# Studies in Health Economics

## Modelling and Data Analysis of Costs and Survival

Mattias Ekman

AKADEMISK AVHANDLING

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# Studies in Health Economics: Modelling and Data Analysis of Costs and Survival

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## Modelling and Data Analysis of Costs and Survival

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# Acknowledgements

I am writing this foreword with a combined sense of melancholy and relief. I feel melancholy because I have enjoyed being a doctoral student, and this period of my life is now coming to an end. It has been a true privilege to be able to devote a few years to independent study and research. My life as a doctoral student has offered me a freedom that I have enjoyed tremendously, even though I sometimes have a feeling that I have perhaps read too much, and too widely, and written too little. I do hope that the 18th-century English writer Samuel Johnson was right when he said: "A man ought to read just as inclination leads him; for what he reads as a task will do him little good." Be that as it may, my doctoral studies have been a great experience in many ways. Nevertheless, I also have a feeling of relief, since it is certainly high time to go on with new projects.

The subject of my research efforts has been health economics. Health economics is in many ways a marvellous subject. It draws upon several branches of economics, primarily microeconomic theory, public economics, and welfare economics. A good grasp of economic theory is useful, but theoretical insights have to be combined with empirical knowledge about specific institutions and practices that have evolved in the health care sector. You also have to make frequent detours into areas like medicine, statistics, politics, and even philosophy. Many of the deeper matters in economic evaluations in health care, e.g., the value of life, border on moral philosophy. Even though I do not treat any moral issues explicitly in my thesis, I have tried to keep in mind that behind almost every figure in my thesis there are human beings of flesh and blood.

I am now coming to the acknowledgements, which is, without doubt, the most important part of this foreword. Who reads a foreword anyway, except those who expect to appear in the acknowledgements? It is with great pleasure that I offer my heartfelt thanks to my thesis advisors Peter Jennergren, Bengt Jönsson, Ingolf Ståhl, and Niklas Zethraeus. I am indebted to all four for valuable comments and suggestions along the way. Since I did not always follow their advice, I take full responsibility for remaining errors and deficiencies.

During my doctoral studies I have been associated both with the section for Managerial Economics within the Department of Business Administration, and with the Centre for Health Economics within the Department of Economics. Belonging to two different units puts you at the risk of falling between two stools. This need not happen, however,

as long as no one tries to pull the stools apart. In this respect, my advisors have been ideal. They have been able to provide a fruitful research environment, which I believe has been of much benefit for me.

Niklas Zethraeus was particularly helpful in introducing me to cost-effectiveness analysis based on clinical-trial data. His consistent emphasis on clarity and simplicity was also valuable, although his efforts to curb my somewhat rambling way of writing were sometimes in vain. I owe a debt to Ulf Gerdtham and Magnus Johannesson for getting me started on the study on consumption and production by age. I am also obliged to various participants in the seminar series in Health Economics, e.g. Freddie Henriksson, Per-Olov Johansson, Douglas Lundin, and Erik Grönqvist.

The life as a doctoral student does not only consist of research efforts. During my years as a doctoral student, I have taught both managerial economics and microeconomics, and I would like to express my thanks to my brothers and sisters in arms in the rough business of undergraduate education: Björn Leonardz and Nils-Erik Norén in managerial economics; Nina Constantinescu, Niclas Damsgaard, Erik Grönqvist, Martin Hill, AnnaMaria Oltorp, and Jonas Vlachos in microeconomics.

I wish to express a special thanks to my former room-mate Jan Edman, who spiced up my life as a doctoral student through his great sense of humour, curiosity, seriousness, and playfulness. Our lively discussions, ranging from experimental research designs to the latest football scores, were most enjoyable. My gratitude also goes to Patric Andersson, Ingolf Ståhl, and Jan Tullberg for wide-ranging discussions on many topics, both academic and non-academic. Other splendid individuals who have contributed to stimulating lunchtime and coffee-break discussions are Robert Aulin, Lena Bengtsson, Björn Leonardz, Joakim Levin, Nils-Erik Norén, and Bo Sellstedt. To these and other colleagues I offer my sincere thanks. I am very grateful to Mari Bergmark and Carin Blanksvärd for offering friendly and generous assistance on practical matters. Finally, of course, I wish to thank my family for unfailing encouragement and support.

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Stockholm, May 2002
Mattias Ekman

# List of papers

Study I. Economic evaluations in health care: Basic principles and special topics.

Study II. Consumption and production by age in Sweden: Basic facts and health economic implications.

Study III. The possibility of predicting health care costs in the future from predicted changes in age structure and age specific mortality: The case of Sweden.

Study IV. The cost-effectiveness of bisoprolol in the treatment of chronic congestive heart failure in Sweden: Analysis using data from the cardiac insufficiency bisoprolol study II trial.
(Co-authors: Niklas Zethraeus and Bengt Jönsson. Published in *Pharmacoeconomics* 2001; 19: 901-916.)

Study V. Assessing uncertainty in cost-effectiveness analysis by combining resampling of clinical trial data with stochastic modelling: The economic evaluation of bisoprolol re-examined.

Study VI. Survival analysis techniques for estimating the costs attributable to head and neck cancer in Sweden.

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# Economic evaluations in health care: Basic principles and special topics

## 1. Introduction

The purpose of this introduction to economic evaluations in health care is to provide a background for the studies included in this thesis. Apart from being a survey of some basic principles and special topics in economic evaluations, it is at least in part also a study in its own right, since a couple of results of interest for cost-effectiveness studies are included.

In section 2, I motivate why economic evaluations in health care are needed. One important reason is that the price mechanism is to a large extent out of work in the relation between patients and health care providers. The major part of the total health care expenditures in Sweden is covered by the government through health insurance, which is ultimately paid by the taxpayers. The fact that the patients do not pay the full cost of the health care they consume themselves means that some kind of rationing mechanism is necessary. Otherwise, we may collectively spend more money on health care than we would be willing to pay for. Rationing may of course also be too strict. Economic evaluations may have a role to play in assessing whether the benefits of a particular treatment outweigh its costs from a societal perspective.

In section 3, I describe the major elements of economic evaluations: 1) estimation of costs, 2) estimation of benefits, and 3) discounting of costs and benefits. Even though I primarily deal with cost-effectiveness analysis in my studies, I begin my survey of economic evaluations with cost-benefit analysis. In my view, it is a good idea to keep a cost-benefit framework in mind also when performing a cost-effectiveness analysis, since mistakes can more easily be avoided in that way. After all, cost-benefit analysis is grounded in welfare economic theory, while the theoretical basis of cost-effectiveness analysis is somewhat unclear. The difference between cost-benefit and cost-effectiveness analysis is primarily that in the latter methodology, health effects are not valued explicitly in monetary terms. However, this may make cost-effectiveness results difficult to interpret in a consistent way. (For a survey of welfare economics, see for

example Johansson, 1991. For a survey of economic evaluation in health care, see for example Johannesson, 1996.)

Discounting of health effects is a controversial topic that has generated a lot of discussion among health economists. If health effects are valued directly in monetary terms, as in cost-benefit analysis, they should be discounted at the same rate as costs. If health effects are measured as gained years of life, which is common in cost-effectiveness analysis, it is not as evident what discount rate to choose. However, if cost-effectiveness is seen as a simplification of cost-benefits analysis (with a constant value per unit of health effect), it can be shown that it is not health effects as such that are discounted. Details are presented in section 3.7.6.

In section 4, I present some issues that are of interest for Study V and Study VI. Like discounting of health effects, or measurements of willingness to pay for medical treatments, the role of modelling and the handling of uncertainty have been important topics of research in medical cost-effectiveness analysis in recent years. In particular, I discuss modelling as a complement to experimental data from clinical trials, and statistical methods for analyzing and representing uncertainty in cost-effectiveness analysis. Finally, I present survival analysis techniques for estimating the costs attributable to a disease. Special statistical techniques are required for estimating the average lifetime and the average cost in survival studies, since the data in clinical and epidemiological studies are often incomplete. The incompleteness may be the result of patients dropping out from the study during its follow-up time. More generally, the lifetimes and costs for those who are alive at the end of follow-up are not known, and therefore have to be estimated statistically based on certain assumptions.

All of the studies in this thesis are interrelated in one way or the other. The investigation of the relationship between age-specific mortality and age-specific health care costs in Study III builds on figures on health and elderly care expenditures compiled in Study II. Furthermore, Study V builds on material in Study IV, but with a more elaborate model for extrapolating uncertainty in the estimation of costs and health effects. Study IV, V and VI are all related in a more indirect sense. All three studies deal with methods of handling survival data, but while Study IV and V use a modelling approach

(deterministic and stochastic respectively), Study VI instead uses a statistical approach in order to estimate survival and costs. See the summary of the studies on page 52 onwards for a quick review. After Study VI, there is a glossary of terms that are perhaps unfamiliar or forgotten.

## 2. Background

### 2.1. Prices and rationing

According to the textbook definition, economics is about the allocation of scarce resources between competing ends. A leisurely interpretation of this is that economics answers the question of who gets what, when, how (Friedman, 1976, p.3). Health economics then answers the question of who gets what, when, how in health and medical care.

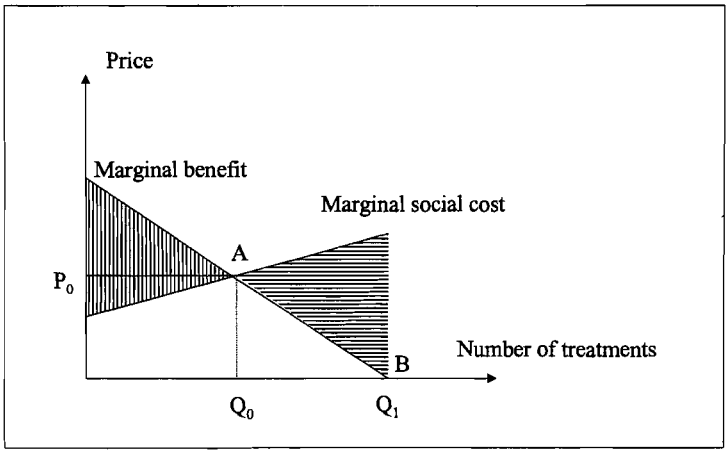
A central concept in economics in general, and in economic evaluations in health care in particular, is willingness to pay (WTP). The WTP is the maximum amount that a consumer would be willing to pay for a certain amount of a good. The *marginal* WTP is the amount that a consumer would be willing to pay for one additional unit of the good. To take a concrete example, suppose that an individual would be willing to pay SEK 12 for the first carton of milk bought in a given week, SEK 10 for the second, SEK 8 for the third, and SEK 6 for the fourth. If the actual price for one carton of milk were SEK 7, then the consumer would buy three cartons, since the cost of the fourth carton exceeds its marginal value for the consumer. The consumer's total willingness to pay for the three cartons is equal to SEK $12 + 10 + 8 = 30$. Since the cost is equal to SEK $3 \cdot 7 = 21$, the consumer surplus, i.e. the difference between WTP and cost, is SEK $30 - 21 = 9$.

