e., savings in lifetime coronary heart disease treatment costs) of 10-40 percent cholesterol reductions by pretreatment cholesterol level and age at initiation of therapy are presented in Table 5.3. All estimates reflect a 5 percent discount rate.

The direct economic benefits of therapy increase with increasing pretreatment serum cholesterol levels at all ages among both men and

Table 5.3 Discounted direct economic benefits, by cholesterol level and age at initiation of therapy for selected cholesterol reductions.

Cholesterol reduction (%)	*Age at initiation of therapy (Years)*	*Direct economic benefits for men/women (NLG) (discount rate: 5%)*		
		7 mmol/l	8 mmol/l	9 mmol/l
10	35 - 39	910 / 290	1344 / 373	1874 / 454
	40 - 44	917 / 324	1308 / 418	1762 / 516
	45 - 49	871 / 352	1198 / 453	1562 / 563
	50 - 54	756 / 358	1001 / 457	1269 / 567
	55 - 59	598 / 334	776 / 419	968 / 515
	60 - 64	402 / 278	509 / 350	625 / 431
	65 - 69	203 / 185	248 / 229	296 / 279
	70 - 74	87 / 105	103 / 131	120 / 160
20	35 - 39	1632 / 549	2401 / 707	3362 / 870
	40 - 44	1661 / 613	2365 / 790	3204 / 982
	45 - 49	1595 / 666	2192 / 856	2876 / 1067
	50 - 54	1401 / 679	1856 / 866	2361 / 1074
	55 - 59	1122 / 635	1455 / 796	1820 / 977
	60 - 64	764 / 531	965 / 667	1185 / 819
	65 - 69	391 / 354	476 / 438	568 / 532
	70 - 74	170 / 202	201 / 251	234 / 306
30	35 - 39	2200 / 777	3216 / 1000	4499 / 1239
	40 - 44	2258 / 869	3201 / 1117	4340 / 1391
	45 - 49	2191 / 945	3002 / 1211	3942 / 1510
	50 - 54	1947 / 966	2572 / 1227	3276 / 1522
	55 - 59	1578 / 906	2040 / 1132	2553 / 1387
	60 - 64	1087 / 760	1369 / 951	1679 / 1166
	65 - 69	564 / 508	686 / 627	817 / 759
	70 - 74	249 / 291	294 / 360	342 / 437
40	35 - 39	2643 / 977	3836 / 1255	5347 / 1556
	40 - 44	2734 / 1093	3853 / 1401	5211 / 1744
	45 - 49	2677 / 1191	3650 / 1521	4786 / 1894
	50 - 54	2405 / 1221	3164 / 1545	4024 / 1911
	55 - 59	1970 / 1148	2539 / 1430	3172 / 1747
	60 - 64	1374 / 967	1724 / 1205	2110 / 1473
	65 - 69	724 / 648	877 / 797	1042 / 962
	70 - 74	325 / 373	383 / 459	445 / 555

women. For instance, the benefits of a 30 percent cholesterol reduction among 35- to 39-year-old men with pretreatment cholesterol levels of 9 mmol/l are 4,499 NLG, compared to 2,200 NLG among men of the same age but with pretreatment cholesterol levels of 7 mmol/l.

For all pretreatment cholesterol levels and all ages at initiation of cholesterol lowering less than 70 years, the direct benefits of therapy are greater among men than among women. For instance, the benefits of a 30 percent cholesterol reduction among 35- to 39-year-old men with pretreatment cholesterol levels of 9 mmol/l are more than 3 times higher than those among women of similar age and pretreatment cholesterol level: 4,499 NLG compared to 1,239 NLG. When therapy is started at later ages, the difference decreases until finally, when therapy is started over the age of 70 years, the direct benefits in women exceed those in men of similar pretreatment cholesterol level.

When examined by age at initiation of therapy, the direct economic benefits seem to reach a maximum between the ages of 35-45 years among men and 50-54 years among women, and then decline steadily for both in later years. One would expect that the direct benefits decrease continuously with increasing age at initiation of cholesterol lowering, because earlier intervention implies that more cases of coronary heart disease can be averted. Table 5.4, which presents the direct economic benefits of a 30 percent cholesterol reduction at a discount rate of both 0 percent and 5 percent, shows that this is indeed the case at a 0 percent discount rate. When discounting future costs at a rate of 5 percent, the direct economic benefits show a maximum at an age of initiation of therapy that depends on sex and pretreatment cholesterol level.

Table 5.4 Direct economic benefits (present values of future savings in coronary heart disease treatment costs) of a 30 percent cholesterol reduction, by pretreatment serum cholesterol level and age at initiation of therapy.

	Age at initiation of therapy (Years)	*Direct economic benefits (NLG) 0% discount rate / 5% discount rate*		
		7 mmol/l	8 mmol/l	9 mmol/l
Men	35 - 39	6022 / 2200	8141 / 3216	10413 / 4499
	40 - 44	5353 / 2258	7145 / 3201	9054 / 4340
	45 - 49	4552 / 2191	5967 / 3002	7468 / 3942
	50 - 54	3613 / 1947	4630 / 2572	5708 / 3276
	55 - 59	2642 / 1578	3345 / 2040	4093 / 2553
	60 - 64	1666 / 1087	2069 / 1369	2500 / 1679
	65 - 69	817 / 564	983 / 686	1158 / 817
	70 - 74	337 / 249	396 / 294	456 / 342
Women	35 - 39	2923 / 777	3595 / 1000	4221 / 1239
	40 - 44	2719 / 869	3365 / 1117	4012 / 1391
	45 - 49	2489 / 945	3092 / 1211	3721 / 1510
	50 - 54	2177 / 966	2701 / 1227	3260 / 1522
	55 - 59	1779 / 906	2187 / 1132	2629 / 1387
	60 - 64	1324 / 760	1637 / 951	1980 / 1166
	65 - 69	809 / 508	992 / 627	1193 / 759
	70 - 74	416 / 291	514 / 360	622 / 437

5.6 Discussion

In this chapter, the effects of 10-40 percent cholesterol reductions on coronary heart disease risk, life expectancy, and coronary heart disease treatment costs have been reported. The results suggest that cholesterol lowering can lead to considerable improvements in some of these outcomes, especially if therapy is started at an early age.

Cholesterol lowering can reduce the risk of coronary heart disease substantially. For instance, a 30 percent cholesterol reduction, which can easily be achieved by a combination of diet and medication, will lower the 40-year risk of coronary heart disease in 35- to 39-year-old men with serum cholesterol levels of 8 mmol/l by more than 40 percent from 543 per 1,000 persons to 318 per 1,000. However, using reductions in coronary heart disease risk as an outcome measure makes it difficult to compare the effectiveness of cholesterol lowering with that of other health care interventions.

The gains in life expectancy that can be achieved by cholesterol lowering are also substantial. For instance, a 30 percent cholesterol reduction among 35- to 39-year-old individuals with serum cholesterol levels of 8 mmol/l increases life expectancy by 2.5 years among men and 1.2 years among women. A 10 percent cholesterol reduction, which can be obtained by adhering to a dietary regimen, increases life expectancy by one year among men and six months among women of similar age and cholesterol level. These results are comparable with those of other health care interventions. The average gain in life expectancy from intracoronary thrombolysis with streptokinase in acute myocardial infarction is 1.5 years.[1] Participation in a screening program for breast cancer improves life expectancy by one to two months.[2]

The gain in years of life free of coronary heart disease, an effect measure that may be more appealing to many individuals, not only exceeds the increase in life expectancy, but also takes place at a much younger age. However, the expected gain in years of life free of coronary heart disease is an outcome that provides only limited information since it only adjusts the quality of life for the presence or absence of coronary heart disease. It does not account for impairments in the quality of life before the onset of coronary heart disease due to

other diseases, and it implicitly assumes that coronary heart disease will impair the quality of life to such an extent that the value of life years with such disease is negligible. Furthermore, it is an outcome measure that does not allow a comparison of the effectiveness of cholesterol lowering with that of other health care interventions. For such a purpose, quality-adjusted life years or healthy year equivalents are much more suitable.

Finally, the savings in coronary heart disease treatment costs seem fairly modest. The findings in this chapter confirm the observation by Oster and Epstein that cholesterol-lowering interventions, regardless of their costs, are unlikely to result in important savings to the health care system.[3] In the absence of such savings, the relevant question is whether the net cost of cholesterol-lowering therapy is justified by the gains in health that result from such therapy. The next chapter will compare the cost effectiveness of cholesterol-lowering therapy with simvastatin with that of cholestyramine and other generally accepted health care interventions.

References

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6 THE COST-EFFECTIVENESS OF CHOLESTEROL-LOWERING THERAPY WITH SIMVASTATIN

6.1 Introduction

In this chapter, the cost per year of life saved of cholesterol-lowering therapy with simvastatin is compared to cholestyramine. These costs are then examined against other generally accepted health care interventions in the Netherlands. Cost-effectiveness ratios will be presented for those patients who would be eligible for therapy according to the guidelines of the Dutch Cholesterol Consensus Conference.

6.2 Cost-effectiveness model

The cost-effectiveness of cholesterol-lowering therapy was calculated as the ratio of the net treatment costs (i.e., cost of therapy minus any savings in the cost of treating symptomatic coronary heart disease) to the net change in life expectancy due to therapy. The net change in life expectancy for a cohort of any given age and sex was calculated as the discounted sum of the changes in the proportion of persons remaining alive in each future year due to therapy. The net change in medical care costs was calculated similarly, as the discounted sum of the changes in annual medical care costs in each future year of life. Since the coronary heart disease model does not assign benefits to cholesterol-lowering therapy after the age of 79 years or after the onset of clinically symptomatic coronary heart disease, the lifetime cost of cholesterol-lowering therapy was calculated as the discounted sum of the annual

therapy costs in all future life-years free of coronary heart disease before the age of 80 years.

Costs and changes in life expectancies were discounted at a 5 percent annual rate. All costs were adjusted to reflect 1988 price levels.

6.3 Costs and effectiveness of cholesterol-lowering therapy

The guidelines of the Dutch Cholesterol Consensus Conference recommend that dietary counseling should be given to persons with serum cholesterol levels higher than 6.5 mmol/l and that cholesterol-lowering medication should be prescribed if, despite several months of dietary therapy, serum cholesterol remains above 8 mmol/l or, in the presence of additional coronary risk factors, above 6.5 mmol/l.[1] The cost-effectiveness of cholesterol-lowering medication is reported as the incremental cost-effectiveness of adding such medication to a diet.

The cost of cholesterol-lowering therapy was estimated using the assumptions about the management of hypercholesterolemia with diet and drugs in the report of the Committee on Cholesterol of the Health Council of the Netherlands.[2] It was assumed that although dietary counseling will be provided by a registered dietician, patients will visit their physicians twice per year. In order to monitor the effectiveness of therapy, physicians will order cholesterol testing twice in the first year of therapy and once per year thereafter.

The number of physician visits and laboratory tests differs between cholestyramine- and simvastatin-treated patients because of the need to monitor the liver function of those treated with simvastatin. Patients were assumed to visit their physicians four times per year to get a new prescription regardless of the drug prescribed. Evaluation of serum cholesterol levels, which, according to the guidelines of the Dutch

Cholesterol Conference, consists of 3 laboratory tests, will take place twice in the first year of therapy and once per year thereafter. According to the estimates of the Committee on Cholesterol of the Health Council of the Netherlands, liver function will be tested every six weeks in the first year of simvastatin therapy and twice per year thereafter.

It was assumed that cholestyramine-treated patients would receive three 4-gram packets per day, which, according to IMS data (diagnostic index), was the average prescribed dose of cholestyramine in the Netherlands in 1988. The annual drug cost of this regimen is 1547.40 NLG. Including physician visits and laboratory testing, the annual cost of adding cholestyramine dietary counseling is estimated to be 1,722.20 NLG in the first year of therapy and 1,577.60 NLG in later years.

For patients with on-diet serum cholesterol levels between 6.5 and 8.0 mmol/l, drug therapy with simvastatin was assumed to consist of one 10-mg tablet daily. For patients whose on-diet serum cholesterol levels exceeded 8 mmol/l, the daily dose was assumed to be increased to one 20-mg tablet. The annual drug cost of these regimens is 899.98 NLG and 1,241.49 NLG respectively. Including drug costs, physician visits, and laboratory testing, the annual cost of adding 10 mg simvastatin per day to diet counseling is 1,387.58 NLG in the first year of therapy and 978.18 NLG in later years of therapy. Adding 20 mg simvastatin daily to a diet costs 1,729.09 NLG in the first year of therapy and 1,319.69 NLG per year thereafter.

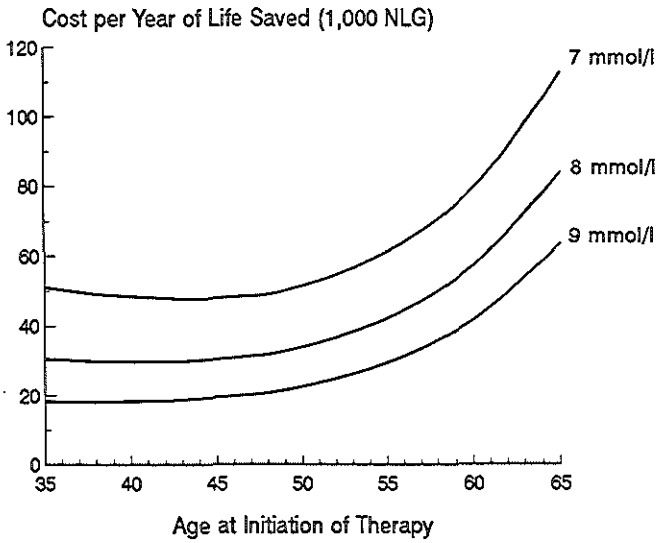
The reduction in serum cholesterol levels due to cholestyramine therapy was estimated using the dose-response relationship between total serum cholesterol and the daily intake of cholestyramine reported in the Lipids Research Clinics study.[3,4] Three 4-gram packets of cholestyramine daily are assumed to lower serum cholesterol by 6.2 percent, calculating this change as a reduction from on-diet baseline cholesterol

levels. Based on the multicenter studies cited in the Marketing Authorization Application for Zocor, it was estimated that patients receiving one 10-mg tablet of simvastatin daily will experience a 21 percent reduction in total serum cholesterol,[5] and patients receiving one 20-mg tablet of simvastatin daily will experience a 27 percent reduction.