For each given price per carton of milk, each consumer demands a certain number of cartons. If the individual quantities demanded for each given price are added together, the demand curve for this particular market is obtained. It describes how many cartons of milk that consumers would be willing to buy at any given price. The demand curve also shows the marginal benefit, i.e. the marginal WTP for one more unit of the good. In an analogous way, the supply curve represents the marginal cost of producing one more

unit. In the point of intersection between the demand and supply curves the market clears, i.e. the quantity demanded is equal to the quantity supplied. In this point marginal benefit is equal to marginal cost. (For a more detailed discussion of these concepts, see any text on microeconomics or price theory, e.g. Katz & Rosen, 1998).

A typical feature of health care is that the patients usually do not pay the full costs of their consumption on a fee-for-service basis. Often the out-of-pocket costs paid by the patients themselves are more or less negligible compared to the total treatment costs. This has consequences for the allocative efficiency. Consider the supply and demand schedule in figure 1. The demand curve, which shows the quantity of treatments that the patients' would be willing to purchase at any given price, can also be interpreted as the patients' marginal willingness to pay (marginal benefit) as a function of the number of treatments demanded. The supply curve, which shows the quantity of treatments that the health care provider would be willing to sell at any given price, can also be seen as the marginal social cost as a function of the number of treatments supplied. (I assume here that the health care provider takes all relevant costs into account, irrespective of by which parties they are borne.)

**Figure 1.** *Marginal benefit and marginal social cost for a medical treatment.*




Source: Adapted from Ståhl (1986, p.44).

Since the patients do not bear the full costs of the treatments they demand, they will demand a quantity close to $Q_1$, which is not socially efficient. If the treatment is

supplied beyond the point A, i.e. the quantity $Q_0$, then the marginal cost is higher than the marginal benefit. If the patient charge is zero we end up in point B, after which more treatments will not lead to any further gains in health. It may even be the case that in point B, the total social costs are larger than the total social benefits. The shaded area to the left measures the net benefits (benefits – costs) of the treatment for quantities from 0 to the socially efficient allocation $Q_0$. The shaded area to the right measures the net costs (costs – benefits) of further treatments beyond this point. If the area to the right is larger than that to the left, the total benefits are smaller than the total costs. The shapes of the supply and demand curves determines whether or not this will be the case for particular treatments.

In the public debate in Sweden it is sometimes claimed that costs should not be a consideration when health care is supplied to patients. Only need should count. However, the fallacy of those who argue for neglecting costs is that they do not take account of the fact that scarce health care resources have alternative uses. The resources spent on treatments beyond the socially efficient point A could be used with a larger benefit for other health care interventions, or for useful projects in any other fields contributing to human welfare (Ståhl, 1986). In the absence of rationing, the low fee policy carries the risk of diverting resources away from more productive uses.

Given that rationing is needed, the question is how it is to be carried out. It seems that in practice, rationing is often carried out implicitly through a queuing system. In the Swedish public debate, health care queues are seen as an anomaly that proves that health care provision is inefficient and/or that the allocated resources are insufficient. This viewpoint is natural if you neglect costs and promote a purely needs-based approach. From an economic point of view, however, the existence of queues does not in itself prove that the production is too low.[1] The reason for the existence of queues is rather that the price does not reflect equilibrium between supply and demand. More treatments are demanded than the health provider is willing to supply.

Since the queues are a sign of restricted supply and not necessarily of inefficiency, how can we determine whether or not a particular allocation of resources is efficient or not?

Here cost-benefit analysis may have a role to play. Before going into the details of cost-benefit analysis and related methods of economic evaluation, I will make a short detour into the characteristics of the medical care market. An interesting question is why the patients pay such a small part of their expenditures for medical care out of their own pockets. Why is the price for health care interventions typically not determined by the patients' marginal willingness to pay, as for most consumption goods and services sold on a market?

### 2.2. The economics of medical care

In a classic paper, often mentioned as something of a starting point for health economics as separate field of research, Kenneth Arrow (1963) argues that what explains the special features in the economics of medical care is the uncertainty in the incidence of disease and in the efficacy of treatment.

Arrow lists a number of stylized facts about the medical-care market:

- From the individual's point of view, the demand for medical care is irregular and unpredictable. Medical care is costly in itself, and also reduces earning ability.
- Since the customer cannot test the product before consuming it, there is an element of trust in the relation between patient and physician. A more ethical behavior is expected from a physician than from an ordinary businessman. Furthermore, the predominance of public and nonprofit hospitals is striking. This must be explained by the preference on the part of some group, whether donors or patients, against the profit motive in the supply of hospital services.
- Both patients and physicians are uncertain about the effects of medical treatment. However, both parties generally believe that the physician has a considerable informational advantage (asymmetric information).
- Supply is limited by restricted entry in the medical profession by way of licensing. This increases the costs of medical care. However, licensing is defended as guaranteeing a minimum of quality.

[1] In practice, it can be difficult to disentangle restricted supply and inefficiency. They often seem to go hand in hand, as in centrally planned economies.

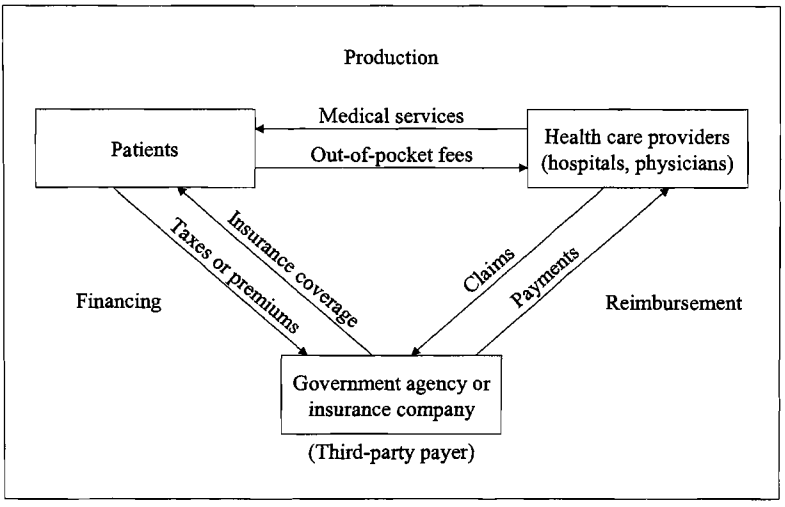
- The pricing practices are also unusual. In particular, there is extensive price discrimination by income.

Although Arrow wrote his paper almost 40 years ago, most if not all of his points are still relevant today, not only for the US but also for most other countries. The only point that is perhaps not relevant for today's Swedish medical care market is the one about extensive price discrimination by income. With the exception of the elderly care sector, patient charges in Sweden are independent of income. (On the other hand, those who have higher incomes generally pay higher taxes).

A natural solution to Arrow's first observation about the unpredictability and the high cost of disease would be private insurance, as for fire insurance. However, asymmetric information could easily result in adverse selection, i.e. those with ill health will be most eager to buy insurance, thus making it questionable whether such a market could be well functioning. For insurance companies, it could be difficult to sort out those with ill health from those with good health. If they could, the result would be that those who need insurance most, would have to pay the highest premiums, which could be objectionable in terms of equity. The typical solution to the problem of adverse selection in health insurance is group health plans through the employer, which is widespread in the US, or general tax-financed public health insurance as in many Western European countries.

Whether health care services are financed through taxes or through insurance premiums, we will get a situation where the incentives for cost control are low. The situation has even been compared to a dinner for three, where one of the guests orders, the second eats, and the third pays for it all. Neither patients nor health care providers have any natural incentives to hold the costs down. The general picture of flows of money and services in health care is illustrated in figure 2.

**Figure 2.** *The triangle of health care financing, production, and reimbursement.*




Source: Adapted from Santerre & Neun (1996, p.132).

Health economics is concerned with all parties and with all relations illustrated in figure 2. Important topics for research are health insurance, organization and financing of health care services, and medical cost-benefit analysis. Here I will primarily deal with how health care providers or third party payers can determine whether or not treatments are worthwhile from a societal viewpoint. Since the price mechanism is to a large extent out of work in the relation between patients and health care providers, the question is how to evaluate whether the benefits of treatments outweigh the costs. This is the realm of medical cost-benefit analysis.

## 3. Economic evaluations

### 3.1. Perspective of analysis

Costs and benefits can be seen from several different perspectives. Economic evaluations can be performed from four major viewpoints:

(a) society (considers costs and benefits for society as a whole)
(b) third party payers (primarily government and health insurance companies)
(c) the health care provider (clinics and hospitals)

(d) patients

Academic economists generally take the societal viewpoint. Nevertheless it can be of value to consider other viewpoints as well, since the costs and benefits for the different parties involved in decision-making determine their incentives. Their incentives in turn could be expected to affect their behaviour. Often savings from one party's point of view may mean higher costs for another.

### 3.2. Cost-benefit analysis

I will start the discussion of economic evaluations in health care by giving a description of cost-benefit analysis. The reason why it is a good idea to begin with cost-benefit analysis is that other common methods of evaluation that are used within the health care field can be seen as simplifications of cost-benefit analysis.

It is here assumed that we deal with "small" projects, i.e. projects that do not influence the market prices for goods and production factors in the economy (see Boadway & Bruce, 1984, or Johansson, 1991). For most medical care interventions this seems to be a reasonable assumption. Typical examples could be the introduction of a new pharmaceutical or a new surgical procedure.

Any project causes a reallocation of resources in the economy. The role of cost-benefit analysis is to assess whether society as a whole is better off with the project than with the best possible alternative use of the resources. The qualification that we should compare the project with the best possible alternative use of the resources is important. What investment alternative we choose as a basis for our comparison is of utmost importance for the outcome of the analysis. In many cases the resources used in the project are goods available on the market, and in the absence of market imperfections the market prices can be used directly for assigning costs to the inputs. On a perfectly competitive market the prices will reflect the true opportunity cost of the goods, but on many markets there are market imperfections that will distort market prices so that they do not reflect the opportunity costs. Examples of such imperfections (market failures) are monopoly and other forms of market power, and missing markets due to asymmetric

information, externalities, or public goods. The rationale for using cost-benefit analysis is that one or more of these market imperfections are present.

In principle, cost-benefit analysis can be applied both to private and public investment projects. In practice, it is more often used for public projects, especially infrastructure projects with environmental consequences that are not reflected in any market prices. Market imperfections can be used as an argument for government intervention, especially for public goods. However, the effectiveness of government interventions is often called in question, and therefore cost-benefit analysis may have a role for evaluating projects within the public sector.

Cost-benefit analysis is not much different from investment appraisal in the private sector, but there are some crucial differences:

(a) In investment appraisal in the private sector only consequences that affect the firm's profitability are included in the analysis, while in social cost-benefit analysis all relevant consequences are included, irrespective of whom they may concern.
(b) Market prices may be missing or misleading. Market prices may be missing because the inputs and outputs are not sold on the market. Examples could be clean air, or in the health care sector, lives saved. As mentioned above, market prices may be misleading in the presence of market failures, in which case market prices do not reflect the true social opportunity cost.
(c) There may be concerns for the effects of a public program on the income distribution. Higher weights may be attached to benefits to poor people than to benefits to rich people. The rationale behind this is diminishing marginal utility of income, which means that an extra dollar of benefits given to a poor individual is worth more than an extra dollar of benefits given to a rich individual (Stiglitz, 1988, p. 272).

In order to perform a cost-benefit analysis we need to estimate the benefits and the costs that will accrue in each period of time (e.g. in a year), and choose an appropriate discount rate in order to take account of the time value of money. In a cost-benefit analysis we value all inputs and outputs in monetary terms, so we can use the usual net-present-

value (NPV) criterion from investment appraisal as a measure of the project's desirability.

The net present value (NPV) of a health care intervention can be written as

$$NPV = -I_0 + \sum_{t=1}^{T} \frac{(B_t - C_t)}{(1+r)^t}, \quad (1)$$

where $I_0$ is the initial investment (if any), $B_t$ the benefits in year $t$, $C_t$ the costs in years $t$, and $r$ the discount rate.

In the absence of capital constraints, health care interventions with an NPV larger than zero are worth undertaking. If there are capital constraints, projects can be ranked according to their present value. The higher the NPV, the more desirable the project (Cullis & Jones 1998). If a project has a positive NPV, and the cost-benefit analysis has been properly performed, then the beneficiaries from the project gain more than the losers. This means that the project fulfills the compensation principle (or Kaldor-Hicks criterion), which says that a project is desirable if the gains from it are hypothetically possible to redistribute from gainers to loser so that everyone is better off with the project than without it. The idea behind this is that if compensation were costless, then actual redistribution would lead to a Pareto improvement, i.e. a gain in economic efficiency (Johansson, 1991; Johannesson, 1996).

In the health care sector the most difficult problem is to estimate the value of the benefits, since these are usually expressed as changes in health risks. For serious illnesses like cancer or heart failure the natural measure to use is the number of gained years of life. The number of gained years of life can be estimated from the change in mortality that is the result of a medical intervention. Since a gained life year in full health is more valuable than a gained life year in poor health we also have to take account of the quality of life when we compare different treatments.

We will now deal in turn with the estimation of costs, benefits, and the discount rate. The examples will be taken from the health care sector, but the general principles are of course valid for other fields as well.

## 3.3. Cost estimation

### 3.3.1. Types of costs

In economic evaluations of medical interventions costs are usually divided between direct and indirect costs (see e.g. Luce & Elixhauser, 1990). It should be noted that the costing terminology in health economic evaluation differs somewhat from that of cost accounting. According to Horngren & Foster (1991), direct costs are costs that can be identified to a given cost object in an economically feasible way, while indirect costs cannot.

In health economic evaluations direct costs are costs that are directly linked to the medical intervention. Examples are inpatient care at hospitals and nursing homes, outpatients care at primary care units, pharmaceuticals, diagnostic tests, prevention programs such as screening and vaccination, and rehabilitation. From a cost-accounting viewpoint, such costs may be direct or indirect. There may for example be administrative costs at hospitals that are difficult to link to specific treatments. Such costs would still be called direct in health economic terminology, while they would normally be classified as indirect in cost-accounting terminology. However, if overhead costs for administration and capital costs for buildings and equipment can be regarded as fixed in relation to a particular medical intervention they need not be included in the analysis.

Direct costs may also involve care provided by family members, and transportation to and from medical services. Indirect costs, on the other hand, are costs that are consequences of disease rather than linked to its treatment. These costs can be further subdivided into time costs and production losses (expressed in monetary terms), and intangible costs (non-monetary). Production losses include changes in productivity resulting from changes in health status, either because of absenteeism or lower productivity while on the job. Productivity losses by family members are included under

this heading as well. Time costs include time spent by patients seeking medical services, and time spent by family members attending the patient. In general, all leisure time forgone because of the disease belongs to this category. The question is how to value such costs. A common suggestion is simply to use the wage rate, since on the margin leisure time is about as valuable as working time. (Otherwise the individual would choose to work more or less.) Involuntary unemployment and fixed-hour working weeks pose problems for this, but as an approximation it is certainly better than nothing.

Intangible costs include pain, psychosocial suffering, and changes in social functioning and activities of daily living. In this area, the costs are hard to estimate. Measurement of the willingness to pay (WTP) for avoidance of pain and suffering is probably the most viable method. However, a risk of double counting arises here, since the WTP for changes in quality of life may include changes in income due to disease. These costs are already included in the productivity losses. The WTP estimation thus has to be performed in a way that takes account of only disease related pain and suffering, not of income loss. Ideally, the valuation others put on the patient's well-being should also be included among the intangible costs.

Another important distinction is that between average and marginal costs. An important principle in economics is that decisions should be based on evaluating marginal changes.[2] For example, the marginal cost of a Computed Tomography (CT) scan is much different from the average cost during a year. The charge or price usually reflects the average cost, including capital costs. This is the cost that a third party payer would care about. For the hospital it is the marginal cost of the CT scan that matters for decision making once the CT scanner is in place (Luce & Elixhauser, 1990; Dranove, 1995).

### 3.3.2. Cost estimation in practice

The increase (or decrease) in costs if we compare a medical intervention with its best possible alternative (often labeled "standard treatment") is usually straightforward when it comes to the direct treatment costs. We register all costs for medicines, medical visits,

hospital days etc. Ideally, the costs are collected on a patient by patient basis, but often only the resource utilization in terms of hospital days or days on a certain medication is available. The costs then have to be estimated by combining the patients' resource utilisation with unit costs obtained from average per diem costs (bed days) or costs per admission based on DRG weights. Diagnosis-Related Groups, or DRGs for short, is a system for classification of patients into groups with similar medical conditions and processes of care. DRGs are used for prospective payment of health care services.[3] Each DRG is assigned a relative weight that compares its costliness to an average for all DRGs (Folland et al., 1997). Medication costs can be estimated by calculating the average cost per DDD (defined daily dose). There are two problems associated with this kind of cost calculation. The first is that DRG-weights, or per diem costs, may not reflect the true opportunity cost, and the second is that we lose some variation in the data by using unit costs that are equal for all.

### 3.4. Estimation of benefits

#### 3.4.1. Is health different?

Some claim that health is different from other commodities, and that health therefore cannot be valued in monetary terms. Fuchs & Zeckhauser (1987, p.263) answer both yes and no to the question of whether health is different from other commodities. Health is a commodity in the sense that it contributes to utility and is affected by supply and demand, like any other commodity. However, health differs from other commodities in important ways. Fuchs & Zeckhauser (1987) emphasize that an individual's health status is largely self-produced and is strongly affected by initial endowments and the individual's consumption of other commodities. Health is difficult to trade inter-personally. Unless you donate a vital organ, you cannot sell your good health to someone who is ill. These conditions imply that health will not be valued equally at the margin by all individuals. In any case, I will here present a short introduction to the difficult task of valuing health effects in monetary terms.

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[2] Gregory Mankiw (2001) even includes this as one of "ten principles of economics" in his introductory economics text.

[3] Prospective payment – In order to control costs, the reimbursement fees for medical services are fixed in advance, irrespective of the actual cost for a particular case.

### 3.4.2. The value of a human life

When dealing with health risks in the evaluation of investments in medical care, some value must be assigned to saving lives. Several approaches to valuing a human life have been proposed. One is to value the loss of output that occurs when life is lost. However, using the wage rate as an estimate of expected gross earnings is only acceptable if there is perfect competition and full employment. Otherwise the wage rate will overestimate the marginal product of labour, since no allowance is made for the use of capital (Cullis & Jones, 1998). Another problem with this approach is that it makes use of a gross estimate that does not take into account the fact that the individual himself would consume some of the output that he produces. Taking only the loss to the survivors of the individual into account, we would arrive at the following estimate of the net output:

$$V = \sum_{t=j}^{T} \frac{S_j^t (Y_t - C_t)}{(1+r)^{-(t-j)}} \tag{2}$$

where $V$ is the value of a life, $r$ is the rate of discount, $Y_t$ is the gross expected earnings, and $C_t$ is the personal consumption expenditure of the individual during the $t^{th}$ period that is expected at time $j$, and $S_j^t$ is the probability in the current year $j$ of the person being alive in the $t^{th}$ year (Mishan, 1971). A deficiency of the human capital approach is that it implies that the value of life is to be gauged in terms of the objective of maximizing the gross national product. The net-output method can be seen as ethically objectionable, since the death of a person whose output is negative confers a net benefit to society. As Mishan (1971) says: "It restricts itself to the interests only of the surviving members of society: it ignores society ex ante and concentrates wholly on society ex post."

The shadow prices ought to reflect the values that the individuals themselves place on goods and services. An alternative way of estimating the value of life is thus to investigate how much individuals would pay for a reduction in the probability of the loss of life (Mishan, 1971; Jones-Lee, 1974). When it comes to investments in public safety and public health care we do not know in advance whose lives will be saved. Then the concept of the *value of a statistical life* is useful. Assume that we have somehow calculated the individual compensating variation (CV), i.e. the maximum sum that

the individual will be prepared to give up for a reduction in the probability of dying. Assume further that there are H affected individuals, b of which can be expected to be saved by the measure, and that the risk reduction b/H is a small number. Then it can be shown that the value of a statistical life is equal to $\Sigma_h dCV^h/b$, where $dCV^h$ is the marginal CV of individual *h*. The value of a statistical life is thus equal to the aggregate willingness to pay ($\Sigma_h dCV^h$) for the measure, divided by the number of lives saved (b) by it (Johansson, 1995). To take a concrete example, if a prevention program reduces the mortality of a disease from 20 to 10 people in a population of 1 000 000 people, and the aggregate willingness to pay for the program in that population is 150 MSEK, then the value of a statistical life is 150/10 = 15 MSEK.

There are two ways of estimating the willingness to pay (Johannesson, 1996):

- Hypothetical willingness to pay, which can be found by using questionnaires where people are asked to state their valuations (expressed preference approach).
- Actual willingness to pay, which can be found by studying, e.g., wage premiums for hazardous jobs, or expenditures on safety equipment (revealed preference approach).

The willingness-to-pay approach to shadow pricing has several methodological problems. It is doubtful that individuals are fully informed about the risks when they make choices, for example. Also, the probabilities involved in questionnaire studies about health and safety risks are often very small, and there is evidence that individuals find it difficult to cope with small probabilities (Cullis & Jones, 1998).