6.4 Cost per year of life saved with cholesterol-lowering therapy

Figures 6.1 and 6.2 present cost-effectiveness ratios for simvastatin therapy among Dutch men and women respectively by pretreatment cholesterol level and age at initiation of therapy. Shown are the costs per year of life saved due to therapy with simvastatin 20 mg per day.

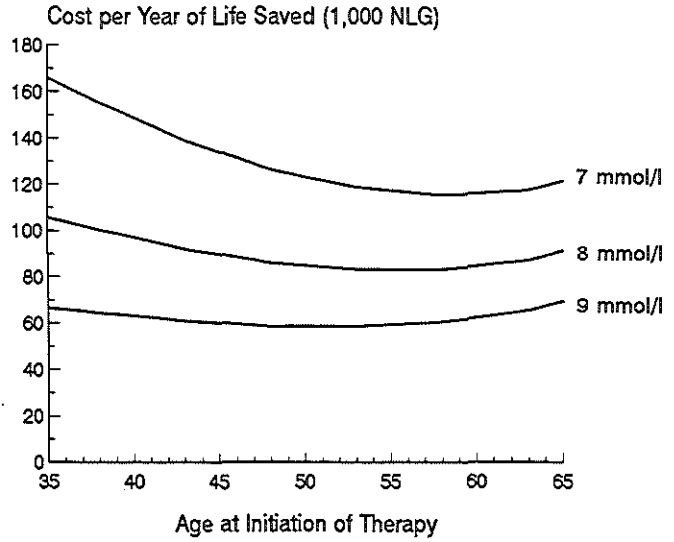
Figure 6.1 The cost per year of life saved by cholesterol-lowering therapy with simvastatin (20 mg/day) in Dutch men.



Among men, costs per year of life saved are fairly constant when therapy is initiated between the ages of 35 and 50 years, but rapidly increase thereafter. For instance, costs per year of life saved among men with pretreatment cholesterol levels of 8 mmol/l are 30,000 NLG when therapy is started at ages 40-44 years, versus 66,000 NLG when therapy is started at ages 60-64 years. Among women, the cost per year of life saved does not vary substantially when therapy is started between the ages of 35 and 65 years. For women with an initial cholesterol level of 8 mmol/l, the cost per year of life saved ranges from 85,000 NLG to 105,000 NLG.

Among both men and women, costs per year of life saved rapidly increase with decreasing pretreatment cholesterol level. For instance,

Figure 6.1 The cost per year of life saved by cholesterol-lowering therapy with simvastatin (20 mg/day) in Dutch women.



when therapy with simvastatin is initiated among 35- to 39-year-old men, costs per year of life saved are 50,000 NLG and 18,000 NLG for men with cholesterol levels of 7 and 9 mmol/l respectively.

The cost per year of life saved among women is greater than among men, although the difference decreases when therapy is initiated at later ages. When therapy is started among 40- to 44-year-old women with serum cholesterol levels of 8 mmol/l, costs per year of life saved are more than three times greater than those among men of similar age and serum cholesterol: 105,000 NLG versus 30,000 NLG. However, when therapy is started among 60- to 64-year-old women, the cost per year of life saved is only 30 percent higher than for men of similar age: 86,000 NLG versus 66,000 NLG.

Table 6.1 shows the costs per year of life saved due to cholestyramine therapy by pretreatment cholesterol level and age at

Table 6.1 Cost per year of life saved by cholesterol-lowering therapy with cholestyramine (12 grams/day), by pretreatment cholesterol level and age at initiation of therapy.

Age at initiation of therapy	*Cost per year of life saved for men/women (1,000 NLG)*		
(years)	7 mmol/l	8 mmol/l	9 mmol/l
35-39	208 / 678	126 / 420	78 / 258
40-44	206 / 621	129 / 400	83 / 257
45-49	216 / 565	141 / 376	94 / 251
50-54	250 / 535	172 / 370	121 / 258
55-59	309 / 525	220 / 380	159 / 278
60-64	424 / 532	313 / 392	234 / 294

initiation of therapy. For both men and women, at all cholesterol levels and ages at initiation of therapy, costs per year of life saved with cholestyramine are more than 4 times greater than those with simvastatin. For instance, when therapy is started among 35- to 39-year-old men with cholesterol levels of 8 mmol/l, costs per year of life saved with simvastatin are 30,000 NLG versus 126,000 NLG with cholestyramine.

In addition to hypercholesterolemia, a number of other coronary risk factors have been identified, notably hypertension, diabetes mellitus, and smoking.[6] Data from the Framingham Heart Study suggest that the combined presence of such risk factors greatly increases the risk for coronary heart disease. As a result, cholesterol consensus conferences advise physicians to treat hypercholesterolemia more aggressively when additional coronary risk factors are present. Since our model is based on multivariate logistic risk functions from the Framingham Heart Study, pre- and post treatment coronary risk is calculated as a function of the presence of these other risk factors. It is therefore possible to assess the cost-effectiveness of therapy for patients with varying risk profiles.

Table 6.2 examines the cost-effectiveness of simvastatin therapy among persons with different combinations of coronary risk factors in addition to elevated serum cholesterol levels. Shown are costs per year of life saved when therapy is initiated among 40- to 44-year-old men and 50- to 54-year-old women. These age groups have been chosen for purposes of illustration since they represent the ages at which cholesterol-lowering therapy is most cost-effective. It was assumed that the diastolic blood pressure of persons with hypertension is controlled at 95 mm Hg.

Among men, the presence of diabetes or hypertension decreases the cost per year of life saved by 19-23 percent depending on pretreatment cholesterol level. When both hypertension and diabetes mellitus are present, costs per year of life saved decrease by approximately 35

percent. Among women, the presence of hypertension causes a modest decrease in the costs per year of life saved. When therapy is targeted at women with diabetes mellitus, however, the cost-effectiveness of therapy increases considerably: costs per year of life saved among women with diabetes are more than 60 percent lower than among women without this disorder. As with men, treating women with a combination of risk factors has the lowest cost per year of life saved.

Table 6.2 Cost per year of life saved due to simvastatin therapy, by different combinations of risk factors and pretreatment cholesterol level for men aged 40-44 years and women aged 50-54 years.

	Cost per year of life saved by cholesterol level (1,000 NLG)						
	10 mg/day				*20 mg/day*		
	6.5	7.0	7.5	8.0	8.0	8.5	9.0
Men aged 40-44 years							
Average risk	54	42	33	26	30	24	19
Hypertension	44	34	27	21	24	19	15
Diabetes mellitus	42	33	26	20	23	19	15
Diabetes and hypertension	35	27	21	17	19	15	12
Women aged 50-54 years							
Average risk	131	109	91	76	85	71	60
Hypertension	118	99	82	69	76	64	54
Diabetes mellitus	48	41	34	29	32	28	24
Diabetes and hypertension	45	38	32	27	30	26	22

6.5 Discussion

Using a model of the incidence and prevalence of coronary heart disease in The Netherlands based on logistic risk functions from the Framingham study, the cost-effectiveness of cholesterol-lowering therapy with simvastatin and cholestyramine was estimated. Since cholestyramine is more costly and less effective than simvastatin, the cost per year of life saved by cholestyramine is substantially higher than that of simvastatin. Both agents would be equally cost effective in the hypothetical situation that 12 grams of cholestyramine per day lower serum cholesterol levels by 36 percent. Although cholestyramine is not well tolerated by many patients, its long-term safety has been established by the Lipid Research Clinics Coronary Primary Prevention Trial.[3,4]

The cost per year of life saved among men rapidly increases when therapy is initiated at later ages. The identification of hypercholesterolemia and the subsequent initiation of treatment should, therefore, be accomplished at an early age. For women, the cost per year of life saved does not vary substantially when therapy is started between the ages of 35 and 60 years. However, the results presented in chapter 5 indicate that if therapy is initiated at an early age, the gains in life expectancy are considerably higher than if therapy is started at later ages.

The inverse relationship between the cost per year of life saved and the pretreatment serum cholesterol level provides an economic rationale for the Consensus Conference's guideline to limit drug treatment to persons with very high cholesterol levels. From a clinical point of view, it is rational to lower cholesterol levels in the entire population since the relationship between serum cholesterol and coronary heart disease mortality is continuous and graded.[7]

According to the guidelines of the Dutch Cholesterol Consensus Conference, drug treatment should be initiated when serum cholesterol levels remain higher than 8 mmol/l after several months of diet. When cholesterol-lowering therapy with cholestyramine is initiated among 40- to 44-year-old persons with serum cholesterol levels of 8 mmol/l, the costs per year of life saved are 129,000 NLG among men and 400,000 NLG among women. These costs are substantially higher than those of other health care programs in The Netherlands, such as screening for breast cancer, screening for cervical cancer, heart transplantation, and the end stage renal disease program, which have costs per year of life gained which approximately 10,000 NLG, 24,000 NLG, 52,000 NLG, and 54,000 NLG.[8-11] When therapy is started among men aged 40-44 years with cholesterol levels of at least 8 mmol/l, simvastatin results in gains life years at a cost of 30,000 NLG and less, which compares favorably with the above-mentioned health care interventions. Among women of similar age and cholesterol level, however, the cost of simvastatin compares unfavorably with that of other health care programs in the Netherlands. For instance, when therapy is initiated among 50- to 54-year-old women with serum cholesterol levels of 8 and 9 mmol/l, the cost per year of life saved by simvastatin therapy ranges from 85,000 NLG to 60,000 NLG respectively.

It is important to note that although the cost-effectiveness of other accepted health care programs can serve as an indicator of willingness to pay, it would be a mistake simply to use the highest cost per year of life saved as a cut-off level that would be acceptable for cholesterol-lowering therapy. The relevant question is whether society's willingness to pay for gains in life expectancy for a particular condition is higher than the cost per year of life saved of treating that condition. For example, heart transplantation and the end stage renal disease program involve small

groups of patients whose health and quality of life is seriously impaired. Cholesterol-lowering therapy on the other hand will be initiated in large groups of mostly healthy persons who do not experience any ill effects of their hypercholesterolemia. Perhaps society's willingness-to-pay for medical care in the latter case is lower. The cost-effectiveness of programs targeted at prevention, such as screening for breast cancer and screening for cervical cancer, may serve as a better benchmark for assessing willingness to pay for cholesterol-lowering therapy.

According to the guidelines of the Dutch Cholesterol Consensus Conference, drug therapy should be considered for persons with post-diet cholesterol levels between 6.5 and 8 mmol/l when additional coronary risk factors are present. The coronary risk factors mentioned in the guidelines are pre-existing coronary heart disease, a family history of coronary heart disease before the age of 60 years, one or more symptoms of hereditary hypercholesterolemia, diabetes mellitus, and hypertension.

When therapy is initiated among 40- to 44-year-old men with either hypertension or diabetes mellitus and a serum cholesterol level between 6.5 and 8 mmol/l, the cost per year of life saved by simvastatin therapy ranges from 20,000 NLG to 44,000 NLG. When hypertension and diabetes mellitus are both present, costs per year of life saved range from 17,000 NLG to 35,000 NLG depending on cholesterol level.

When therapy is initiated among 50- to 54-year-old women with serum cholesterol levels between 6.5 and 8 mmol/l and hypertension, the cost per year of life saved by simvastatin therapy ranges from 118,000 NLG to 69,000 NLG. These cost-effectiveness ratios compare unfavorably with those of other health care programs in the Netherlands. When therapy is started among women of similar age and cholesterol level, but with diabetes mellitus, costs per year of life saved range from

29,000 NLG to 48,000 NLG, depending on cholesterol level and the presence of hypertension.

The results of this cost-effectiveness analysis have a number of important implications for the treatment of elevated serum cholesterol levels in the Netherlands. The costs per year of life saved by cholesterol-lowering therapy with cholestyramine compare unfavorably with those of generally accepted health care programs in the Netherlands. Costs per year of life saved by simvastatin among men with cholesterol levels in excess of 8 mmol/l appear to be acceptable when therapy is started at a younger age. At cholesterol levels between 6.5 mmol/l and 8 mmol/l, however, therapy would have to be limited to men with at least one risk factor such as diabetes mellitus or hypertension; a further restriction to men with both hypertension and diabetes would lead to a further improvement in cost-effectiveness. Among women, the age at initiation of therapy does not affect the cost-effectiveness of therapy greatly, but the gain in life expectancy increases when therapy is started at an earlier age. When therapy is limited to women with diabetes mellitus or severely elevated serum cholesterol levels, the cost-effectiveness of cholesterol-lowering therapy among women compares well with that of currently accepted health care programs.

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7 SENSITIVITY ANALYSIS

7.1 Introduction

Sensitivity analysis has been described as an analytic process that examines the effect of changes in the values of key variables on the results of an analysis.[1] Such an analysis is necessary because every evaluation will contain some degree of uncertainty, imprecision, or methodologic controversy. Since the results of economic evaluations, especially in the case of analyses that require extensive modeling, are rarely reported with confidence intervals or other statistical measures of uncertainty, sensitivity analysis is the only test of the robustness of the conclusions. In addition, sensitivity analysis reveals how controlled changes in key variables can affect the cost-effectiveness of therapy.