In the end, it is difficult to specify any precise cut-off value for when the incremental cost-effectiveness ratio of a health care intervention is too high to warrant its adoption. A problem with estimations of the value per year of life gained that are based on measurements of the willingness to pay for risk reductions is that the results differ widely between various types of study. For example, according to a study by Hirth et al. (2000), non-wage related risk reductions had a median value of USD 93 402 per quality-adjusted life-year (QALY), while wage premiums for hazardous jobs had a median value of USD 428 286.

In Sweden, the Swedish National Road Administration (Vägverket) uses results from surveys measuring people's hypothetical willingness to pay for saving statistical lives on the roads (SIKA Rapport 1999:6). What is measured is the amount of money people claim they would be prepared to pay out of their own pocket to reduce their expected (statistical) risk of being killed in a road accident. Based on these surveys, the Swedish National Road Administration has decided to use a value per statistical life saved of MSEK 13 when considering investments in road safety.

By combining statistics on fatal road accidents in Sweden and mortality data given in life tables, a value per life year gained can be calculated. The value of a statistical life can be seen as consisting of several components. In the formula below, $S_t$ is the survival probability in year $t$, $V_t$ is the value per year of life (or per quality adjusted year of life if quality weights are used) in year $t$, $Q_t$ is the quality weight in year $t$, and $r$ is the discount rate.

$$\text{Value per statistical life} = \sum_{t=0}^{T} \frac{S_t \cdot V_t \cdot Q_t}{(1+r)^t} \tag{3}$$

If we assume that the quality weight is set to 1 for all years, and the value per life year is constant (i.e. independent of age), then the value per life year gained $V_t = V$ can be expressed as:

$$V = \frac{\text{Value per statistical life}}{\sum_{t=0}^{T} \frac{S_t}{(1+r)^t}} \tag{4}$$

If we want to take account of quality of life, the formula could be slightly modified by introducing a quality weight $Q$ in the denominator (a constant quality-of-life weight is assumed here):

$$V = \frac{\text{Value per statistical life}}{Q \cdot \sum_{t=0}^{T} \frac{S_t}{(1+r)^t}} \qquad (5)$$

We see that since $Q \leq 1$, the value per QALY will always be (equal to or) higher than the value per life year.

Let us now take a look at an actual calculation of the value per life year based on fatal road accidents in Sweden, and carried out along on the principles outlined above. First, the number of victims in each age group is multiplied with the value of a statistical life. The estimated value of a life (MSEK 13) has been divided by a tax factor of 1.53 to take account of crowding out effects of public investments (SIKA Rapport 1999:6).[4] The estimated number of discounted life years lost is then calculated by using life tables for the Swedish population.[5] This is achieved by calculating the discounted expected remaining lifetime for each age group in the road accident statistics by using actuarial life tables, and then multiplying with the number of victims in each age group. Finally, the value per life year is calculated by dividing the total value of lives lost (MSEK 4 597) with the estimate of the total number of life years lost (10 346). The result is presented in table 1.

[4] It is actually the costs in a cost-effectiveness analysis that should be multiplied with the tax factor. Since the tax factor is usually not incorporated in health economic evaluations, the health effects that are used for calculating the threshold value per year of life gained are here divided with the tax factor in order to achieve the same effect.

[5] Strictly speaking, it is not life years that are being discounted. The discounting implicitly applies to the value per life year. Discounting of life years as such would lead to absurd effects. At a 3% discount rate, the discounted value of eternal life would be equal to 1/0.03 = 33.3 years. (See also section 3.7.6).

**Table 1.** *Calculation of the value per life year from 1997 road accident statistics.*

| *Age* | *Road accident victims* | *Assumed mean age* | *Discounted average remaining lifetime* | *Life years lost* |
|---|---|---|---|---|
| **0-6** | 13 | 3.5 | 30.36 | 395 |
| **7-14** | 11 | 11 | 29.41 | 324 |
| **15-17** | 14 | 16.5 | 28.57 | 400 |
| **18-24** | 67 | 21.5 | 27.71 | 1 856 |
| **25-44** | 152 | 35 | 24.70 | 3 754 |
| **45-64** | 113 | 55 | 18.02 | 2 036 |
| **65+** | 171 | 75 | 9.25 | 1 582 |
| **Sum** | 541 | | | 10 346 |

| *Value* | *(MSEK)* | *Value per life year* | *(SEK)* |
|---|---|---|---|
| | 541* 13/1.53 = 4 597 | MSEK 4 597/10 346 = | 444 295 |

Sources: Statistical Yearbook of Sweden 1999, and SIKA Rapport 1999:6.

If quality of life weights are used, the value will become higher. For example, a constant quality of life weight of, say, 0.85 leads to a value per QALY of 522 700 SEK. This value is obtained simply by dividing the value per life year in table 1 with 0.85.

It should be noted that these values are not directly comparable with the values per statistical life mentioned in Study IV, since the latter values have not been divided by a tax factor.

### 3.5. Cost-effectiveness analysis

In economic evaluations of health care programs costs are of course always measured in monetary terms, but health effects can be measured in various ways. The most common way has been to measure the health effects in "natural units" on a one-dimensional scale. The choice of unit depends on the nature of the disease, but for serious conditions like heart failure and cancer, the number of life years gained is the usual measure. This type of economic evaluation is called cost-effectiveness analysis.

Consider two alternative treatments A and B. The health effects of A are higher than those of B, but so are the costs. In order to compare costs and health effects for the two treatments, a so-called incremental cost-effectiveness ratio (R) can be formed:

$$R = \frac{\text{Cost (A)} - \text{Cost (B)}}{\text{Life years (A)} - \text{Life years (B)}} = \frac{\Delta C}{\Delta E} \quad (6)$$

If the cost-effectiveness ratio R is lower than some prespecified value, then treatment A is cost-effective compared to treatment B.

The problem is how to determine a reasonable threshold value for the cost-effectiveness ratio. According to Johannesson and Meltzer (1998), one of the most persistent myths in the cost-effectiveness analysis field has been that cost-effectiveness analysis avoids expressing health effects in monetary terms. A cost-effectiveness analysis essentially consists of estimating a cost function for health effects, but it does not in itself say whether a particular health care intervention should be implemented or not. Given a fixed health care budget, the health effects can be maximized, but since costs outside the budget are ignored, such an analysis is likely to be sub-optimal from a societal viewpoint. To be useful for decision making, a cost-effectiveness analysis therefore requires that the health effects be assigned a monetary value.

If health effects are measured in terms of life years gained, only the length but not the quality of life is taken into account. This problem can be remedied by introducing a quality weight, where all states of health are usually placed on a scale between 0 and 1, with 0 signifying death and 1 full health. This method is sometimes called cost-utility analysis, but it can also be seen as a special case of cost-effectiveness analysis where multidimensional health effects are combined into a single index. The cost-effectiveness ratio will be the same as above, but for a new definition of $\Delta E$, which will be measured in terms of quality-adjusted life years (QALYs) instead.

The advantage of the QALY is that it combines gains from reduced morbidity (quality gains) and reduced mortality (quantity gains) in a single one-dimensional measure (Drummond et al., 1997). There are three main ways of devising QALYs, 1) the rating scale method, 2) the standard gamble method, and 3) the time trade-off method. A problem with the first method is that it lacks theoretical foundation, and a problem with the two other methods is that the responses are to hypothetical choices. Preferences also depend on the amount and the quality of the information given to the respondents. The

individuals' valuations will also depend on personal characteristics, such age, sex and health status. In this context, it is debatable whether the appropriate respondents should be current patients, past patients, or members of the general public (Cullis & Jones, 1998; Johannesson, 1996).

A further problem is that a QALY is not generally a measure of utility, since two persons can have the same QALY status and yet experience very different utilities. Consequently, a rule that minimizes the total cost per QALY will not necessarily lead to the maximization of utility for the community. A QALY is regarded as having equal value to everyone, but the utility of a QALY may be different (Cullis & Jones, 1998; Drummond et al., 1997). Just as for other health effect measures, a monetary value per QALY has to be found in order to make useful decisions.

### 3.6. The inclusion of costs in added years of life

In health economic evaluations, future costs for related illnesses are usually included, but not costs for unrelated illnesses and general consumption. The reason why this is an issue for debate is that the theoretical foundations of cost-effectiveness analysis have been somewhat unclear (Meltzer, 1997). In order to investigate the welfare economic foundations of cost-effectiveness analysis, Meltzer developed a general expected utility model. The details of Meltzers model will not be given here, but the basic idea behind his approach is to set up an expression for the expected lifetime utility, where survival is dependent on medical consumption, and utility is dependent on both medical and non-medical consumption. The optimal combination of medical and non-medical consumption is then found by maximizing the expected utility, subject to the individual's budget constraint. The expressions obtained from the first order conditions of the optimization are finally rearranged to find a condition for the optimal allocation of health care resources.

A main conclusion from the model is that cost-effectiveness analysis should include the total change in future expenditures resulting from a medical intervention. It does not matter whether these expenditures are medical or non-medical. The intuition behind this is that the benefits of extending life include utility derived from the total consumption

expenditures rather than medical expenditures alone. Therefore the general consumption costs necessary to obtain that level of utility should also be included in the analysis (Meltzer 1997). As Meltzer says: "If the intervention had never taken place, those resources would have been available for other uses."

A complete economic evaluation from a societal viewpoint should include all future consequences of choosing one alternative rather than another. There is no reason to make a difference between medical and non-medical resource consumption. However, this may raise ethical concerns. Since the costs of added years of life are defined as the expected future difference between consumption and production, unemployed and elderly people carry the risk of receiving a lower priority than individuals participating in the labour force. In fact, many analysts have favoured traditional cost-effectiveness analysis over cost-benefit analysis precisely because it is seen as more equitable (Meltzer, 1997). However, as noted by Meltzer, it is better to discuss ethical issues openly rather than hiding them behind imprecise analytical techniques.

## 3.7. Discounting

### 3.7.1. Timing of costs and benefits in health care programs

Competing health care programs may have cost and effect profiles that differ considerably in the timing of their outcomes. For example, if an illness can be cured either surgically or by medication, then it is often the case that the surgical treatment requires a large initial outlay, but provides a quick cure, whereas for the medical treatment both costs and health effects are spread out over a longer time. An example is the choice between surgery or long-term medication with proton pump inhibitors in the treatment of reflux oesophagitis, a disease where acid-pepsin from the stomach is refluxed to the gullet, with ulceration and bleeding as a result. In such a case, the choice of discount rate may have a substantial impact on the result of a cost-effectiveness analysis. Preventive programs may also have different timing. Immunization programs generally give immediate benefits, whereas programs for hypertension and cholesterol screening give rise to benefits many years, or even decades, into the future. In order to compare different time profiles of costs and benefits, it is necessary to apply discounting, i.e.

money spent or saved in the future should account for less weight in health care decisions than money spent or saved now.