Recently, efforts have been undertaken to develop cost-effectiveness models in which the model parameters, if possible, have been defined as a distribution, typically a normal distribution characterized by a mean value and a standard deviation.[2] Such models do not result in a point estimate of the net treatment costs or costs per life year gained, but, through Monte Carlo simulation, present such results as a distribution. Although such models provide insight into the uncertainty surrounding their results, they do not eliminate the need for sensitivity analysis. Most economic evaluations use data from a variety of sources, which raises the issue that model parameters have often been obtained from specific populations in epidemiological and clinical studies and may not be generalizable to the potential patient population. The uncertainty in the different parameter estimates is accounted for in the distribution that results from the Monte Carlo simulation, but the effect of biased point

estimates on the results of the analysis can only be evaluated by assessing the impact of changes in individual model parameters on the results of the analysis.

The first step in a sensitivity analysis is the identification of model parameters and assumptions that, for a number of reasons, would benefit from further scrutiny. These assumptions may be subject to debate first because no estimates were available and informed guesses had to be made. Second, there may be a known imprecision in the estimates. Third, the methodology may be controversial. Finally there may be a potential for opposing value judgements.[3] The next step is to set upper and lower bounds for the possible range of estimates of each variable and to present results for the lower bound, base case, and upper bound.[4] Setting the upper and lower bounds might be done using empirical evidence from the literature or expert opinion. It may be difficult, however, to indicate the uncertainty in point estimates in certain parameters. In that case, analysts sometimes choose to assess the effect of a given percentage change in the model parameters, which enables them to identify those parameters for whom the results of the analysis are most sensitive.[5] If an economic evaluation results in the conclusion that one therapy is more cost-effective than another, analysts often perform a threshold analysis, in which they compute the required change in one or more model parameters to reverse that conclusion.[6]

This chapter will explore the effect of changes in a number of model assumptions on the cost per year of life saved by cholesterol-lowering therapy with simvastatin. The sensitivity of the cost per year of life saved will be reported for therapy started among 40- to 44-year-old men with pretreatment cholesterol levels of 8 mmol/l and otherwise average risk factors.

The analytic assumptions under consideration in this sensitivity analysis have been divided into two categories: assumptions that are part of the coronary heart disease model and assumptions about the cholesterol-lowering therapy, that is, drug therapy with simvastatin. For some assumptions, it will be possible to indicate lower and/or upper bounds; for other assumptions, the effect of arbitrary changes will have to be assessed.

In order to compare the sensitivity of the model results to changes in different assumptions, the concept of "relative sensitivity" will be introduced. The relative sensitivity is defined as the ratio of the percentage change in the cost per year of life saved and the percentage change in the variable under consideration.

7.2 Coronary heart disease model assumptions

Costs of treating coronary heart disease

The costs of treating coronary heart disease were estimated using typical patterns of care that were developed by a panel of cardiologists. In order to obtain treatment costs, the frequency of procedures was multiplied by an estimate of the price of that procedure (see Appendix 2). A simultaneous change in all the prices that were used was made in an attempt to capture both the uncertainty in the estimated rates of procedures, as well as uncertainty in the prices that were used. A 25 percent decrease in the cost of treating coronary heart disease results in a 4.5 percent increase in the cost per year of life saved from 29,800 NLG to 31,100 NLG (relative sensitivity: -0.18).

The cost-effectiveness model assumes that the costs of treating symptomatic coronary heart disease are the same for men and women. Ayanian and Epstein recently described that, at least in the United States,

there is evidence that women who are hospitalized for coronary heart disease undergo fewer major diagnostic and therapeutic procedures than men do.[7] Although there is no evidence that such differences exist in the Netherlands, it is possible that the average treatment patterns that were developed by the panel of cardiologists overestimate utilization in women and underestimate utilization in men. This would imply that the reported cost-effectiveness ratios for women underestimate the actual cost per year of life saved and that the cost-effectiveness ratios for men overestimate the actual cost per year of life saved. However, given the low sensitivity of the cost-effectiveness ratios for changes in the cost of treating coronary heart disease, it is unlikely that adjustment for such differences would result in major changes in the cost-effectiveness of cholesterol-lowering therapy.

Fraction of unrecognized myocardial infarctions

Although the fraction of unrecognized myocardial infarctions in the Framingham Study was approximately 28 percent, the model assumes that this percentage will be considerably lower in contemporary clinical settings: 15 percent. Increasing this fraction to 20 percent will increase the cost per year of life saved by 2.4 percent from 29,800 NLG to 30,500 NLG (relative sensitivity: 0.07). The low sensitivity of the cost-effectiveness of cholesterol lowering for this assumption is due to the fact that the model, in accordance with the observations in the Framingham Study, assumes equal long-term mortality rates after unrecognized and after recognized myocardial infarction. Classifying an additional proportion of myocardial infarctions as unrecognized rather than recognized will not considerably change life expectancy and gains in life expectancy in the model; most of all, it will lower the present value of

future treatment costs as well as the expected savings in these treatment costs due to therapy.

Fraction of patients who die before hospital admission

The model assumes that 28 percent of the patients who experience coronary heart disease death or recognized myocardial infarction will die before they are admitted to a hospital. Decreasing the fraction of patients with severe coronary events who die before hospitalization to 25 percent increases the cost per year of life saved by 2.7 percent from 29,800 NLG to 30,600 NLG (relative sensitivity: -0.11).

Mortality rate after the first year after myocardial infarction

The mortality rate after the first year after myocardial infarction for men is assumed to be 4.25 percent per year, based on the Minnesota Heart Study. Decreasing this mortality rate to 3.75 percent per year increases the cost per year of life saved by 3.9 percent from 29,800 NLG to 301,00 NLG for a relative sensitivity of -0.33. Similarly, an increase in this mortality rate to 4.75 percent decreases the cost per year of life gained by 3.5 percent from 29,800 NLG to 28,800 NLG (relative sensitivity: -0.30). The model results appear to be fairly sensitive to changes in this model parameter, which is explained by the fact that the mortality in all coronary heart disease states is modeled using the long-term mortality after myocardial infarction.

Fraction of benefits

The cost-effectiveness model does not estimate the benefits of cholesterol-lowering therapy using the results of clinical trials of cholesterol lowering, but uses the results of an epidemiologic study. It is assumed that there is no change in coronary heart disease risk during

the first two years after the cholesterol-lowering intervention is started. After this initial two-year period, the coronary heart disease risk is assumed to equal the risk that has been observed among persons with the naturally occurring lower cholesterol level. The assumption that the risk reduction due to cholesterol lowering equals 100 percent of the difference in coronary heart disease risk observed between persons with the naturally occurring higher and lower cholesterol levels does not seem to overestimate the benefits of cholesterol lowering, as our simulation of the Lipid Research Clinics Coronary Primary Prevention Trial--described in the discussion section of Chapter 4--suggests. Decreasing the fraction of benefits to 90 percent increases the cost per year of life saved by 12.8 percent from 29,800 NLG to 33,600 NLG for a relative sensitivity of -1.28.

Medical costs in added years of life

A consequence of health care interventions that result in gains in life expectancy is additional medical care costs that will be incurred in the years added to life. Although these costs are a real effect of these interventions, they are often excluded from cost-effectiveness analyses. In this dissertation, society's willingnesss to allocate health care resources to cholesterol-lowering medication is assessed by comparing the costs per year of life gained of such medication with the results of other cost-effectiveness studies. Since this comparison is more valid when the studies being compared use the same methodology, we chose not to account for medical costs in added years of life in our baseline estimates, but evaluated the sensitivity of the costs per year of life saved for such medical costs. The sensitivity analysis is based on two estmates of the medical costs in added years of life, which were developed by Roos.[8] First, when we added age- and sex-specific estimates of the

average annual cost of medical care, the cost per year of life saved increased by 17.2 percent to 34,900 NLG. However, the increase with age of the average annual expenditures on medical care not only reflects increased morbidity with age, but is due also to the combination of the increase of mortality rate with age and the fact that a large part of lifetime medical costs is incurred during the last year of life. Increasing life expectancy is of value in itself, but it also has the added economic benefit that it postpones the high cost of caring for the terminally ill. Using average annual costs of medical care is therefore likely to overestimate the effect of medical care costs during added years of life on the cost per year of life saved. Second, we therefore added age- and sex-specific estimates of the annual cost of care stratified by whether a person survives or dies during the year. Adding thses costs increased the cost per year of life gained by only 6.5 percent to 31,700 NLG compared to the base case analysis.

Discount rate

Adjusting costs and changes in both clinical and economic outcomes for differential timing is essential in economic evaluation.[9] In the case of screening pregnant women for hepatitis b and subsequently immunizing the newborns of women who tested positive, it has been shown that failure to discount future benefits leads to the incorrect conclusion that such a program is cost saving.[10] Although health economists generally apply a 5 percent discount rate, this rate may differ between studies for instance based on government recommendations in specific countries. The discount rates used in recent studies from Japan and Norway, for example, are 3 percent and 7 percent respectively.[11,12] In the Netherlands, the government has recently decided to accept the recommendations of the Klaassen Report to apply a uniform discount rate

of 5 percent for potential public projects.[13] Because economic assessments of medical technology adopt the same societal viewpoint, recent Dutch cost-effectiveness studies in health care have used this discount rate.[14-16] Presenting the effects of varying discount rates on the cost-effectiveness ratios is considered to be useful despite existing government recommendations, because any discount rate reflects a value judgment and the relative cost-effectiveness of interventions is heavily influenced by the discount rate.[2] Although the limited space available in journals sometimes prohibits the reporting of the results of a sensitivity analysis altogether, it is common to report results for a base case discount rate of 5 percent and alternative rates of 3 and 7 percent.[17,18]

The cost-effectiveness of cholesterol-lowering therapy with simvastatin is rather sensitive to changes in the discount rate. Increasing the discount rate to 7 percent increases the cost per year of life saved by 26 percent from NLG 29,800 to NLG 37,400 (relative sensitivity: 0.64). Similarly, a decrease in the discount rate to 3 percent decreases the cost per year of life saved by 21 percent from NLG 29,800 to NLG 23,500 (relative sensitivity: 0.53). The sensitivity of the cost-effectiveness ratios for changes in the discount rate does not vary much across different pre-treatment cholesterol levels, but shows a considerable decrease with increasing age at initiation of therapy. Among men with pre-treatment cholesterol levels of 8 mmol/l, increasing the discount rate from 5 percent to 7 percent increases the cost per year of life gained by 30 percent when therapy is started among 35- to 39-year-old men, and by 14 percent when therapy is started among 60- to 64-year-old men. This finding reflects first the fact that the incidence of coronary heart disease sharply increases with age, which implies that the benefits of cholesterol-lowering therapy are further in the future when therapy is started at a young age than when therapy is started at a later age. Furthermore,

when cholesterol-lowering therapy is initiated at a young age, it will save lives on the average at a younger age than when therapy is initiated at a later age. In the first case, the life years gained will be timed much further ahead due to a lower competing mortality.

7.3 Therapy assumptions

In the base-case analysis, certain assumptions have been made about the cost and cholesterol-lowering effect of therapy. The model also contains a number of implicit assumptions with respect to patient compliance and the side-effects and safety of therapy. The sensitivity of the cost-effectiveness ratios to these assumptions will be analyzed in this section.

Cost of therapy

In the Netherlands, drug prices are not regulated, but wholesale margins and dispensing fees are. As a result, there are uniform retail drug prices throughout the Netherlands. The retail price of cholesterol-lowering medication thus is an example of how sensitivity analysis can be used to indicate the effect of controlled changes in key variables on the cost-effectiveness of therapy.

A 10 percent decrease in the retail price of the medication lowers the cost per year of life saved by almost 11 percent from 29,800 NLG to 26,600 NLG (relative sensitivity: 1.09). Since the total cost of therapy is largely--but not completely--determined by the cost of the medication, this 10 percent change in the retail drug price corresponds with a 9.4 percent change in the total cost of therapy. The relative sensitivity of the cost-effectiveness ratios for changes in the total cost of therapy is therefore even slightly higher: 1.16.

Cholesterol-lowering effect of therapy

The assumed reductions in serum cholesterol levels due to simvastatin therapy are taken from phase III clinical trials. Apart from the fact that these data have an inherent uncertainty, they may also be biased since they reflect the efficacy of therapy under controlled conditions rather than the effectiveness in routine medical practice, which is the outcome measure that should be used in the economic evaluation of cholesterol lowering.

Cochrane made the distinction between efficacy–"the effect of a particular medical action in altering the natural history of a particular disease for the better under ideal conditions of use"–and effectiveness, defined as "the effect of a particular medical action in altering the natural history of a particular disease for the better in routine clinical practice".[19] There are a number of reasons why results from clinical trials, especially phase II and III trials of medications, reflect the efficacy rather than the effectiveness of a particular medical action.

First, the diagnosis and treatment in clinical trials generally takes place according to a strict protocol that outlines all actions by the physician and the time at which they ought to be performed. Clinical trials are designed to demonstrate the effect of a particular drug, and whose organization is geared towards maximizing the effect that is to be demonstrated. In routine medical practice, the management of a patient is less strictly organized and often deviates from the ideal treatment plan for the comfort and/or convenience of patients and/or physicians.

Furthermore, there is a selection bias with respect to both the centers and physicians participating in clinical trials. Clinical trials are often conducted in so-called centers of excellence and even when trials are conducted outside such centers, it is unlikely that the physicians who

are willing to participate in clinical trials are representative of all physicians.

In addition, patients participating in clinical trials may not be representative of the potential users of a medication. Clinical trial protocols often include patients with only mild or moderately severe disease and generally exclude patients with certain co-morbidities. It is conceivable that the effect of a particular medication in the patient population not participating in the trial is lower given their poorer health at baseline. In routine medical practice, where all patients are treated, the effectiveness across all categories of patients would therefore be lower than the efficacy data from the clinical trial suggest.

Finally, patient compliance with the prescribed regimen may differ between clinical trials and routine medical practice. Although there are no data that demonstrate such an effect, one would expect that the compliance in clinical trials is higher than in routine medical practice. In the case of drug therapy, the increased compliance in the clinical trial would result in not only a higher effect of the medication, but also in a higher incidence of adverse effects since these are generally dose related.