### 3.7.2. The social discount rate

The social discount rate, which seems to be the most sensible discount rate to use for health economic interventions, should reflect the society's rate of time preference, i.e. the rate of interest that society requires in order to forgo consumption today for consumption in the future. By definition, the social time preference discount factor is equal to the marginal rate of substitution between consumption in the current period and consumption in the next period. However, the social rate of discount should also take the allocation of resources between the private and the public sector into account. Ideally, no public investment should displace a private investment that has a higher social rate of return (Cullis & Jones, 1998).

### 3.7.3. Discounting in theory

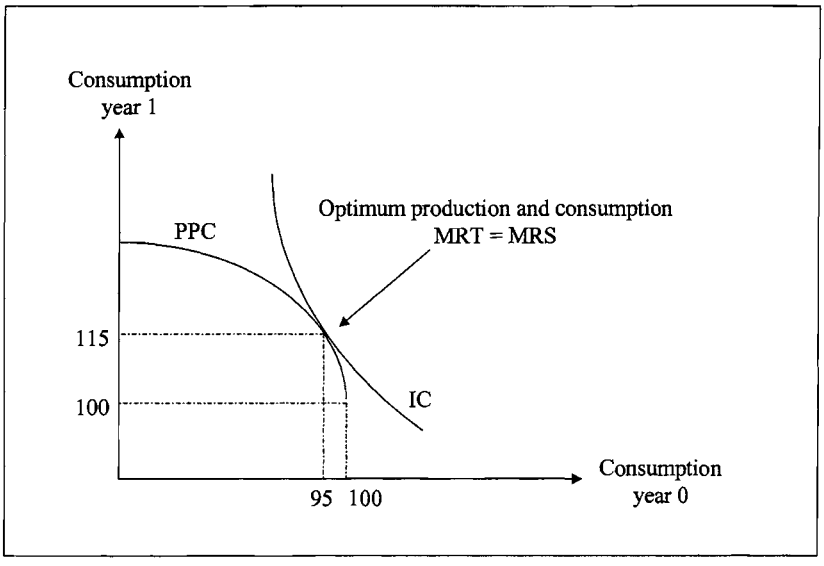
In order to understand what discounting is and where it comes from, it could be of value to consider some theory. Essentially, what value to assign to the social discount rate is based on three competing views, or some combination of these (Stiglitz, 1982).

- The social discount rate should equal the producer rate of interest
- The social discount rate should equal the consumer rate of interest
- The social discount rate should equal the social rate of time preference

A common view is that the social discount rate should be a weighted average of the producer rate of interest and the consumer rate of interest (Stiglitz, 1982; Johansson, 1991). In an ideal economy of the type encountered in economics textbooks, i.e. an economy without taxes, transaction costs, and credit rationing, and with full information and perfect competition, the producer and consumer rates of interest will in fact be identical. To see why, let us take a look at a simple textbook example (a Robinson Crusoe economy) that describes why discounting arises (the example is taken from Layard and Glaister, 1994). The basic question behind the discount rate is this: How much of our present consumption are we willing to give up in order to increase our future consumption? As we all remember, Robinson Crusoe lives alone on an isolated

island (at least before the arrival of Friday). He supports himself by fishing and by collecting coconuts. The coconuts need not concern us here, since they are not a scarce resource (Crusoe can easily collect more of them than he could possibly eat). The fish, by contrast, do not jump out of the sea by themselves. With the present equipment he can catch at most 100 fish a year. However, if he takes time off from fishing and spends it on improving his fishing equipment, he will be able to catch more fish next year. The tradeoff he faces is illustrated in figure 3.

**Figure 3.** *Optimum production and consumption over time in a two-period Robinson Crusoe economy.*




The production possibilities curve (PPC) describes his investment opportunities. It shows how many extra fish he will be able to catch next year if he gives up some of this year's consumption. His indifference curve (IC) shows consumption patterns over time between which he is indifferent, i.e. they give him the same utility. Crusoe will try to achieve the highest possible utility, given his time preferences of consumption and his production possibilities. The optimal consumption and production is given by the point at which the tangents are equal for the production possibilities curve and the indifference curve. At this point the marginal rate of substitution (MRS) between consumption this year and next is equal to the marginal rate of transformation (MRT) between fish

given up this year and fish gained next year. The MRS represents the slope of the indifference curve. This slope can also be described as $1 + \rho$, where $\rho$ is the marginal rate of time preference (or consumer rate of interest). The MRT represents the slope of the production possibility curve, which can also be described as $1 + r$, where $r$ is the marginal rate of return on investment (or producer rate of interest). In optimum, $\rho = r$. In this particular example, Crusoe gives up 5 fish this year in order to gain 15 fish next year. In optimum, Crusoe's marginal rate of time preference is about 30%, which is also the value of the marginal rate of return on investment. This means that for the last unit of fish given up by Crusoe, he gains 1.3 fish next year.

The most important lesson to be learned from this simple example is that the producer and consumer interest rates are identical and determined simultaneously by matching the production possibilities (investment opportunities) to the preferences of consumption over time. The optimal choice of consumption (=production) over time also determines the savings rate and the growth rate. In the Crusoe example, the savings rate is 5/100 = 5%, and the growth rate is 15/100 = 15%.

In practice, consumer and producer rates of interest are not equal. First and foremost taxation creates a wedge between consumer and producer rates of interest, but transaction costs, imperfect competition, the level of risk and other factors also play an important part. The *producer rate of interest* can be seen as an opportunity cost, namely the real rate of return on investments in the private sector. This rate, $r$, corresponds to the producer's marginal rate of transformation, $1 + r$, which should ideally be equal to the rate at which the producer can lend and borrow. The basic idea behind using this rate as the social rate of discount is that money spent on government programs could profitably have been invested in the private sector. This is a quite reasonable proposition. If a government program is not carried out, at least in principle the money saved could be used to reduce corporate taxes, thus enabling the producers' to reinvest the money in their businesses.

Apart from the problem of measuring the producer rate of interest, the assumption that the money not invested in public programs is instead invested in the private sector is questionable. Of course you could say that this is the appropriate discount rate because

it is the proper opportunity cost, i.e. the best alternative use of the money. However, that would disregard they way public programs are funded. In Sweden, at least, taxes are not earmarked to specific means. Thus it is difficult, if not impossible, to tie a certain public program to a certain tax.

The *consumer rate of interest* is equal to the consumers' marginal rate of substitution, i.e., if they are lenders the amount of income they require at time $t + 1$ to compensate for a decrease in income at time $t$. The marginal rate of substitution will be the same as the lending and borowing rates if the capital markets are perfect. If income taxes or indirect taxes are lowered, the consumers will increase both savings and private consumption. Those who promote the consumer rate of interest as a suitable discount rate for public investments base their claim on the observation that consumption is the sole end and purpose of all investments. Perhaps the most common view, however, is that the social rate of discount should be a weighted average of producer and consumer interest rates. This leaves the problem of how to do the weighting.

An alternative more theoretical approach is to postulate a social welfare function for the time preference of consumption. The social welfare function values the social utility associated with a certain level of consumption. According to this approach, the social discount rate should equal the social marginal rate of substitution as defined by the postulated social welfare function. However, choosing an appropriate social welfare function implies a difficult normative choice: Should the social welfare function be utilitarian, or of some other type? (For details of social welfare functions, see e.g. Johansson, 1991, chapter 3.)

### 3.7.4. The discount rate in practice

The most common approach is probably to use real consumer or producer interest rates as a basis for the social discount rate, rather than a discount rate based on a social welfare function. Under certain assumptions (no market imperfections, taxes or uncertainty), the consumer rate of interest will be equal to the producer rate of interest. However, in the real world these simplifying assumptions are not fulfilled. As a result of this, the producer interest rate is higher than the consumer interest rate. Since the social discount rate should be an estimate of the social opportunity cost, it is therefore

necessary to incorporate the effects of a project on both consumption and production possibilities throughout the economy.

Lind (1990) discusses two distinct approaches to this problem. The first approach is to build a simple model of the economy where marker imperfections are taken into account, then solve for the optimal policy and finally solve for the social discount rate that will produce the optimal policy. The result from such an optimization is usually that the social discount rate should be some weighted average of the marginal return on capital and the consumer's rate of time preference. The problem with this approach is that it is not easy to build a model of the economy that is both realistic and mathematically tractable.

The second approach described by Lind (1990) is to convert all costs and benefits to consumption equivalents and then apply a single rate of discount, the consumer rate of interest, to all cost and benefit streams. This is the so-called shadow price of capital approach. The shadow price is meant to give an accurate account of the opportunity cost, i.e., the highest alternative social value to be forgone. A shadow price is attributed to a good because the actual price is either inappropriate or lacking.

The principles of the shadow price of capital approach are the following. First compute the present value of a consumption stream generated by $1 of private investment on the assumption that the investment will produce a return equal to the marginal before-tax rate of return on private investment. These returns will be divided between consumption, taxes and savings and reinvestment over time. The present value of the infinite consumption stream should be computed using the consumer rate of interest as the discount rate. The resulting number is the shadow price of capital, which is then used to convert costs and benefits that take the form of investments into their consumption equivalents.

Though the shadow price of capital approach leads to a single discount rate for all projects, it is difficult to apply in practice, since it requires a lot of information: The marginal rate of return on private capital, the consumer rate of interest and marginal propensity to save, the rate of depreciation and reinvestment of depreciation expenses

by investors, and the marginal rate of taxation on capital income.

Another difficulty that applies to both of these approaches is that the opportunity cost of a project has to be evaluated at the margin. As Lind (1990) points out, these costs will differ depending on how the project is financed, what it displaces and what form the benefits have. A public program may be financed via a tax increase, a loan or within a fixed budget. An income tax increase, for example, will partially lower consumption, and partially lower savings. As mentioned earlier, it is also difficult to link any public program to a particular tax increase. In the case of financing within a fixed budget, any additional program will come at the expense of some other program or programs. Though it is probably easier to link a new program to displaced programs, it is nevertheless not easy to say what the relevant opportunity cost should be.

Apparently, there is no easy way the obtain a reasonably correct discount rate. Estimating the discount rate is ultimately an empirical question. Consequently, the value will be sensitive to how the measurement is carried out. A sensible approach, which I have already discussed, is to calculate some weighted average of real producer and consumer interest rates. According to Viscusi (1995), most estimates of the real risk-free rate of return to capital range from 1 to 3 percent. I have not made any attempts to investigate what this rate could be in Sweden, but I think that it would be appropriate to use discount rates of this magnitude in Sweden as well.