It has been suggested that, due to diet-drug interaction, HMG-CoA reductase inhibitors might be more effective when patients adhere to a strict diet. Since patients who participate in trials are often under strict metabolic control, the efficacy data from clinical trials may over-estimate the cholesterol-lowering effect of these drugs in routine medical practice where cholesterol-lowering drugs are often introduced without an adequate trial of dietary intervention. A recent study demonstrated, however, that lovastatin produces a comparable improvement in lipoprotein profiles in persons on high- and low-fat diets, suggesting only a minor contribution, if any, of diet-drug interaction in lovastatin responsiveness.[20]

It seems, however, unlikely that the use of the phase III clinical trial data will lead to biased estimates of the cholesterol-lowering effect of simvastatin for reasons other than differences in drug compliance between clinical trials and routine medical practice.

Based on the Phase III studies cited in the Marketing Authorization Application for Zocor, the base case analysis assumes that simvastatin 20 mg/day lowers serum cholesterol levels by 27 percent.[21] In the literature, higher reductions, up to over 30 percent, have been reported.[22,23] Assuming that simvastatin 20 mg/day lowers serum cholesterol levels by 30 percent (an 11 percent increase) lowers the cost per year of life saved by 7.6 percent from 29,800 NLG to 27,600 NLG (relative sensitivity: -0.68). Alternatively, the assumption that simvastatin 20 mg/day lowers serum cholesterol levels by 24 percent increases the cost per year of life saved by 9.7 percent from 29,800 NLG to 32,700 NLG (relative sensitivity: 0.86). The difference in sensitivity for a 3 percentage-points increase and a 3 percentage-points decrease from the base case assumption reflects the curvilinear relationship between serum cholesterol levels and the incidence of coronary heart disease.

Compliance

The expectation exists that a patient who accepts a prescription from a physician not only will fill the prescription but will also take the medication as indicated.[24] Taking medication as indicated does not refer only to the number of doses and the amount of tablets per dose, but also to the timing of doses. For instance, evening administration of HMG-CoA reductase inhibitors is believed to optimize drug efficacy since HMG-CoA reductase, the rate-limiting enzyme in cholesterol biosynthesis, has its maximum activity during the night.[25] Additional

ways of noncompliance are that patients prematurely discontinue their medication (which is especially relevant in the case of antibiotics and drugs that need to be taken continuously such as immunosuppressants, antihypertensives, and lipid-lowering drugs) and that patients do not adhere to other aspects of the therapy such as maintaining a diet or exercise program.[26] Noncompliance has even been observed in organ transplant recipients where the intake of immunosuppressants is essential for graft survival.[27]

Noncompliance may be prevalent in the treatment of elevated serum cholesterol levels because drug treatment has neither an immediate nor a recognizable effect on patients' perception of health. Krall cites two unpublished studies in which patients were treated with the same medicine but for different indications: hypertension and angina pectoris.[28] Patients with hypertension had a much higher rate of noncompliance than those with angina, which supports the hypothesis that drug-taking behavior is affected by patients' ability to discern the benefits of treatment.

The worst consequence of failing to comply with medication regimens is generally considered to be the loss of the intended effect.[28] In addition, noncompliance can waste resources, for instance when patients discard unused medication. In order to assess the effect of noncompliance on the cost-effectiveness of therapy, the simultaneous effect of noncompliance on both the cost and the effectiveness of therapy has to be taken into account.

It is generally assumed that compliance is higher in clinical trials than in routine medical practice. There are, however, few data available for a quantitative assessment of the relationship between noncompliance and therapeutic effectiveness. If, for instance, a patient is supposed to take one 20-mg tablet of simvastatin per day and actually adheres to that

regimen, then clinical trials provide a good estimate of the effect on lipid levels. If, on the other hand, this patient would take the prescribed medication only five out of every seven days, then there are no clinical data available that provide estimates of the cholesterol-lowering effect at that level of noncompliance. Similarly, there is a lack of data on the effect of noncompliance on resource utilization. The patient who takes medication only five out of seven days can either discard unused medication or postpone obtaining a new prescription until all medication from the previous prescription is almost completely used.

In the following, the effect of noncompliance on the cost-effectiveness of cholesterol-lowering therapy will be described using the example of lovastatin. Contrary to simvastatin, which is taken once daily, lovastatin needs to be taken twice daily. For purposes of illustration, the results from clinical trials evaluating the effectiveness of 20-mg lovastatin per day will be used to simulate a 50 percent compliance with a prescribed dosage of two 20-mg tablets of lovastatin per day. Lovastatin 40 mg per a day lowers total serum cholesterol levels by 28 percent; 20 mg lovastatin per day lowers total cholesterol by 21 percent.[29] Since lovastatin is not marketed in the Netherlands, a hypothetical price of 1 NLG per 20-mg tablet will be assumed. The assumptions about the maintenance costs of therapy will also be simplified: patients on lovastatin therapy are assumed to see their physician four times per year and the total cost of a physician visit, including lab tests, is 35 NLG.

In order to evaluate the effect of noncompliance on resource utilization, certain assumptions have to be made about the way in which patients handle surplus medication. In chronic drug therapy, such as cholesterol-lowering and antihypertensive therapy, patients typically visit their physician at regular intervals in order to obtain a new prescription

and to monitor therapy and possible side effects. Some countries have legislation that limits the period of time for which physicians can write a prescription for chronic drug therapy. In the Netherlands, for instance, this period of time is three months. In the case of noncompliance, the patient will have unused medication at the end of that three month period. In what could be called 'fixed span compliance models', the patient will visit the physician at regular intervals whether or not there is any medication remaining from the old prescription. In that case, there are two possible ways to model the patient's handling of the remaining medication. In the first model, the patient immediately gets the new prescription filled and discards the remaining medication from the old prescription. This model will be referred to as DSPILLS (the patient discards surplus pills). In the second model, the patient obtains a new prescription from the physician, but does not get it filled until all medication from the previous prescription has been taken. This model will be referred to as NOSPILLS (no surplus pills).

The DSPILLS model has a more profound effect on cost-effectiveness than the NOSPILLS model. At the same compliance rate, both models yield the same therapeutic effectiveness, but discarding unused medication incurs additional costs without obtaining the additional benefits of that medication, thus lowering the cost-effectiveness of therapy. It is likely that the co-payment for prescription drugs determines to a large extent whether patients discard surplus medication.

In addition to fixed span compliance models, one can also define variable span models; that is, models where the length of the time period between two physician visits is not constant. It is conceivable that some patients will visit their physician only when they are close to running out of medication and a new prescription is required. This model will be referred to as LPILLCDOC (acronym for: last pill, see doctor).

Table 7.1 reports the cost-effectiveness of lovastatin when therapy is initiated in men aged 40-44 years with pretreatment cholesterol levels of 8 mmol/l. When full compliance is assumed, cholesterol levels decrease by 28% at an annual cost of 870 NLG, resulting in a cost per life year gained of 16,000 NLG. At a 50% compliance rate, cholesterol levels will decrease by 21%. Under the DSPILLS model, where patients discard their surplus medication, the annual cost of therapy would still be 870 NLG. This results in a substantial increase in the cost per life year gained to 21,000 NLG. Under the NOSPILLS model, where patients get their prescription filled only when all medication from the previous prescription has been taken, the lower effectiveness is accompanied by a decrease in the annual cost of therapy, resulting in a cost per life year gained of 10,000 NLG, which is considerably lower than the cost-effectiveness ratio at full compliance. When patients visit their physician only when all medication has been used (LPILLCDOC), fewer physician visits occur and the annual cost of therapy is even lower than in the case of the NOSPILLS model, resulting in a cost per life year gained of 8,000 NLG.

Table 7.1 The effect of noncompliance on the cost effectiveness of cholesterol-lowering therapy with lovastatin.

Compliance	Change in total cholesterol (%)	Drug Cost (NLG)	Monitoring Cost (NLG)	Total Cost (NLG)	Cost per year of life saved (NLG)
100%	-27	730	140	870	16,000
50% DSPILLS	-21	730	140	870	21,000
50% NOSPILLS	-21	365	140	505	10,000
50% LPILLCDOC	-21	365	70	435	8,000

These results confirm the intuition that discarding unused medication will decrease the cost-effectiveness of therapy; the unexpected conclusion is that certain forms of noncompliance actually improve the cost-effectiveness of therapy. The latter is the result of the non-linear relationship between drug dose and life years gained, which is largely caused by the non-linear dose-response relationship of lovastatin: doubling the daily dose of lovastatin from 20 mg to 40 mg increases the cholesterol-lowering effect from 21 to 28 percent, which is less than a 35% increase. The incremental cost-effectiveness of the second daily tablet is considerably lower than the cost-effectiveness of the first tablet, causing the overall cost-effectiveness to be somewhere in between these two values. Eliminating both the cost and the cholesterol-lowering effect of the second daily tablet will lower the cost per life year gained to that of the first tablet.

Although this example is based on the use of lovastatin in cholesterol-lowering therapy, it is likely that noncompliance will lead to a similar range of effects on the cost-effectiveness of simvastatin therapy. It should be noticed that the noncompliance models presented here do not take into account that noncompliance would be reflected in the cholesterol levels of the patient and that the physician, assuming compliance on the patient's behalf, may simply increase the prescribed dose. In the case of the DSPILLS model, this would further lower the cost-effectiveness of therapy, but would not affect the cost-effectiveness of therapy in the NOSPILLS and LPILLCDOC models.

Side effects and safety

The cost-effectiveness analysis of cholesterol-lowering therapy with simvastatin does not account for the fact that therapy has to be discontinued in a small fraction of patients because of changes in liver

function. In clinical studies with lovastatin and simvastatin, fewer than three percent of patients had to be withdrawn from treatment, mainly because of elevations of liver enzymes to greater than three times the upper limit of normal. These episodes were asymptomatic and reversible upon discontinuation of therapy.[30] However, discontinuation takes place after only a short period of treatment and the costs incurred in this time period are too small to contribute significantly to the lifetime treatment costs of the average patient in the cohort.

In accordance with the clinical experience with lovastatin and simvastatin, the cost-effectiveness analysis assumes no costs for the treatment of side-effects. However, to the extent that any treatment of side effects would increase costs, they would be reflected in the sensitivity analysis of the total cost of therapy.

One of the primary assumptions of the cost-effectiveness model is that the use of simvastatin is safe; that is, simvastatin improves the lipid profile and thereby lowers the risk of coronary heart disease without increasing the risk of morbidity or mortality from other diseases. This assumption often troubles epidemiologists and clinicians because of the experience in the WHO Cooperative Trial of clofibrate, which demonstrated that the beneficial effect of clofibrate on non-fatal myocardial infarctions was accompanied by a 27 percent increase in all-cause mortality, suggesting that clofibrate has long-term toxic effects.[31,32] Many clinicians feel that until the time that long-term studies of lovastatin and simvastatin have been completed, the possibility of an adverse effect of these drugs on mortality from causes other than coronary heart disease, especially cancer, should not be dismissed and that these medicines should be prescribed only with great care. In the following, the sensitivity of the cost-effectiveness ratios for adverse effects due to simvastatin therapy will be examined for two assumptions:

1) a small proportion of patients will die at initiation of therapy or shortly thereafter and 2) therapy with simvastatin increases the mortality from causes other than coronary heart disease.

By 1988, the clinical experience with simvastatin included over 3,500 patients.[30] At that time, it would have become clear if 1 out of 1,000 patients died when simvastatin therapy was started or shortly thereafter. Such an increased mortality would increase the cost per year of life saved when simvastatin therapy is started among 40- to 44-year-old men with cholesterol levels of 8 mmol/l by 2.7 percent from NLG 29,800 to NLG 30,600.

In the disease history model, persons either develop coronary heart disease and subsequently die, or die from causes other than coronary heart disease. Assuming that simvastatin therapy would increase the mortality from causes other than coronary heart disease by 10 percent increases the cost per year of life saved among 40- to 44-year-old men with cholesterol levels of 8 mmol/l by 35 percent from NLG 29,800 to NLG 41,800. When therapy is started among men with similar cholesterol levels but older than 55 years, such an increase in mortality would lead to net losses in life expectancy. For 40- to 44-year-old men, there is no net gain in life expectancy if therapy with simvastatin causes an increase in the mortality from causes other than coronary heart disease of 25.5 percent.

7.4 Discussion

This chapter reports the sensitivity of the cost-effectiveness of simvastatin to a number of assumptions in the disease history model and a number of assumptions about therapy with simvastatin. Table 7.1 summarizes the effect of changes in these assumptions on the cost per year of life

Table 7.1 Summary of sensitivity analysis. Shown is the effect of changes in model assumptions on the cost per year of life saved when simvastatin therapy is started among 40- to 44-year-old men with pretreatment cholesterol levels of 8 mmol/l.

Parameter	*Baseline value*	*High/low value*	*Cost per year of life saved (1,000 NLG)*
Model baseline			30
Discount rate	5%	7%	37
		3%	23
Medical care costs in additional years of life	-	average	35
		stratified	32
Fraction of benefits achieved	100%	90%	34
Cholesterol reduction	27%	24%	33
		30%	28
Annual therapy costs	1319 NLG	+10%	33
		-10%	26
Fraction of myocardial infarctions that is recognized	15%	20%	31
		10%	29
Annual mortality among those surviving the first year after myocardial infarction	4.25%	3.75%	31
		4.75%	29
Fraction of persons with myocardial infarction who die before hospitalization	28%	25%	31
		31%	29
Coronary heart disease treatment costs	100%	75%	31
		125%	28

saved when simvastatin therapy is started among 40- to 44-year-old men with pretreatment cholesterol levels of 8 mmol/l. Substantial changes in the treatment costs of coronary heart disease, the fraction of unrecognized myocardial infarctions, the fraction of patients with a severe coronary event who die before hospitalization, and the mortality rate more than one year after myocardial infarction result in only small changes in the cost per year of life.

Changes in the assumptions about the discount rate and the cholesterol-lowering effect of simvastatin have a considerable effect on the cost per year of life saved. However, there seems to be little controversy about the use of a five percent discount rate in economic evaluations of health care programs in the Netherlands. Furthermore, the cholesterol-lowering effect that was assumed in this analysis is generally contested only in relation to expectations of lower compliance in routine medical practice than in clinical trials. The analysis of different compliance models demonstrates that noncompliance can lead either to an increase or a decrease in the cost-effectiveness of therapy, depending on the way in which patients handle their surplus medication.

The cost-effectiveness of therapy is very sensitive to changes in the cost of therapy, which primarily consists of the price of simvastatin. Under the current drug-pricing system in the Netherlands, the retail price of simvastatin is determined by the ex-factory price, which is set by the manufacturer.

The cost-effectiveness of therapy is also very sensitive to changes in mortality from causes other than coronary heart disease. Although there are no data indicating that simvastatin has serious adverse effects in more than a small fraction of patients, clinical trials of HMG-CoA reductase inhibitors are now under way in the United Kingdom and the

United States that should help shed light on their impact on all-cause mortality.

In summary, the results of the analysis appear to be reasonably stable for changes in most model assumptions. In addition, there is little controversy about the assumptions for which the model results are fairly sensitive, with the exception of the hypothetical effect of simvastatin on non-cardiovascular mortality. The ambiguity of the results of modeling the effect of compliance on the cost-effectiveness of therapy suggests the need for primary data collection on the relationship between noncompliance and both the cost and effectiveness of therapy.

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8 CONCLUSION

The research presented in this dissertation shows that the cost per year of life saved by cholesterol-lowering therapy varies substantially depending on sex, age at initiation of therapy, pretreatment cholesterol level, and the presence of additional coronary risk factors. The main conclusions are that 1) the 1987 Cholesterol Consensus Conference's endorsement of cholestyramine as a drug of first choice cannot be justified by the cost per year of life saved by that medication and 2) although simvastatin is more cost-effective than cholestyramine, its costs per year of life saved compare well with that of other health care programs in the Netherlands only for a fraction of the patients who are eligible for cholesterol-lowering drug therapy according to the conference's guidelines.

The 1987 Cholesterol Consensus Conference in the Netherlands recommended physicians to prescribe cholesterol-lowering medication if, after an adequate trial of diet, serum cholesterol levels remain above 8 mmol/l. In that case, the cost per year of life saved by therapy with simvastatin compares well with that of other health care interventions in the Netherlands, but only if therapy is started among men and if therapy is started at a young age. The costs per year of life saved by treatment with cholestyramine by far exceed those of other health care programs.

The consensus conference advised physicians to consider cholesterol-lowering medication if, after an adequate trial of diet, serum cholesterol levels are between 6.5 and 8 mmol/l and additional coronary risk factors are present. Evaluation of this guideline for two coronary risk factors–hypertension and diabetes mellitus–shows that the costs per year of life saved with simvastatin compare well with that of other

therapies only for a fraction of the patients eligible for therapy: young men with cholesterol levels above 7.5 mmol/l and women with diabetes and cholesterol levels above 8 mmol/l. The cost-effectiveness model does not permit estimation of the cost per year of life saved for the other coronary risk factors that are mentioned in the guidelines of the consensus conference: clinically manifest coronary heart disease, a family history of coronary heart disease before the age of 60 years, and the presence of symptoms of hereditary hypercholesterolemia.

The analysis described in this dissertation was included in the report submitted by the committee on cholesterol of the Health Council of the Netherlands to the Minister of Welfare, Health, and Cultural Affairs on February 12, 1990. The committee recommended narrowing the guidelines of the 1987 Cholesterol Consensus Conference and restricting the prescription of HMG-CoA reductase inhibitors to patients with serum cholesterol levels exceeding 6.5 mmol/l and at least two additional coronary risk factors, or to patients with cholesterol levels higher than 8 mmol/l and at least one additional coronary risk factor. On March 6, 1990, the State Secretary of Health issued an administrative order restricting the reimbursement of cholesterol-lowering medication accordingly. A revised text of the Dutch Cholesterol Consensus was subsequently prepared and published in 1991.

Although the guidelines for the treatment of elevated cholesterol levels in the Netherlands appear to be very conservative, especially in comparison with such guidelines in the United States, a cautious approach to cholesterol lowering is understandable given the cost-effectiveness of therapy, the lack of evidence of the effectiveness of cholesterol lowering in preventing coronary heart disease among women, and the concerns about potential long-term side effects of HMG-CoA reductase inhibitors.

SUMMARY

The research presented in this dissertation was conducted to answer the question: how does the cost-effectiveness of therapy with simvastatin compare with that of current cholesterol-lowering therapy and that of other generally accepted medical practices in the Netherlands?

Chapter 2 reviews the available evidence of the role of cholesterol in the development of coronary heart disease and the efficacy of cholesterol lowering in reducing the incidence of such disease. Epidemiologic studies, notably the Framingham Heart Study and the follow-up of the original screening cohort of the Multiple Intervention Risk Factor Trial, have provided convincing evidence that, at least for men and women at younger ages, there is a relationship between serum cholesterol levels and the incidence of coronary heart disease, mortality from coronary heart disease, and mortality from all causes. Clinical studies of the primary prevention of coronary heart disease have been able to demonstrate that reducing serum cholesterol levels lowers the morbidity and mortality from coronary heart disease, but have not demonstrated a beneficial effect on total mortality. Although the lack of effect on total mortality is often assumed to be the result of a lack of statistical power, there is considerable concern that cholesterol-lowering medication may adversely affect mortality from causes other than coronary heart disease, notably from cancer. Such adverse effects have been noticed in a number of primary and secondary prevention trials. In addition, evidence that cholesterol lowering will reduce the incidence of coronary heart disease among women is lacking since the intervention studies have almost exclusively been conducted among men.

Chapter 3 reviews a number of publications that describe economic evaluations of cholesterol-lowering therapy. Partial evaluations, that is, studies that examine only the costs or, in this case, the effects of therapy, have shown that 1) the relatively small gains in life expectancy due to diet are unlikely to provide an incentive for most patients to adhere to their diet, and 2) cholesterol lowering is unlikely to result in substantial savings in health care costs and that the trade-off for the cost of therapy has to be found in increases in life expectancy or improvement in quality of life. A number of studies analyzing the cost-effectiveness of, among others cholestyramine and lovastatin, have concluded that cholesterol-lowering medication may only be cost-effective for selected groups of patients.

Chapter 4 describes the model for the incidence and prevalence of coronary heart disease that was used to estimate costs and effects of cholesterol-lowering therapy in the Netherlands. The cost-effectiveness model does not use the results from intervention studies to estimate the benefits of cholesterol lowering, but uses observational data from the Framingham Study and assumes that the coronary heart disease risk after cholesterol reduction gradually becomes equal to that corresponding with the naturally occurring lower cholesterol level. A simulation of the Lipid Research Centers Coronary Primary Prevention Trial showed that the model does not overestimate the benefits of cholesterol lowering. Because of the use of multivariate risk functions from the Framingham Study to estimate coronary heart disease incidence, the cost-effectiveness model shows a structural resemblance to some of the models that have been published by other researchers. The study described in this dissertation distinguishes itself from other economic evaluations of cholesterol lowering in that it is the only study that accounts for the

effect of intra-individual biological variation and analytical variation in cholesterol measurement.

Chapter 5 describes the effect of cholesterol lowering on outcomes such as lifetime coronary risk, life expectancy, and coronary heart disease treatment costs. The results suggest that cholesterol lowering can lead to considerable improvements in these outcomes, especially if therapy is started at an early age.

Chapter 6 analyzes the cost-effectiveness of cholesterol-lowering therapy with simvastatin and cholestyramine and evaluates the guidelines of the Dutch Cholesterol Consensus Conference. The cost per year of life saved among men rapidly increases when therapy is initiated at later ages, whereas for women, the cost per year of life saved does not vary substantially when therapy is started between the ages of 35 and 60 years. For both men and women, there is an inverse relationship between the cost per year of life saved and the pretreatment serum cholesterol level, which provides an economic rationale for the Consensus Conference's guideline to initiate drug treatment only for persons who have particularly high cholesterol levels. The results also indicate that simvastatin is substantially more cost-effective than cholestyramine.

The resulting cost-effectiveness ratios seem to have a number of implications for the treatment of elevated serum cholesterol levels in the Netherlands. The costs per year of life saved by cholesterol-lowering therapy with cholestyramine compare unfavorably with those of generally accepted health care programs in the Netherlands. Costs per year of life saved by simvastatin among men with cholesterol levels higher than 8 mmol/l appear to be acceptable when therapy is started at an early age.

However, for persons with cholesterol levels between 6.5 mmol/l and 8 mmol/l, therapy would have to be limited to men with at least one risk factor such as diabetes mellitus or hypertension. Among women, the age at initiation of therapy does not affect the cost-effectiveness of therapy greatly, but the gain in life expectancy increases when therapy is started at an earlier age. When therapy is limited to women with diabetes mellitus or severely elevated serum cholesterol levels, the cost-effectiveness of cholesterol-lowering therapy among women compares well with that of currently accepted health care programs.

Chapter 7 examines the sensitivity of the model results to changes in key parameters of the disease history model and for assumptions about the cost, effectiveness, and side-effects of therapy with simvastatin. There are only a few assumptions for which the costs per year of life saved are fairly sensitive, such as the discount rate and the price of simvastatin. There is, however, little uncertainty or controversy surrounding these assumptions.

The results of the analysis described in this dissertation were taken into consideration by the committee on cholesterol of the Health Council of the Netherlands in its report to the Minister of Welfare, Health, and Cultural Affairs. The committee recommended narrowing the guidelines of the 1987 Cholesterol Consensus Conference and restricting the prescription of HMG-CoA reductase inhibitors to patients with serum cholesterol levels exceeding 6.5 mmol/l and at least two additional coronary risk factors, or patients with cholesterol levels higher than 8 mmol/l and at least one additional coronary risk factor. On March 6, 1990, the State Secretary of Health issued an administrative order restricting the reimbursement of cholesterol-lowering medication to those

patients who would be eligible for therapy according to the guidelines of the committee on cholesterol. *Chapter 8* concludes that although the guidelines for the treatment of elevated cholesterol levels in the Netherlands appear to be very conservative, especially in comparison with such guidelines in the United States, such a prudent approach to cholesterol lowering is understandable given the cost-effectiveness of therapy, the lack of evidence of the effectiveness of cholesterol lowering in preventing coronary heart disease among women, and the concerns about potential long-term side effects of HMG-CoA reductase inhibitors.

SAMENVATTING

Dit proefschrift beschrijft een kosten-effectiviteits analyse die onderzoekt hoe de kosten-effectiviteit van cholesterolverlaging middels simvastatine bij personen zonder coronairlijden zich verhoudt met de kosten-effectiviteit van 1) het huidige cholesterolverlagende geneesmiddel van eerste keuze, d.w.z. cholestyramine en 2) andere gezondheidsinterventies in Nederland? In wezen wordt getracht om vanuit het perspectief van de gezondheidseconomie antwoord te geven op de vraag of en aan wie cholesterolverlagende middelen voorgeschreven dienen te worden. Daarbij wordt er van uitgegaan, dat een dieet de eerste stap in de behandeling van verhoogde serumcholesterolwaarden is en dat deze geneesmiddelen alleen voorgeschreven worden aan mannen en vrouwen bij wie een dieet niet tot de gewenste verlaging in serumcholesterol-waarden heeft geleid.

Hoofdstuk 2 is een overzicht van de literatuur met betrekking tot de rol van cholesterol in het onstaan van coronaire hartziekten en de effectiviteit van cholesterolverlaging in het voorkómen van coronairlijden. Epidemiologische studies, met name de Framingham Study en de analyse van de mannen die zich oorspronkelijk aanmeldden om deel the nemen aan de Multiple Intervention Risk Factor Trial, hebben overtuigend aangetoond dat, ten minste voor mannen en vrouwen op jongere leeftijd, er een samenhang is tussen het serumcholesterolgehalte enerzijds en de incidentie van coronairlijden en de sterfte aan coronaire hartziekten en alle doodsoorzaken anderzijds. Interventie studies hebben aangetoond dat serumcholesterolverlaging resulteert in een lagere morbiditeit en mortaliteit ten gevolge van coronaire hartziekten, maar geen effect heeft

op de sterfte aan alle doodsoorzaken. Alhoewel dit laatste vaak gezien wordt als het gevolg van een gebrek aan statistisch vermogen van zulke studies, wordt ook de mogelijkheid aanwezig geacht dat cholesterolverlagende geneesmiddelen een ongunstig effect hebben op de sterfte aan doodsoorzaken anders dan coronair hartziekten. Een dergelijk effect is waargenomen in een aantal studies, bijvoorbeeld met clofibraat. De klinische studies die het effect van cholesterolverlaging op morbiditeit en mortaliteit onderzochten vonden bijna uitsluitend onder mannen plaats. Er zijn dan ook geen aanwijzigingen dat cholesterolverlaging bij vrouwen de kans op coronaire hartziekten verlaagt.

In *Hoofdstuk 3* worden een aantal publicaties van economische evaluaties van cholesterolverlaging besproken. Er is op gewezen, dat het onwaarschijnlijk is dat cholesterolverlaging tot aanzienlijke besparingen op de kosten van de gezondheidszorg zal leiden and dat de kosten van de cholesterolverlagende behandeling enkel gerechtvaardigd kunnen worden met de te verwachten winst in levensverwachting of verbetering in de kwaliteit van leven. Amerikaanse kosten-effectiviteitsstudies van een aantal geneesmiddelen hebben er de aandacht op gevestigd, dat cholesterolverlaging enkel kosteneffectief is in bepaalde patienten, met name die patienten die additionele risicfactoren hebben.