Another good benchmark that could be used to estimate a sensible discount rate for public programs is the real growth rate of the economy. The real growth rate could perhaps be seen to reflect the societal economic yield. If long-term historic growth rates for the industrialized countries were to be used as an indication of the relevant discount rates, a discount rate of about 2 percent would be the result.[6]

A third proposition could be to use the real interest for government loans on the international money market (Lind, 1990). After all, if a government program gives a lower marginal yield than the rate of interest on government debt, then it does not make much sense to carry it out. It would be better to use the funds to pay-off some debt

[6] Estimated from table 35-1 in Fisher, Dornbusch, and Schmalensee (1988).

instead. This approach would probably also result in a discount rate of about 2-3%. The real interest for government loans on the international money market would reflect an appropriate opportunity cost if government programs were entirely debt financed, which is not the case. How to take the whole financing mix including debt and taxes from corporations and consumers into account is, however, a complex problem.

All three figures mentioned above are in line with the recommendations of Lipscomb et al. (1996). They recommend using a real discount rate of 3 percent as the base case for economic evaluations in health care and medicine.

Individual consumer interest rates and time preferences could also be used as estimates for the social rate of discount. One problem in this area is that many consumers behave in a way that does not seem to be economically rational. Lind (1990) exemplifies with individuals simultaneously borrowing on their Visa cards, investing in retirement plans, and putting money aside for their children's educations. The puzzling thing about this is that the individual would be better off if he took money from the college fund instead of borrowing from the Visa card with its higher interest rate, and then put the money back into the college fund with the earnings he would use to pay off the Visa account. However, this behavior may not be as economically irrational as it seems. Behavioral economics suggest that people keep separate budgets for reasons of self-control. As Lind puts it, the person who regularly raided the children's college fund to pay off consumer debts might soon find that the children had no money for college.

If it is true that individuals split their assets into separate budgets to impose self-control of themselves, then their marginal rate of substitution will not be equal to the marginal rate at which they can transform present into future income. Economic theory implies that consumers should make intertemporal trade-offs so that their marginal rate of time preference equals the interest rate. Consistency over time and across situations is also implied by theory.

The problem is that research shows that the implications of the theory do not seem to hold very well for actual economic behavior. In reality, discount rates can vary from negative to several hundred percent per year depending on the context (Loewenstein &

Thaler, 1989). See also Ben-Zion et al. (1989), Chapman & Elstein (1995), Loewenstein & Prelec (1992), and Örtendahl (1996).

The pure individual discount rate seems to vary depending on the circumstances. It is thus hard to imagine that any consistent discounting policy could come out of such measurements. For one thing, a new measurement of consumer interest rates may have to made for every public program, since there is no a priori reason to believe that individual discount rates for environmental choices, for example, would apply equally well to health care decisions. There could also be substantial differences between measured discount rates for different types of health care programs, in a way that is out of line with the relevant opportunity costs. Market interest rates are in my view preferable to surveys using either hypothetical questions, or relatively insignificant choices, since the market rates express revealed preferences about important intertemporal decisions.

### 3.7.5. On the discounting of health effects

It is uncontroversial that if the future health benefits are valued in monetary terms, then the same discount rate should be applied to both benefits and cost. However, the question of whether health effects not valued in monetary terms should be discounted, and if so, at what rate, remains an issue for debate.

Drummond et al. (1997, p.107f) mention a couple of common reasons for not discounting health effects: (1) Individuals cannot invest in health or trade flow of healthy years through time. (2) Discounting life years gained in the future is unfair to future generations. Why should their life years count for less than ours? Even if future generations can be expected to be wealthier than we are, it is not certain that their health will also be better.

Arguments in favor of discounting health effects have also been put forward. The argument most difficult to refute has been the postponement argument, also called the Keeler-Cretin paradox after its originators. Leaving health effects undiscounted while discounting costs can lead to absurd effects. According to Keeler & Cretin (1983), the discount rate for monetary and nonmonetary effects must be equal. They claim that if

costs but not health benefits are discounted, then the decision-maker will be paralyzed. No matter how attractive a program is, there is always a superior delayed program. Thus no program could ever be started, because it will always be better to defer it to a later period in time. In fact, the program will be postponed indefinitely into the future.

Johannesson (1996, p.162) illustrates the postponement argument with a simple example: A program yields 10 gained life-years this year and costs $100 000. The cost-effectiveness ratio is thus $10 000. An identical program can be carried out next year at the same costs and with the same effects. If the cost next year is discounted at 5% while the gained life years are left undiscounted, then the cost-effectiveness ratio is $9500. Extending this argument to the year after next year, and so on, shows that it is profitable to postpone the project eternally, since the cost-effectiveness ratio is continually sinking lower and lower. Peculiar spending patterns may occur even if the discount rate is not zero for health effects. In fact, any cost-effectiveness analysis using lower discount rates for benefits than for costs will display a strange behavior.

The postponement argument has not been left undisputed. Parsonage & Neuburger (1992, p.74) claim that Keeler & Cretin have applied the criteria of cost-effectiveness incorrectly. The postponement argument would only be valid if the projects are mutually exclusive. In reality, Parsonage & Neuburger note, a decision-maker would go ahead with a worthwhile project even if the benefits will be more highly valued in the future, and then review the possibility of doing it again later. Cost-benefit calculations are not used for setting the size of health care budgets or their distribution over time, but rather for setting priorities within a fixed yearly budget. Therefore, it is not relevant to consider the effect of differential timing on the cost-benefit ratios.

Lipscomb et al. (1996, p.224) are not of the same opinion. Many cost-effectiveness analyses in health care are not carried out under the constraints described by Parsonage & Neuburger, and without such contex-specific information it is sensible to take the postponement argument into account, i.e., discount costs and health benefits at the same rate.

Another argument for a positive discount rate for health effects considers the indi-

vidual's possibilities of trading of health over time. In fact, health is perhaps not so different from other commodities as one may like to think. Even though trading health between individuals is not possible, an individual can so to speak invest in her own health and thus make trading through time possible. For example, smoking and drinking can give immediate pleasure, at the expense of a potentially damaged future health. (Rational addiction hypothesis). Likewise, healthy food and physical exercise can be seen as sort-term sacrifice that will probably promote long-term well being.

Since the risks of for example smoking are well known in the industrial countries, the prevalence of smoking would seem to imply some positive rate of time preference. Instant well being created by the nicotine is traded for increased health risks in the future. A high fat intake, excessive alcohol consumption, and other potentially harmful behavior can also be seen in this way. But is this really an argument in favor of discounting? Does the existence of widespread behavior that gives short-term gratification at the expense of long-term health risks mean that policymakers should take it into account? Not necessarily, since the fact that a certain behavior exists does not make it justified.

### 3.7.6. Is it really health effects that are being discounted?

In the economic evaluation of bisoprolol (Study IV), we state that life years were discounted at a real rate of 3%. Discounting of health effects such as life years is a controversial issue in health economics. However, in an analysis such as that presented in paper two, is it strictly correct to say that it is life years that are being discounted? Not really, as I will show below. The apparent discounting of life years is actually a consequence of the fact that we eventually have to compare the cost-effectiveness ratio with a monetary threshold value in order to decide whether or not the treatment is cost-effective.

In the equation below, a simplified cost-benefit formula for a medical intervention is shown. $S_t$ represents the survival probability, $V_t$ the value of the life, and $C_t$ the net costs, all in year t. The discount rate is as usual represented by $r$. The medical intervention is worth undertaking if the benefits exceed the costs, i.e. if the inequality is fulfilled.

$$\sum_{t=0}^{T}\frac{S_t \cdot V_t}{(1+r)^t} - \sum_{t=0}^{T}\frac{S_t \cdot C_t}{(1+r)^t} > 0 \tag{7}$$

If we rearrange the above equation, so that we get a ratio with the sum of discounted costs in the numerator and the sum of discounted benefits in the denominator, then the following expression is obtained:

$$\text{C/B - ratio} = \frac{\sum_{t=0}^{T}\frac{S_t \cdot C_t}{(1+r)^t}}{\sum_{t=0}^{T}\frac{S_t \cdot V_t}{(1+r)^t}} < 1 \tag{8}$$

If we assume that the value per life year is constant for all $t$, then $V_t = V$ can be moved from the sum in the denominator to the right hand side of the inequality sign. We have now obtained a cost-effectiveness ratio, with $V$ as a threshold value.

$$\text{C/E} - \text{ratio} = \frac{\sum_{t=0}^{T}\frac{S_t \cdot C_t}{(1+r)^t}}{\sum_{t=0}^{T}\frac{S_t}{(1+r)^t}} < V \tag{9}$$

In the denominator of the inequality above, we have what appears to be a sum of discounted life years. However, since we started from a cost-benefit formulation, we can see that the reason for discounting the life years is that the life years were originally multiplied with a monetary value. Thus we do not discount life years per se. It is instead the monetary value per year of life ($V$) that is implicitly discounted. Otherwise the cost-effectiveness ratio could not be compared with the threshold value $V$ in a correct way.

The rearrangement of formulas from a cost-benefit formulation to a cost-effectiveness formulation also illustrates that cost-effectiveness analysis can be viewed as a subset of cost-benefit analysis. Essentially, a cost-effectiveness analysis is a cost-benefit analysis with a constant price (willingness to pay) per health effect for all individuals and for all sizes of the change in health (Johannesson, 1996).

A note should perhaps also be added about possible growth over time in the costs of added life years. We assumed, rather unrealistically perhaps, that the costs of added years of life would remain the same during all years. A more reasonable assumption would have been to let these costs grow with, say, about 2 percent per year in real terms. The value per life year could also be expected to grow over time. A simple way of introducing a constant growth rate of costs and benefits is to adjust the discount rate. If the expected growth rate is $g = 2\%$, then with good approximation we can let the new discount rate be equal to $r - g = 3\% - 2\% = 1\%$ (See Gravelle & Smith, 2001, for a good treatment of this, and other topics dealt with in this section).

## 4. Modelling, data analysis, and uncertainty

### 4.1. Clinical trials as a basis for economic evaluations

An ideal health economic evaluation would estimate costs and health effects as they would occur in actual clinical practice. However, it is difficult to perform such a study from scratch, since it would require a controlled naturalistic study comparing two treatments in a realistic setting, often over a period of several years. Such a study would be expensive and time-consuming to perform, and thus it is not surprising that economic evaluations are usually based on epidemiological data or clinical-trial data comparing different treatments. Another problem with a naturalistic study is that it could only be performed once the treatment is reasonably widespread. However, if the purpose is to aid decision making in evaluating whether a particular treatment should be adopted or not, then an early economic evaluation that is performed before the treatment has become part of established medical practice is needed. An early economic evaluation generally has to be based on data from a randomised controlled clinical trial. An advantage is that such studies are always available for new pharmaceuticals, since industry-sponsored clinical trials are required for their registration.

A further advantage of basing an economic evaluation on a clinical trial is that clinical trials have a high internal validity, i.e. demonstrates the safety and efficacy of the treatment for the population included in the study in a non-biased and reliable way. How-

ever, the external validity, i.e. the possibility of generalising the results to patient groups not included in the study, is more questionable (Rittenhouse, 1995). The external validity may vary from case to case, depending on how representative the patient group in the clinical trial is, compared with a more general population of patients with the same disease. Patients who participate in clinical trials are usually younger and less ill than the whole population of patients who are afflicted with the disease. The typical patient may also suffer from several diseases, while participants in clinical trials should ideally suffer from only the disease that the treatment under evaluation is intended to cure.