Hoofdstuk 4 beschrijft het model dat gebruikt werd om de kosteneffectiviteit van cholesterolverlaging met simvastatine en cholestyramine te berekenen. Met betrekking tot het effect van cholesterolverlaging is aangenomen, dat de kans op coronaire hartziekten na cholesterolverlaging gelijk is aan die van personen die het lagere serumcholesterol van nature bezitten. Een vergelijking van de resultaten van een met het rekenmodel uitgevoerde simulatie van de Lipid Research

Clinics Coronary Primary Prevention Trial met het door deze onderzoekers gepubliceerde Cox's proportional hazards model leidde tot de conclusie dat het kosten-effectiviteitsmodel de baten van cholesterolverlaging niet overschat.

Het rekenmodel vertoond een structurele gelijkenis met dat van andere auteurs, hoofdzakelijk vanwege het gebruik van de multivariate logistische risicofuncties ontleend aan de Framingham Study. Het model dat in dit proefschrift wordt beschreven is uniek in die zin, dat het het enige kosten-effectiviteitsmodel is dat die risicofuncties corrigeert voor de analytische en intra-individuele biologische variatie in het serumcholesterol.

Hoofdstuk 5 beschrijft het effect van cholesterolverlaging op coronairrisico, levensverwachting, en behandelkosten van coronaire hartziekten.

Hoofdstuk 6 beschrijft de kosten per gewonnen levensjaar met simvastatine en cholestyramine. De kosten per gewonnen levensjaar nemen bij mannen snel toe als met de behandeling na het 50ste levensjaar aangevangen wordt. Bij vrouwen variëren de kosten per gewonnen levensjaar aanzienlijk minder met de leeftijd waarop de medicatie ingesteld wordt dan bij mannen. Zowel bij mannen als bij vrouwen nemen de kosten per gewonnen levensjaar snel toe naarmate personen met een lager serumcholesterol behandeld worden. De resultaten geven bovendien aan, dat simvastatine aanzienlijk kosten-effectiever is dan cholestyramine.

De kosten-effectiviteits ratios bevatten een aantal aanwijzingen voor het beleid bij de behandeling van verhoogde serumcholesterolwaarden. De kosten per met cholestyramine gewonnen levensjaar verhouden zich

ongunstig t.o.v. die van andere in Nederland geëvalueerde gezondheidsvoorzieningen. De kosten per gewonnen levensjaar van cholesterolverlaging met simvastatine bij mannen met serumcholesterolwaarden hoger dan 8 mmol/l kunnen acceptabel zijn, mits de therapie op jonge leeftijd begonnen wordt. Bij serumcholesterolwaarden tussen 6,5 en 8 mmol/l zal de behandeling op zijn minst beperkt moeten worden tot mannen met hypertensie of diabetes, terwijl een beperking tot mannen met hypertensie èn diabetes de kosten-effectiviteit zeer ten goede komt. Alhoewel voor vrouwen de kosten per gewonnen levensjaar niet zo gevoelig zijn voor de leeftijd waarop met cholesterolverlaging begonnen wordt, neemt de winst in levensverwachting af naarmate men op latere leeftijd tot behandeling over gaat. Cholesterolverlagende therapie met simvastatine bij vrouwen lijkt, gezien de alhier gerapporteerde kosten per gewonnen levensjaar, alleen aangewezen bij vrouwen met diabetes mellitus of zéér sterk verhoogde serumcholesterolwaarden.

De gevoeligheid van de modelresultaten voor veranderingen in de modelparameters wordt beschreven in *Hoofdstuk 7*. De kosten per met simvastatine gewonnen levensjaar zijn met name gevoelig voor de prijs van simvastatine en de disconteringsvoet.

De resultaten van de in dit proefschrift gepresenteerde kosten-effectiviteitsanalyse maakten deel uit van de overwegingen van de commissie cholesterol van de Gezondheidsraad in haar rapport aan de Minister van Welzijn, Volksgezondheid en Cultuur. De commissie deed onder meer de aanbeveling om het voorschrijven van cholesterolsynthese-remmers te beperken tot personen met serumcholesterolwaarden boven 6,5 mmol/l en tenminste twee additionele risicofactoren voor coronaire hartziekten en personen met serumcholesterolwaarden boven 8 mmol/l

en tenminste één additionele risicofactor. In maart 1990 beperkte de Staatssecretaris voor Volksgezondheid de verstrekking van simvastatine in het ziekenfondspakket in evereenstemming met deze aanbeveling. De behandeling van hypercholesterolaemie in Nederland is zonder meer conservatief te noemen, zeker in vergelijking met bijvoorbeeld de Verenigde Staten. Een voorzichtige benadering in de behandeling van verhoogde serumcholesterolwaarden lijkt evenwel aangewezen gezien de in dit proefschrift gerapporteerde kosten-effectiviteits ratio's, het gebrek aan bewijs dat serumcholesterolverlaging coronaire hartziekten voorkómt bij vrouwen en de onzekerheid over de veiligheid van het gebruik van simvastatine op langere termijn.

APPENDIX 1. ANALYTICAL AND BIOLOGICAL VARIANCE IN CHOLESTEROL MEASUREMENT*

Introduction

Numerous efforts have been undertaken in recent years to assess the cost-effectiveness of cholesterol-lowering therapy in the primary prevention of coronary heart disease.[1-8] All but one of these studies use multivariate logistic risk functions from the Framingham Study to estimate the benefits in terms of life extension and savings in coronary heart disease treatment costs that result from a decrease in serum cholesterol level.[4] Although the Framingham Study provides the most comprehensive analysis of coronary heart disease among persons with varying cardiovascular risk, it must be noted that these risk estimates were derived over two decades ago. In the early 1970's, Gardner and Heady demonstrated the effect of error in the measurement of independent variables on estimates of coronary heart disease risk.[9] Using a logistic model, they calculated that a single blood pressure reading of 200 mm Hg carried an estimated risk of 1 in 3.7, whereas a blood pressure of 200 mm Hg based on the average of 6 readings at the baseline examination carried a risk of 1 in 3.0, an increase of 23 percent. Subsequently, Berwick et al. adjusted their estimates of the cost-effectiveness of lowering cholesterol levels through childhood screening for the difference between "true" and "measured" levels of cholesterol.[1] With the exception of Taylor et al.,[8] who adopted Berwick's adjustment,

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*The text in this appendix has been submitted to the American Journal of Preventive Medicine.

further studies of the cost-effectiveness of cholesterol lowering did not address the effect of variance in cholesterol measurement on estimates of coronary heart disease risk.[2-7]

Current use of the Framingham data is likely to result in underestimates of the relationship between serum cholesterol and the incidence of coronary heart disease because current testing methods provide a more precise estimate of cholesterol levels than those existent at the time data were collected in the Framingham Study (between 1950 and 1975). Accuracy and precision of laboratory measurement have improved considerably, especially since the introduction of standardization programs by the World Health Organization in the early 1970's.[10] Furthermore, attention increasingly has been focused on the effect of intra-individual biological variation in cholesterol levels and the need for repeat measurement to estimate patients' cholesterol levels more accurately. Some cholesterol consensus conferences such as the one organized in The Netherlands have advised physicians to take three cholesterol measurements before prescribing cholesterol-lowering therapy.[11] In the United States, the Laboratory Standardization Panel of the National Cholesterol Education Program recently advised that at least two separate cholesterol measurements should be taken before a decision is made about further medical action.[12]

In the following, we will show that due to the combined effect of intra-individual biological variation and analytical variation in cholesterol testing, the risk estimates from the Framingham Heart Study underestimate the relationship between serum cholesterol level and coronary heart disease risk. Next we will develop an algorithm that adjusts the Framingham risk estimates for intra-individual biological and analytical variation. Building on our previously published cost-effectiveness model,[5] we will demonstrate how inclusion of such an

algorithm can improve estimates of the cost-effectiveness of cholesterol-lowering therapy.

Variance in cholesterol measurement

The serum cholesterol level of an individual varies around an average value x_1. Let the population distribution of average cholesterol levels x_1 be characterized by a mean value μ and a standard deviation σ_1. The difference x_2 between a measured value x and the average value x_1 is part of a normal distribution around zero with a standard deviation σ_2. The joint likelihood of the x_1 and x_2 component of x equals $f(x_1,x_2)dx_1dx_2$, where $f(x_1,x_2)$ is the joint density function:

$$f(x_1,x_2) = f_1(x_1-\mu) * f_2(x_2-0) \quad (1)$$

$$= f_1(x_1-\mu) * f_2(x-x_1) \quad (2)$$

$$= c * e^{-\frac{(x_1-\mu)^2}{2\sigma_1^2}} * e^{-\frac{(x-x_1)^2}{2\sigma_2^2}} \quad (3)$$

where c denotes the constant:

$$c = (2\pi\sigma_1^2)^{-1/2} * (2\pi\sigma_2^2)^{-1/2} \quad (4)$$

Although the densities are assumed to be normal, the results presented here hold under much weaker conditions.

Instead of maximizing $f(x_1,x_2)$ with respect to x_1, we can maximize $\ln(f(x_1,x_2))$:

$$\ln f(x_1,x_2) = -\frac{(x_1-\mu)^2}{2\sigma_1^2} - \frac{(x-x_1)^2}{2\sigma_2^2} \qquad (5)$$

$$\frac{\delta \ln f(x_1,x_2)}{\delta x_1} = -\frac{x_1-\mu}{\sigma_1^2} - \frac{x-x_1}{\sigma_2^2} = 0 \qquad (6)$$

which results in:

$$x_1 = \frac{\sigma_2^2 \mu + \sigma_1^2 x}{\sigma_1^2 + \sigma_2^2} \qquad (7)$$

and can be re-written as:

$$x_1 = x + \frac{\sigma_2^2 (\mu-x)}{\sigma_1^2 + \sigma_2^2} \qquad (8)$$

Letting:

$$\sigma_0^2 = \sigma_1^2 + \sigma_2^2 \qquad (9)$$

substitution of (9) in (8) results in:

$$x_1 = x + \frac{\sigma_2^2}{\sigma_0^2}(\mu-x) \qquad (10)$$

Assuming that x is the average of n measurements, then:

$$x_1 = x + \frac{\sigma_2^2}{n\,\sigma_0^2 - (n-1)\,\sigma_2^2}(\mu - x) \qquad (11)$$

where σ_2^2 still denotes the error variance in a single measurement. The intra-individual variance σ_2^2 has a biological component σ_b^2 and an analytical component σ_a^2, which are assumed to be independent:

$$\sigma_2^2 = \sigma_a^2 + \sigma_b^2 \qquad (12)$$

The biological and analytical variatiance are usually expressed as coefficients of variation CV that express the standard deviation as a percentage of the true level:

$$CV_2^2 = CV_a^2 + CV_b^2 \qquad (13)$$

Equation (11) indicates that when a measured cholesterol value x, whether it is a single measurement or the average of n measurements, is higher than the population average μ, the expected value x_1 of the average cholesterol level of an individual is lower than the measured value x. Similarly, when a measured cholesterol value x is lower than the population mean μ, the expected value x_1 of the average cholesterol level of an individual is higher than the measured value x. In other words, cholesterol levels above the population mean are on average measured too high; levels below the population mean are on average measured too low. This systematic error in cholesterol measurement results in a phenomenon that is usually referred to as regression towards the mean: re-testing all persons with a cholesterol measurement x will yield values that are normally distributed around x_1, which is closer to the population mean than x. The second measurement of most of these

persons will therefore be closer to the population mean than the first measurement. As a result, the actual relationship between the incidence of coronary heart disease and the true cholesterol level x_1 is stronger than the relationship reported in the Framingham Study.

By using the Framingham risk functions in their studies of cost-effectiveness, authors implicitly assume that a person with a certain cholesterol level x that is measured in a contemporary laboratory has an average cholesterol level x_1 equal to a person who had a cholesterol measurement x in the Framingham Study; i.e., there is no accounting for improved measurement methods over time. Equation (11) shows that repeated measurement will lead to a more precise estimate of cholesterol level, even if the improvement in analytical variation would not have taken place.

Example: the cost-effectiveness of cholesterol-lowering therapy in the Netherlands

Methods

We used equation (11) in an algorithm that incorporates the effect of analytical and intra-individual biological variation in the coronary heart disease risk estimates from the Framingham Study and updates these estimates to clinical settings where there is improved cholesterol measurement as the result both of lower analytical error and the addition of multiple cholesterol measurements. Using a previously published model of the cost-effectiveness of cholesterol-lowering therapy with simvastatin in the Netherlands,[5] we demonstrate the effect of different assumptions about biological and analytical variation on the costs per year of life saved.

Assuming three cholesterol measurements, the cholesterol distribution in the Netherlands (μ_{NL}, σ_{NL}), and the analytical error $CV_{a,NL}$ in cholesterol measurement in laboratories in the Netherlands, equation (11) shows the expected value of the average cholesterol level x_1 when the average of 3 cholesterol measurements equals x_{NL}:

$$x_1 = x_{NL} + \frac{\sigma_{2,NL}^2}{3\,\sigma_{NL}^2 - 2\,\sigma_{2,NL}^2}(\mu_{NL} - x_{NL}) \qquad (14)$$

where:

$$\sigma_{2,NL}^2 = \mu_{NL}^2 * (CV_{a,NL}^2 + CV_b^2) \qquad (15)$$

Based on one measurement, the cholesterol distribution among participants in the Framingham Study (μ_F, σ_F), and the analytical error $CV_{a,F}$ in cholesterol measurement in the Framingham Study, equation (11) can be rewritten into equation (16) to provide the expected value of a single cholesterol measurement $x=x_F$ of participants in the Framingham Study whose average cholesterol level equals x_1:

$$x_F = \frac{x_1\,\sigma_F^2 - \mu_F\,\sigma_{2,F}^2}{\sigma_F^2 - \sigma_{2,F}^2} \qquad (16)$$

where:

$$\sigma_{2,F}^2 = \mu_F^2 * (CV_{a,F}^2 + CV_b^2) \qquad (17)$$

The third step of the algorithm is to use the cholesterol value x_F, rather than the cholesterol value x_{NL}, in the multivariate risk functions from the Framingham Study.