### 4.2. Modelling as a complement to clinical-trial data

One way of solving the problem of representativeness associated with clinical trials is to use modelling assumptions that take account of the differences between clinical trials and actual or expected clinical practice. A disadvantage of clinical trials is that the follow-up time is usually rather short. For medical purposes, there is no reason to let a clinical trial go on longer than is necessary for establishing the safety and efficacy of the treatment.

If the survival of the patients is only measured during the follow-up time of the trial, some kind of assumption has to be made about costs and health effects after the end of the clinical trial. What we would like to know is the total number of gained life years over the entire lifetime rather than the difference in survival during a few months. The major part of both costs and health effects often has to be evaluated by modelling. That does not necessarily imply that the modelling has to be based on ad hoc assumptions. Extrapolation of trial results by statistical methods can be used, often in combination with data from epidemiological studies or other clinical trials. In the cardiovascular field, for example, the Framingham Heart Study has been and continues to be an important source of epidemiological data.[7]

If trial results are extrapolated directly from the study, the major problem is to assess how the difference in health effects during the trial will evolve. If the difference in survival between two alternative treatments is measured, for example, will the diffe-

rence increase, decrease or perhaps remain constant over time? Actually, this is a question that cannot even be answered with hindsight. It is in a sense purely hypothetical, since, after the trial, all patients will have access to the same treatment, and the patients who do not receive a new treatment even after a successful clinical trial may differ from those who do.

As the heart failure trial CONSENSUS has shown, the difference in effect between the treatment group and the placebo group can persist several years after the end of the clinical trial. The patients in the treatment group, who received an ACE-inhibitor called enalapril in addition to traditional heart failure therapy (diuretics and digitalis), had a lower mortality than the placebo group even after the clinical trial, in spite of the fact that all patients could then potentially be treated with ACE-inhibitors (Swedberg et al., 1999). Even if this is an isolated example, it nevertheless shows that it can be reasonable to assume that beneficial treatment effects will persist after the end of clinical trial.

In the economic evaluation of bisoprolol (Study IV), we therefore explored several alternative assumptions about the survival after the trial in the sensitivity analysis, such as a persistent mortality difference and a mortality difference that converges during the course of a few years. If costs of added years of life were included, the cost-effectiveness ratios were not very sensitive for different assumptions about the survival after the trial. If costs of added years of life were not included the results were on the contrary quite sensitive to the survival assumptions. However, since our cautious base-case assumption was that the mortality equalises immediately after the end of a trial, these assumptions all lead to lower cost-effectiveness ratios. Thus the assumption of what happens with the difference in survival between bisoprolol and placebo after the end of the trial was not a critical parameter in this case.

### 4.3. Deterministic and stochastic models

Deterministic relationships seldom occur for biological or medical data, since patients differ in their response to a medicine. Consequently, exact prediction is not possible for

[7] The Framingham Heart Study is an ongoing epidemiological study that was initiated in Framingham,

phenomena where the influence of several unknown factors is sizable, but it may still be possible to predict to within a known confidence interval.

In the economic evaluation of the beta blocker bisoprolol presented in Study IV, the number of added life years after the end of follow-up was deterministic, i.e. it was the same for all patients. This made it hard to estimate the uncertainty of the final results in any meaningful way. A more realistic approach requires stochastic modelling of the survival after the trial. In a stochastic model we do not specify the survival time exactly as in the deterministic case; instead we specify a probability function for the survival. This does not change the point estimate of the cost-effectiveness ratio, but it does make it possible assess how the cost-effectiveness ratio is distributed. As it turns out, however, new problems are created when we try to assess the uncertainty of the cost-effectiveness estimate. These problems and how to handle them are the themes of the next three sections.

### 4.4. Methods for the quantification of uncertainty in cost-effectiveness analysis

Much of the recent debate about the quantification of uncertainty in medical cost-effectiveness analysis has centred on the question of how to obtain confidence intervals for cost-effectiveness ratios. O'Brien et al. (1994) noted that economic evaluations of medical treatments have to an increasing extent been based on data from clinical trials. A natural step would therefore be to extend the stochastic analysis of experimental medical evidence to experimental cost-effectiveness data. Traditionally, the uncertainty of medical cost-effectiveness analyses has been assessed through sensitivity analysis. However, sensitivity analysis is associated with some problems that often make the results unreliable. O'Brien et al. (1994) list three major limitations: 1) The choice of variables to include in the sensitivity analysis as well as the ranges of uncertainty are at the discretion of the analyst. 2) It can be difficult to assess what variation of the results is acceptable. 3) Since variables are often varied one at a time, the interactions between variables carry the risk of being neglected.

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Massachusetts in 1948 (Kannel, 2000).

O'Brien et al. (1994) propose instead that confidence intervals should be constructed for cost-effectiveness analyses with more or less standard statistical methods developed for analysing clinical trials. A statistical difficulty in cost-effectiveness studies is that the cost-effectiveness is usually expressed as a ratio. The main solution proposed by O'Brien et al. (1994) is to use a Taylor series approximation[8] for determining the variance of the ratio of the two stochastic variables average costs and average effects. It can be shown that if $R = \Delta C/\Delta E$, then the expected value of $R$ is

$$E[R] \approx \frac{\Delta C}{\Delta E} + \frac{1}{\Delta E^2}\left(s^2_{\Delta E}\frac{\Delta C}{\Delta E} - r_{\Delta E \Delta C} s_{\Delta E} s_{\Delta C}\right), \tag{10}$$

and the variance of $R$ is

$$V[R] \approx \frac{1}{\Delta E^2}\left(s^2_{\Delta E}\left(\frac{\Delta C}{\Delta E}\right)^2 + s^2_{\Delta C} - 2r_{\Delta E \Delta C} s_{\Delta E} s_{\Delta C}\frac{\Delta C}{\Delta E}\right).^9 \tag{11}$$

The problem is that this method is in most cases incorrect, as observed by Van Hout et al. (1994). If two stochastic variables both follow a standard normal distribution, then the ratio of these stochastic variables will follow a Cauchy distribution, which has neither a finite mean, nor a finite variance (Van Hout et al., 1994). If the averages are not standard normal, the distribution is generally unknown (Briggs and Fenn, 1998). However, if there is a substantial risk of $\Delta E$ being close to zero, the distribution is likely to have properties similar to those of the Cauchy distribution, i.e. the tails are much thicker than for a normal distribution, and the mean and variance are perhaps not even defined. The Taylor series method will then give a poor estimate of variance.

Another, and in my view better, method is the application of Fieller's theorem to cost-effectiveness ratios (Fieller, 1954). Fieller's theorem is based on the assumption that $\Delta C$ and $\Delta E$ follow a joint normal distribution (Briggs and Fenn, 1998). The expression $\Delta C -$

[8] This means that the function is approximated by a truncated power series expansion. See any text on calculus, e.g., Edwards & Penney (1998).

[9] Note that in O'Brien et al. (1994), $E[R] = \Delta C/\Delta E$. This is probably not correct if a Taylor series method is used. See Rice (1994). $V[R]$ is the same as here, however.

$R \cdot \Delta E$ will then be normally distributed. If it is then divided by its standard deviation, the ratio will follow a $N(0, 1)$ distribution:

$$\frac{\Delta C - R\Delta E}{\sqrt{V(\Delta C) + R^2 V(\Delta E) - 2R \cdot Cov(\Delta C, \Delta E)}} \sim N(0,1) \tag{12}$$

Here, $V(\Delta C)$ and $V(\Delta E)$ are the variances for the incremental costs and effects, and $Cov(\Delta C, \Delta E)$ is the covariance between incremental costs and effects. If the above expression is set equal to $z_{\alpha/2}$ and then rearranged, we get a quadratic equation in $R$ of the form $aR^2 - 2bR + c = 0$:

$$\left(\Delta E^2 - z_{\alpha/2}^2 V(\Delta E)\right)R^2 - 2\left(\Delta E \Delta C - z_{\alpha/2}^2 Cov(\Delta E, \Delta C)\right)R + \left(\Delta C^2 - z_{\alpha/2}^2 V(\Delta C)\right) = 0. \tag{13}$$

If this equation is then solved for $R$, we get a confidence interval for the cost-effectiveness ratio. A potential problem is that both roots of the quadratic equation can be imaginary. $R$ is then defined for the whole real line (Casella and Berger, 1990). This will be the case if the coefficient $a = \Delta E^2 - z_{\alpha/2}^2 V(\Delta E) < 0$ (Blomqvist, 1998).

Later developments in the study of uncertainty in cost-effectiveness analysis have essentially gone in two directions, a Bayesian trail and a bootstrapping trail. The main advantage of the Bayesian approach is that evidence from several sources can be combined in a statistically valid (but not uncontroversial) way. The main disadvantage is that a prior distribution is needed. The computations can be also difficult, but thanks to developments in computing this is a lesser problem than it used to be. The main advantage of non-parametric bootstrapping techniques is that no distributional assumptions have to be made, in contrast to both classical parametric and Bayesian statistics. This is a potential advantage in cost-effectiveness studies, since distributions of cost-effectiveness ratios can not be expected to follow assumptions of normality.

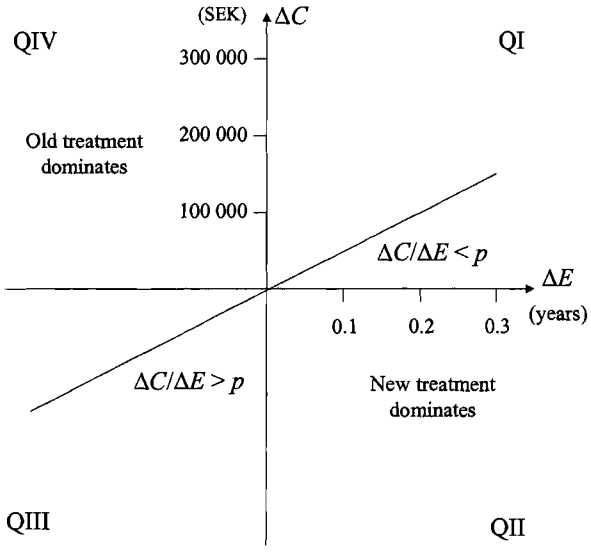
Perhaps with the exception of the bootstrapping method, all of the above methods can be rather diificult to apply in practice, since they depend on assumptions that may or may not be fulfilled in particular cases. Of course, we may also question why we should

have to deal with ratios at all. To set the stage for a further discussion of uncertainty, I will begin by describing the problem of interpreting cost-effectiveness ratios. In this context, I will also present the net benefit method, which is not plagued by the same problems.