From longitudinal studies performed in the 1950's with a laboratory technique similar to that utilized in the Framingham Study, it was estimated that the analytical coefficient of variation at that time was greater than 7 percent.[13,14] As a conservative estimate, we thus assumed that the analytical coefficient of variation $CV_{a,F}$ in the Framingham Study equaled 5 percent at that time. For contemporary laboratories in the Netherlands, we assumed a CV_a of 3.5 percent, which was the reported average long-term intra-laboratory variation in the United States in 1985.[15]

Age- and sex-specific values for the intra-individual coefficients of variation (CV_b) are based on a study by Williams et al.[16] The age- and sex-specific cholesterol distributions for Framingham Study participants and the Dutch population were obtained from the Framingham Study and the Epidemiologic and Preventive Study Zoetermeer (EPOZ) respectively.[17,18]

Based on results of Phase III studies reported in the Marketing Authorization Application for Zocor (simvastatin), we assumed that patients receiving one 20-mg tablet of simvastatin daily would experience a 27 percent reduction in total serum cholesterol levels.[19] The annual cost of therapy with simvastatin was estimated to be 1319.69 Dutch guilders (NLG; 1 NLG equals approximately 0.5 U.S. dollars) in the first year and 1756.09 NLG in subsequent years of therapy.[20]

Results

In Table A1.1, we present the effect on cost-effectiveness of a number of assumptions of the intra-individual and analytical variance in cholesterol measurement. Results are reported for Dutch men aged 35-39 years with pretreatment serum cholesterol levels of 8 mmol/l. Each row gives values of pre- and posttreatment cholesterol level as measured

Table A1.1 The cost-effectiveness of cholesterol-lowering therapy with simvastatin among 35-39 year old men in the Netherlands under various assumptions about the analytical variance in cholesterol measurement and the number of cholesterol tests.

	CVa (%)	CVb (%)	N	Serum cholesterol pre (mmol/l)	Serum cholesterol post (mmol/l)	δTC (%)	CYLS (NLG)
The Netherlands	0	0	1	8.00	5.84	-27	
True Value TC				8.00	5.84	-27	44,300
Framingham Study	0	0	1	8.00	5.84	-27	
The Netherlands	0	7.9	1	8.00	5.49	-31	
True Value TC				7.59	5.54	-27	39,300
Framingham Study	0	7.9	1	7.97	5.44	-32	
The Netherlands	3.5	7.9	1	8.00	5.40	-32	
True Value TC				7.51	5.42	-27	38,300
Framingham Study	3.5	7.9	1	7.96	5.34	-33	
The Netherlands	3.5	7.9	1	8.0	5.72	-32	
True Value TC				7.51	5.84	-27	35,500
Framingham Study	5.0	7.9	1	8.07	5.31	-34	
The Netherlands	3.5	7.9	3	8.0	5.70	-29	
True Value TC				7.81	5.70	-27	30,100
Framingham Study	5.0	7.9	1	8.47	5.61	-34	

Legend

TC: Total serum cholesterol
CVa: Coefficient of analytical variation
CVb: Coefficient of biological variation
N: Number of measurements averaged to obtain serum cholesterol value
pre: Pre-treatment serum cholesterol level
post: Post-treatment serum cholesterol level
δTC: Percentage change in total serum cholesterol due to therapy
CYLS: Cost per year of life saved

in the Netherlands, followed by the corresponding values assuming perfect measurement ("True Value"), and under measurement conditions in the Framingham Study. In the first row of the Table, we present these values before considering intra-individual biological and analytical variation in cholesterol measurement: CVa and CVb are set equal to 0; the number of cholesterol measurements taken is equal to 1; and the cost per year of life saved with simvastatin equals 44,300 NLG.

The second row of the Table demonstrates the effect of intra-individual biological variation in cholesterol measurement on the cost-effectiveness of therapy. Assuming perfect measurement, the expected value of the true serum cholesterol level of these men is 7.59 mmol/l. The 27 percent cholesterol reduction due to therapy is applied to the true value of the serum cholesterol level, which, correcting for the variance in cholesterol measurement, results in a 32 percent difference between the expected values of pre- and posttreatment cholesterol levels in the Framingham study. The application of the 27 percent cholesterol reduction to the true value of serum cholesterol is based on the fact that the efficacy of cholesterol-lowering medications has been reported as the reduction in the mean cholesterol level of the group of study participants. Use of the group mean level minimizes the influence of biological and analytical variance on this measure. The pre- and post-intervention cholesterol levels in this row differ between the Framingham Study and the Netherlands despite the equivalent assumptions about analytical and biological variance, reflecting differences in cholesterol distribution between the two populations. The cost per year of life saved is 11 percent lower than under the assumptions in the first row: 39,300 NLG versus 44,300 NLG.

The third row of the Table demonstrates the effect of adding analytical variation to the intra-individual variation, assuming one

cholesterol measurement and an equal analytical variation in the Netherlands and the Framingham Study equal to 3.5 percent. The resulting cost per year of life saved is 2.5 percent lower: 38,300 NLG vs 39,300 NLG.

Next, we assumed that the coefficient of analytical variation in the cholesterol measurements at the time of the Framingham Study was higher than that in contemporary laboratories in the Netherlands. We conservatively assumed that the Framingham coefficient is 1.5 percent higher (5.0 percent versus 3.5 percent). Based on this assumption, the cost per year of life saved fell by 7.3 percent to 35,500 NLG.

Finally, we assumed that cholesterol-lowering therapy would be initiated based on the average of three cholesterol measurements. The final row in the Table indicates that the cost per year of life saved is almost 15 percent lower when cholesterol lowering is initiated based on an average of three measurements compared to a single measurement: 30,100 NLG v. 35,500 NLG.

Adjusting the Framingham risk estimates for analytical and biological variance and incorporating a conservative estimate of the difference in laboratory precision between contemporary laboratories and the laboratories of the Framingham Study lowers the cost per year of life gained by 20 percent (35,500 NLG versus 44,300 NLG) when therapy with simvastatin is initiated among 35-39 year-old men with serum cholesterol levels of 8 mmol/l. When therapy is initiated at different age groups between 35 and 65 years and at different cholesterol levels between 5 and 8 mmol/l, this percentage ranges from 17 to 29 percent. Initiating therapy based on the average of multiple cholesterol measurements leads to a further reduction in costs per year of life saved.

Discussion

We have developed an algorithm that updates risk estimates from the Framingham Study to account for analytical and intra-individual biological variation in cholesterol measurement. This algorithm accounts for the improvement in laboratory precision since the data from the Framingham Study were collected and allows adjusting these risk estimates for the currently recommended practice of initiating treatment based on the average of multiple measurements. We demonstrated the effect of this algorithm on our previously published study of the cost-effectiveness of cholesterol-lowering therapy in the primary prevention of coronary heart disease in the Netherlands. We found that inclusion of this algorithm reduced our previous estimate of the cost per year of life saved of simvastatin therapy by 20 percent among 35- to 39-year-old men with cholesterol levels of 8 mmol/l. When therapy was initiated based on the average of three cholesterol measurements, costs per year of life saved among these men were reduced by an additional 15 percent.

The improvement in cost-effectiveness that we report is caused by two mechanisms. First, as a consequence of making the distinction between true and measured cholesterol level, the reductions in serum cholesterol that have been reported by clinical studies have been applied to the "true" value of the serum cholesterol. The rationale for doing so is that clinical studies of cholesterol lowering typically show the observed reduction in the group mean cholesterol level, therefore minimizing the effect of intra-individual biological variation and laboratory variation. In our cost-effectiveness model, a given reduction in true cholesterol level will, due to the combined effect of analytical and intra-individual biological variation in cholesterol measurement, correspond with a larger reduction in the expected values of the single cholesterol measurements

that are used in the risk functions from the Framingham Study to estimate the reduction in coronary heart disease risk.

Second, improved precision in cholesterol measurement results in a better identification of persons with elevated serum cholesterol levels. Cholesterol-lowering therapy is initiated among persons whose cholesterol level is in excess of the so-called cutoff level. Due to the combined effect of analytical and intra-individual biological variation, some individuals will be classified as having a cholesterol level higher than the cutoff level and receive cholesterol-lowering therapy although their true cholesterol level is actually lower. Similarly, some individuals will be classified as having a cholesterol level lower than the cutoff level and receive no cholesterol-lowering therapy despite the fact that their true cholesterol level is higher than the cutoff level. Improved measurement precision will reduce the numbers of persons receiving therapy needlessly, as well as result in treatment of a number of persons with hypercholesterolemia who may otherwise have gone undiagnosed. The result of improved measurement precision, whether it occurs through lower laboratory variance or repeated measurement, will be that the true cholesterol of the persons being treated will on average be higher. Since our cost-effectiveness model has shown that costs per year of life saved decrease with increasing pretreatment cholesterol level,[5] improvements in measurement precision will lead to lower costs per year of life saved.

The effect of analytical and biological variance in measuring blood pressure and serum cholesterol levels has been discussed in detail by others,[9,21,22] and has subsequently been incorporated in two studies of the cost-effectiveness of cholesterol lowering.[1,8] What distinguishes our work is that the algorithm we developed allows us to adjust Framingham risk estimates for differences in analytical variation between current laboratories and those at the time of the Framingham Study.

It is important to note that our calculations are based on estimates of laboratory precision, i.e., random analytical error, and that we do not address the problem of inaccuracy, i.e., systematic errors in laboratory measurement. Assuming there was no systematic error in the cholesterol measurements in the Framingham Study, our conclusions are valid for contemporary cholesterol measurements performed by well-standardized laboratories.

The tremendous growth in focus on the relation between hypercholesterolemia and coronary heart disease has led to the establishment of a number of expert panels that have issued guidelines for the detection and treatment of elevated serum cholesterol levels.[11,12] Our results demonstrate how recommendations to initiate treatment based on the average of multiple cholesterol measurements not only improve measurement precision, but as a consequence also improve the cost-effectiveness of therapy. To the extent that physicians now base their treatment decisions on the average of multiple cholesterol measurements, currently published studies of cholesterol lowering continue to overestimate the cost per year of life saved of therapy.

It is unlikely that the overestimation of costs per year of life saved reported in this study will affect the relative cost-effectiveness of two or more cholesterol-lowering interventions. However, in deciding on the priority of funding a therapy, health care decisionmakers will compare the cost-effectiveness of therapy with that of other generally accepted health care interventions.[23-25] Overestimation of the cost per year of life saved by cholesterol-lowering therapy may thus lead decisionmakers to allocate fewer health care resources to cholesterol lowering than they would given more accurate cost information. As health care researchers are increasingly able to provide decisionmakers with more accurate cost-

effectiveness estimates, the process of informed decision making on health care expenditures will ultimately be improved.

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APPENDIX 2. MEDICAL COSTS OF CORONARY HEART DISEASE

A2.1 Introduction

This Appendix presents estimates of the medical costs of treating coronary heart disease. In the coronary heart disease model, patients who survive the onset of coronary heart disease are in one of three possible states: survivors of a myocardial infarction or patients with stable or unstable angina pectoris who have not had a myocardial infarction. The estimates for the costs of treating coronary heart disease have therefore been developed for the following three manifestations: myocardial infarction (i.e., starting with a hospital admission under this diagnosis), angina pectoris, and unstable angina pectoris. The medical costs of these events were estimated by developing typical patterns of care for the initial manifestations as well as for the follow-on care, and by multiplying the expected frequency of a test or treatment by its cost.

A2.2 Patterns of Care for Coronary Heart Disease

Patterns of care for coronary heart disease in The Netherlands were drafted based on a review of the literature on the treatment of myocardial infarction, angina pectoris and unstable angina pectoris, and literature on the outcome of coronary artery bypass surgery and percutaneous transluminal coronary angioplasty. The literature review was almost entirely based on studies that were conducted in The Netherlands. The generalizability of the draft treatment patterns, however, seemed questionable since most of these studies were clinical studies. Clinical studies are generally conducted among a selected group of patients and

in selected health care settings. Their results are unlikely to represent the typical treatment and outcome of patients with coronary heart disease in The Netherlands. Therefore, a panel of six cardiologists was convened to adjust these patterns of care to reflect routine medical practice. The cardiologists represented different geographic regions and several different hospitals in The Netherlands (two university hospitals, two large training hospitals, and two peripheral hospitals). Based on the treatment patterns drafted from the literature and their clinical experience, the cardiologists reached a consensus on the way in which patients with each of the manifestations of coronary heart disease on the average would be treated in The Netherlands. Treatment options and indications in the field of cardiology change rapidly. The panel of cardiologists convened in March 1988. The patterns of care that the cardiologists agreed upon should therefore be seen as representative of that time.

Myocardial infarction

In 1985, 30,711 people were hospitalized with an acute myocardial infarction.[1] Of these patients, approximately 76 percent were transported to hospital by ambulance; the remaining fraction used other means of transportation. The average length of stay was 15 days,[1] 3 days of which are spend in a coronary care unit. Of the patients under the age of 70 years, 15 percent will undergo coronary thrombolysis; all others will receive conventional treatment. The CCU Registry of the Netherlands Interuniversity Cardiology Institute indicates that approximately 85 percent of the patients will be discharged alive. Cardiac rehabilitation is not uncommon in the Netherlands: in 1984, 25 percent of patients with a myocardial infarction underwent outpatient

cardiac rehabilitation,[1] which, according to the panel, corresponds with 40 percent of those under the age of 65 years.

Angina pectoris will have developed in 40 percent of those patients who are discharged alive. Of these patients who are under the age of 70 years, 70 percent will undergo coronary angiography. Of the patients under the age of 70 years who do not have post-infarction angina, only 10 percent will undergo coronary angiography. After angiography, 30 percent of patients will receive coronary by-pass surgery, 30 percent will undergo percutaneous transluminal coronary angioplasty, and 40 percent will receive medical management.

The panel also made estimates of the follow-on care for myocardial infarction, including physician visits, diagnostic tests, and medication. During the first year after the initial infarction, 4 physician visits will take place. During each visit an EKG and a chest X-ray will be made. Exercise testing will be done among 90 percent of the patients under the age of 70 years, 15 percent of which is nuclear exercise testing. Echocardiography will be performed among 24 percent of the patients; 24-hour Holter monitoring among 5 percent. During that first year, 40 percent of patients will take anticoagulants; 40 percent, beta-blockers; 30 percent, long acting nitrates; 20 percent, digitalis; 20 percent, either dipyridamole or aspirin; 18 percent, diuretics; 15 percent, calcium antagonists; 10 percent, ACE inhibitors; and 5 percent, anti-arrhythmics.

During later years, 60 percent of patients will visit their cardiologist twice per year. At each visit an EKG will be made. Drug use among these patients will have decreased after the first year following the initial infarction. The panel estimated that 25 percent of patients will still take anticoagulants; 15 percent, beta-blockers; 15 percent, long acting nitrates; 20 percent, digitalis; 10 percent, either dipyridamole or aspirin;

18 percent, diuretics; 10 percent, calcium antagonists; 10 percent, ACE inhibitors; and 5 percent, anti-arrhythmia.

Angina Pectoris

The panel of cardiologists agreed that although stable angina pectoris is not generally a reason for hospitalization, a small minority of patients may be hospitalized because of the severity of symptoms at the onset of the disease. The panel also agreed that most of these patients would undergo coronary angiography during this initial hospitalization. Since the cost of this hospitalization can largely be attributed to the coronary angiography and these costs will be captured by the panel's estimates of overall rates of coronary angiography, the decision was made not to separate cost estimates for these initial hospitalizations.

The panel estimated that in the first year after disease onset, 95 percent of angina pectoris patients would undergo exercise testing, 15 percent of which would be nuclear exercise testing; 16 percent would undergo coronary angiography followed by coronary artery by-pass surgery; 8 percent would undergo coronary angiography followed by percutaneous transluminal angioplasty; and 16 percent would undergo coronary angiography with no additional procedures. During the first year after disease onset, patients would have 3 visits to a cardiologist at an outpatient department. During each visit, an EKG and a chest X-ray would be made. In later years, two visits to a cardiologist would take place, during each of which an EKG would be made.

The panel also discussed prescribing patterns of medication for these patients. It was estimated that 80 percent of angina pectoris patients would take beta-blockers; 40 percent, calcium antagonists; 10 percent, either dipyridamole or aspirin; 90 percent, long-acting nitrates; and 20 percent, anticoagulants. Short-acting nitrates (sublingual nitroglycerine)

are prescribed to all patients with angina pectoris, to be taken when necessary.

Unstable Angina Pectoris

The panel agreed that all patients with unstable angina pectoris require inpatient treatment. During this hospital stay, 30 percent of patients will not stabilize on medication and will undergo coronary angiography followed by percutaneous transluminal coronary angioplasty (50 percent), coronary artery bypass surgery (40 percent), or drug therapy only (10 percent). Of those who stabilized on medication, 67 percent of the patients younger than 70 years will undergo coronary angiography followed by percutaneous transluminal coronary angioplasty (45 percent), coronary artery bypass surgery (40 percent), or drug therapy only (15 percent).

During the first year after the onset of unstable angina pectoris, patients will have 4 control visits to a cardiologist. In later years, 80 percent of the patients will visit the outpatient department twice per year. During each visit, an EKG is made. The panel estimated furthermore that 80 percent of unstable angina patients take beta-blockers; 50 percent take calcium antagonists; 80 percent take either dipyridamole or aspirin; 70 percent take long-acting nitrates; 5 percent take anticoagulants; and 15 percent take anti-arrhythmia.

Coronary Artery Bypass Grafting

In 1985, 7,109 coronary artery bypass grafts were performed in the Netherlands. The average length of stay was 13.7 days. Perioperative infarction occurs in 8 percent of patients undergoing coronary artery bypass surgery. Ten percent of bypass-surgery patients will have repeat surgery in the five years following this procedure. After discharge, 25

percent of bypass-surgery patients will undergo cardiac rehabilitation. The panel estimated that in the first year after surgery, patients will make on average 3 control visits to the cardiologist.

Percutaneous Transluminal Coronary Angioplasty

Complications during percutaneous transluminal coronary angioplasty that will add to the average cost of angioplasty are myocardial infarction (5 percent) and emergency coronary bypass surgery (3 percent). During the first year after angioplasty, 27 percent of patients will have a repeat procedure. Among patients for whom angioplasty was not successful (17 percent), 52 percent were assumed to undergo coronary artery bypass surgery. During the first six months after angioplasty, patients will visit their cardiologist twice, during which an EKG will be made and exercise testing will be done. The panel estimated that coronary angiography would be performed in 10 percent of patients who underwent angioplasty.

A2.3 Costs of Care for Coronary Heart Disease

Approximately 60 percent of the population of the Netherlands has insurance coverage for medical expenses under the Health Insurance Act, which is a compulsory health insurance plan for employed persons whose annual income does not exceed approximately 50,000 NLG. The other 40 percent of the population are "private patients" who must arrange on their own for health insurance coverage. The so-called "sickness fund patients" pay a fixed percentage of their income for this insurance; their employers contribute an equal amount. There are approximately 60 independent sickness funds that reimburse physicians, hospitals, and other health-care providers for the services that they deliver to

participating patients. Private insurance companies typically offer a number of insurance packages at a lump sum premium that depends on the services that will be reimbursed and the amount of co-payment.

Physicians' Fees

Physicians' fees in the Netherlands are based on a standard income that is negotiated between the government and a number of organizations representing physicians, such as the Landelijke Huisartsen Vereniging (National Association of General Practitioners) and the Landelijke Specialisten Vereniging (National Association of Medical Specialists). In addition, physicians are allowed certain expenses for secretarial support, overhead, transportation, and pension premiums. Based on a standard practice which produces a certain volume of services that are eligible for reimbursement, a fee for service is calculated. The same method of calculation is applied to other health-care providers, such as physical therapists and pharmacists.

There are separate specialists' fees for sickness-fund and private patients, with the latter generally being higher. For each type of service rendered by cardiologists, cardiac surgeons, and anesthesiologists, an average fee was calculated assuming that 60 percent of patients would be sickness-fund patients and that 40 percent would be private patients.[3,4] General practitioners' fees are equal for both types of patients.

Hospital Costs

Hospitals receive two types of reimbursement: a per-diem rate for routine nursing care, and a payment for diagnostic and therapeutic procedures. The payments for diagnostic and therapeutic procedures are reimbursements for direct costs, such as equipment. These reimbursements are the same for sickness-fund and private patients, and

for all hospitals. Every hospital has its own per-diem rate based on its unique operating expenses. This rate is negotiated between each hospital and the sickness fund that services the catchment area of the hospital; private patients pay a slightly higher rate. The hospital receives this negotiated rate for every patient, regardless of the intensity of care actually rendered.

The average cost of routine care per hospital day was estimated using 1985 national financial statistics of general and university hospitals.[5] The 1985 in-patient budget was calculated by subtracting revenues from out-patient care and day treatment from the total 1985 budget. The average cost of routine care per hospital day was calculated by subtracting expenditures on paramedic departments from the inpatient budget and dividing the result by the number of inpatient days generated in 1985. National production statistics for intensive care units have been available only since 1986. The average cost of one hospital day in an intensive care unit and the cost of one hospital day of regular care were calculated using the ratio of intensive care unit days to the total number of hospital days in 1986 and the assumption that one day of intensive care is 2.5 times as costly as one day of regular care.[6] Using the trend in hospital costs and the total number of hospital days,[7] the costs of routine care per hospital day were adjusted to reflect 1988 prices: 1,266 NLG per day of intensive care and 506 NLG per day of regular care.

The panel of cardiologists provided detailed estimates of the diagnostic and therapeutic procedures that would be conducted during the hospitalization of patients with an acute myocardial infarction or unstable angina pectoris. These estimates were combined with physicians' fees for inpatients, average costs of hospital days in intensive and in regular care, and fees and hospital reimbursements for diagnostic and therapeutic procedures. The costs of hospitalization for acute myocardial infarction

and unstable angina were estimated to be 12,486 NLG and 9,759 NLG respectively.

Coronary Angiography

The cost of coronary angiography was estimated at 3,903 NLG based on the materials used,[8] assistance by the X-ray department,[9] physicians' fees, and the assumption that the length of stay in the hospital would be three days.

Coronary Artery Bypass Surgery

The cost of bypass surgery is based on data from a 1984 survey of centers for heart surgery,[10] to which physicians' fees were added. Including estimates of follow-up care and repeat surgery by the panel of cardiologists, the cost of bypass surgery was estimated at 29,647 NLG.

Percutaneous Transluminal Coronary Angioplasty

A cost for angioplasty was calculated based on the cost of materials used,[8] physicians' fees and the assumption that patients would be hospitalized for three days, one of which would be in a coronary care unit. The cardiologists' panel generated typically patterns of follow-up care and provided estimates of the frequency of complications during angioplasty (i.e., emergency bypass surgery and myocardial infarction), repeat angioplasty, and bypass surgery after unsuccessful angioplasty. The one-year cost of angioplasty was estimated to be 14,837 NLG.

Outpatient Cardiac Rehabilitation

Ehren and Janssen estimated the cost of outpatient cardiac rehabilitation at 37.18 NLG per one-hour session.[11] Based on an

average of 28 sessions per patient,[2] the cost of outpatient cardiac rehabilitation was estimated to be 1041 NLG.

Follow-on Care

The panel of cardiologists provided estimates of routine outpatient care (i.e., physician visits, diagnostic tests, and prescription drugs) for each coronary heart disease manifestation. Separate estimates were provided for the first year after disease onset and for subsequent years.

Typical regimens for the classes of drugs mentioned in the follow-on care estimates of the cardiologists' panel were developed using the guidelines of the Sicknessfund Council of the Netherlands[12] and the assistance of a physician. Drug prices are uniform throughout the Netherlands. Pharmacies receive two types of reimbursement: a payment to cover the cost of the product, and a dispensing fee. The cost reimbursement is comprised of the wholesale price of the drug, plus a six percent value-added tax, which was excluded from the analysis. Drug prices as of March 1, 1988 were obtained from a pharmacy in the city of Maastricht. The dispensing fee equals 10.35 NLG for both sickness-fund and private patients. Patients using anticoagulants were assumed to use a thrombosis service to monitor the effectiveness of therapy. The annual cost of using such a service was calculated by dividing the 1986 budget of all thrombosis services in the Netherlands by the average number of patients using these services in that year.[13] Estimates of the cost of follow-on care are included in Table A2.1, which summarizes the primary treatment costs for each manifestation of coronary heart disease.

Table A2.1 shows that the medical costs in the first year after disease onset are highest for patients with unstable angina pectoris (almost 29,000 NLG), followed by myocardial infarction (approximately 20,000 NLG) and angina pectoris (over 9,000 NLG). The difference in costs

between patients with myocardial infarction and unstable angina pectoris is caused primarily by the difference in rates of coronary angiography, percutaneous transluminal coronary angioplasty, and coronary artery bypass surgery. Patients with angina pectoris incur considerably lower costs than patients who have experienced a myocardial infarction because they are not hospitalized. In later years, the cost of follow-on care for patients with angina pectoris equals that for patients with unstable angina pectoris; whereas patients who experienced a myocardial infarction incur only half those costs because fewer drugs are prescribed. The table does not show medical costs incurred by (re)infarction after the initial coronary heart disease event.

Indexing

All costs reported in this Appendix reflect 1988 price levels. Two price indices for costs based on the "Financieel Overzicht Zorg 1989"

Table A2.1 Medical costs of treating coronary heart disease, per patient, first and subsequent years, by disease manifestation (NLG).

	Myocardial infarction	*Angina pectoris*	*Unstable angina pectoris*
Initial hospitalization	12,486	-	9,759
*CAG, CABG, PTCA during first year**	6,209	7,455	17,274
Follow-on care			
First year	1,617	2,014	1,841
Subsequent years	758	1,538	1,549

* CAG stands for coronary angiography; CABG, coronary artery by-pass grafting; PTCA, percutaneous transluminal coronary angiography.

(Financial Survey of Care 1989) were used.[7] A price index for hospital days was estimated from the trend in hospital expenditures and the annual number of hospital days in the period 1984-1988. This price index was also applied to the hospital cost of coronary artery bypass surgery. All other costs were indexed to 1988 prices using the general price index for health care.[7] Costs incurred in future years were discounted at a rate of 5 percent.

A2.4 Discussion

The cost estimates that are presented in this Appendix are largely based on fees and reimbursement rates rather than on an analysis of the use of health-care resources in the treatment of coronary heart disease. Therefore, this analysis is more a reflection of the financial impact of coronary heart disease on third party payers in the Netherlands than of the economic cost to the health-care system.

Wittels et al. recently reported medical costs for the treatment of coronary heart disease in the United States.[14] Converted into 1988 dollars and using an exchange rate of 1.85 NLG per U.S. dollar, their estimates appear to be considerably higher than those presented in this Appendix. For instance, Wittels et al. estimated the cost of hospitalization with an acute myocardial infarction and unstable angina pectoris at 29,500 NLG and 17,153 NLG respectively versus 12,486 NLG and 9,759 NLG in this report. Simillarly, their estimate of the cost of coronary angiography is considerably higher: 6615 NLG versus 3903 NLG.

Sensitivity analysis, described in detail in Chapter 7, revealed that the cost-effectiveness ratios of simvastatin, which was the focus of this research, is not sensitive to changes in the cost of treating symptomatic

coronary heart disease. Although some of the cost estimates of medical care presented here may on close scrutiny appear arbitrary or incomplete, they are sufficiently representative estimates, given their limited effect on the final results of this study.

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