### 4.5. Cost-effectiveness ratios on the cost-effectiveness plane: The problem of interpretation

A deficiency of the cost-effectiveness ratio as a measure of cost-effectiveness is that its interpretation is ambiguous. Consider the cost-effectiveness plane in figure 4 below. The incremental effect is here defined as $\Delta E = \overline{E}_1 - \overline{E}_0$, and the incremental costs as $\Delta C = \overline{C}_1 - \overline{C}_0$. (For reasons of notational economy, I have suppressed the bars over $\Delta E$ and $\Delta C$ throughout). The index 1 represents the treatment under investigation (the "new" treatment) and 0 the alternative treatment (the "old" treatment). The threshold cost-effectiveness ratio, i.e. the maximum amount that society would be willing to pay for an incremental gain in health, is represented by $p$. The threshold value $p$ is reflected in the slope of the "price line" in figure 4.

**Figure 4.** *Decision-making on the cost-effectiveness plane.*



For the new treatment to be unquestionably preferable to the old treatment, it must lie in quadrant II (QII), i.e. it is both more effective ($\Delta E > 0$) and less costly ($\Delta C < 0$). In quadrant IV, the old treatment dominates, since it is both more effective and less costly. In quadrants I and III we are facing a trade-off. In QI the question is how much we are willing to pay for an increased effectiveness (here in terms of added years of life). In QIII the question is how large the cost savings must be for us to accept the decreased effectiveness. If the price we are willing to pay for a gained year of life is equal to the savings at which we are willing to accept a lost year of life, and this amount is constant for all values of ΔE, then the border of acceptability between the old and the new treatment can be illustrated with a straight line going through the origin, and with a slope that is equal to this constant amount (about SEK 500 000 in figure 4). The new treatment is cost-effective at all points lying below the line.

In terms of cost-effectiveness ratios, the new treatment is cost-effective in QI if the inequality $\Delta C/\Delta E < p$ holds. In QIII, however, the condition for cost-effectiveness is $\Delta C/\Delta E > p$. Within both QI and QIII the cost-effectiveness ratios will always be positive. The difference lies in the interpretation of the cost-effectiveness ratios. In QI the amount that we have to pay must not exceed $p$, and in QIII the savings must not be lower than $p$. This contributes to making the interpretation of the cost-effectiveness ratios ambiguous, especially since the two cases are not necessarily equivalent. The willingness to pay may very well differ from the willingness to accept (Stinnett and Mullahy, 1998).

A solution to the problem of ambiguity is to use the net benefit formulation of cost-effectiveness instead of the cost-effectiveness ratio (Tambour et al., 1998; Stinnett and Mullahy, 1998). The condition for cost-effectiveness according to the net benefit method can be obtained by noting that the treatment is cost-effective below the straight line cutting through the cost-effectiveness plane. That line has the equation $\Delta C = p \cdot \Delta E$, so the condition for cost-effectiveness can be expressed as $p \cdot \Delta E - \Delta C > 0$. The net benefit of treatment 1 compared to treatment 0 is defined as $NB(p) = p \cdot \Delta E - \Delta C$. This definition of the net benefit follows Tambour et al. (1998), and is a net *monetary* benefit. Stinnett and Mullahy (1998) instead divide $\Delta C$ with $p$ in order to obtain a measure of the net *health* benefit, $NHB(p) = \Delta E - \Delta C/p$.).

The reformulation in terms of a net benefit is actually equivalent to both of the cost-effectiveness criteria defined above, which can be seen if the inequalities are rearranged (Note that if $\Delta E < 0$, then $\Delta C/\Delta E > p \Leftrightarrow \Delta C < \Delta E \cdot p$, i.e. we have to switch the sign of the inequality.) The net benefit criterion of cost-effectiveness has the benefit of being unambiguous, which is certainly a practical advantage.

### 4.6. Statistical properties of the net benefit method

The net benefit approach to medical cost-effectiveness analysis has been developed in response to statistical problems with cost-effectiveness ratios. As we have seen, there are two problems with cost-effectiveness ratios. First, a ratio of two normally distributed random variables is not normally distributed. In particular, the variance will be very wide, or even infinite as for a ratio of two standard normal variables. Second, the interpretation of the cost-effectiveness ratio is ambiguous. This makes it difficult to compute a confidence interval for a cost-effectiveness ratio in a traditional way.

It should perhaps be mentioned that these problems have nothing to do with the fact that the distribution of individual costs is often highly skewed in medical care records. Most patients have low costs, while a few have very high costs. Thanks to the central limit theorem of probability theory, the average costs (and average benefits) in a sample will be approximately normally distributed regardless of the distribution of individual costs, given that the sample size is large enough (for the central limit theorem, see, e.g., Hogg & Tanis, p.262f ).

Special techniques such as Fieller's theorem have been applied to cost-effectiveness ratios. The net benefit (NB) method makes the need for such techniques much smaller. The statistical advantages of the method of net benefits are discussed, e.g., in Löthgren and Zethraeus (2000), Stinnett and Mullahy (1998), and Zethraeus et al. (2002). According to Zethraeus et al (2001), a parametric confidence interval for NB can be constructed by estimating the variance of NB as

$$\hat{\sigma}^2_{\mathrm{NB(p)}} = \sum_{i=0}^{1} \frac{1}{n_i}\left(p^2 s^2_{E_i} + s^2_{C_i} - 2pr_i s_{E_i} s_{C_i}\right), \tag{14}$$

where $E_i$ and $C_i$ are random variables representing the costs and effects of the intervention, $s_{Ei}^2$ and $s_{Ci}^2$ represent the sample variances of costs and effects, $r_i$ is the sample correlation coefficient between costs and effects, and $n_i$ is the number of observations for each treatment. By the central limit theorem, the net benefit (NB) is asymptotically normal, and a two-tailed confidence interval can be constructed as

$$NB \pm z_{\alpha/2}\sqrt{\hat{\sigma}^2_{NB}}\,, \tag{15}$$

where $z$ is the test statistic for the standard normal distribution.

A nonparametric confidence interval for NB based on bootstrapping can also be constructed, as described in Stinnett and Mullahy (1998), Löthgren and Zethraeus (2000), or in statistics books such as Efron & Tibshirani (1993). One advantage of the NB is that its estimator is asymptotically normal under quite general assumptions, even if the joint distribution of costs and effects is non-normal.

What then is bootstrapping? The bootstrap method is a simulation procedure for investigating the variability of a parameter, e.g. the expected value, which is a function of a distribution function $F$ (Rice, 1994; Efron & Tibshirani, 1993). Efron has named the method "the bootstrap" since the data, in a figurative sense, "pull themselves up by their own bootstraps" by generating resampled data sets through which their variability can be estimated. Let us say that an empirical investigation has generated a sample $x_1, x_2, \ldots, x_n$ of independent random variables, which are all distributed according to some unknown distribution function $F$. We wish to estimate the parameter $\theta$, e.g. the mean. If it is doubtful that the parameter $\theta$ is a function of a particular standard statistical distribution, we can use non-parametric bootstrapping to estimate it. The basic idea of the bootstrap is to replace the unknown distribution function $F$ with the empirical distribution $F_n$ as an approximation to $F$. For simulation purposes, we see $F_n$ as a discrete probability distribution, where each observed value $x_1, x_2, \ldots, x_n$ has a probability equal to $1/n$. In order to approximate a certain parameter $\theta$, we draw samples of size $n$ with

replacement from the observed values $x_1, x_2, \ldots, x_n$. For each new bootstrap sample, a value of the parameter is calculated by plugging in the sample of size $n$ in the formula for $\theta$. The procedure is repeated a very large number of times, say $N$, producing values $\theta_1^*, \theta_2^*, \ldots, \theta_N^*$, where the star indicates that the estimates are simulated.

The standard deviation of $\hat{\theta}$, the estimate of $\theta$, is then estimated by

$$s_{\hat{\theta}} = \sqrt{\frac{1}{N-1}\sum_{i=1}^{N}\left(\theta_i^* - \bar{\theta}^*\right)^2}, \tag{16}$$

where $\bar{\theta}^*$ is the mean of $\theta_1^*, \theta_2^*, \ldots, \theta_N^*$.

A confidence interval can either be constructed parametrically by using the mean and the standard deviation, $\bar{\theta}^* \pm z_{\alpha/2} \cdot s_{\hat{\theta}}$, or by using the percentile method. In the percentile method, the 2.5th and 97.5th percentile of the bootstrap replications $\theta_1^*, \theta_2^*, \ldots, \theta_N^*$ defines a 95% confidence interval. For $N = 1000$, these will be the 25th and 975th order statistics (values from the ordered series of bootstrap replications). These values define the upper and lower limits for the 95% confidence interval.

It should perhaps be mentioned that even if the distribution function $F$ is known, a bootstrapping procedure can still be useful, e.g. if it is difficult to calculate a certain measure of location $\theta$ analytically.

To summarize the method:

1. Approximate the unknown distribution function $F$ with the empirical distribution $F_n$, where each observed value in the sample $x_1, x_2, \ldots, x_n$ has a probability equal to $1/n$.
2. Simulate a bootstrap sample of $n$ observations $x_1^*, x_2^*, \ldots, x_n^*$ from the empirical distribution $F_n$ by drawing $n$ values from $x_1, x_2, \ldots, x_n$ with replacement.

3. Calculate a bootstrap estimate of the parameter of interest in the same way as for an original sample, but plug in the values from the bootstrap samples instead: $\theta^* = \theta(x_1^*, x_2^*, ..., x_n^*)$.
4. Repeat the process $N$ times. The higher the value of $N$, the better the approximation.

### 4.7. Survival analysis techniques for estimating the costs attributable to a disease

#### 4.7.1. The average cost and the problem of censoring

Estimating the health care costs attributable to a disease can be valuable for policy analysis. Though perhaps not so much of interest in itself, an estimate of the costs can be a first step in an analysis that considers both costs and benefits compared to alternative uses of the resources.

If complete cost histories from date of diagnosis to death are available for all patients with a disease, it is a straightforward task to calculate the average cost. The average cost is equal to the total cost divided by the number of patients. This can be expressed as

$$AC = \sum_{j=1}^{T} \sum_{i=1}^{n} c_{ij} \Big/ n, \tag{17}$$

where $AC$ denotes average cost, and $c_{ij}$ is the cost of patient $i$ in time period $j$. $T$ denotes the maximum follow-up (here equal to the longest lifetime from the point of diagnosis), and $n$ the total number of patients.

The formula above can be modified by letting $\bar{c}_j$ denote the average cost per patient in time period j, and $n_j$ the number of patients alive in time period $j$ (Etzioni et al., 1996). We can then rewrite the equation above in the following way:

$$AC = \bar{c}_1 + \frac{n_2 \bar{c}_2}{n} + \frac{n_3 \bar{c}_3}{n} + ... + \frac{n_T \bar{c}_T}{n}. \tag{18}$$

Here, $n_j/n$ is the proportion of cases surviving to the beginning of time period j.

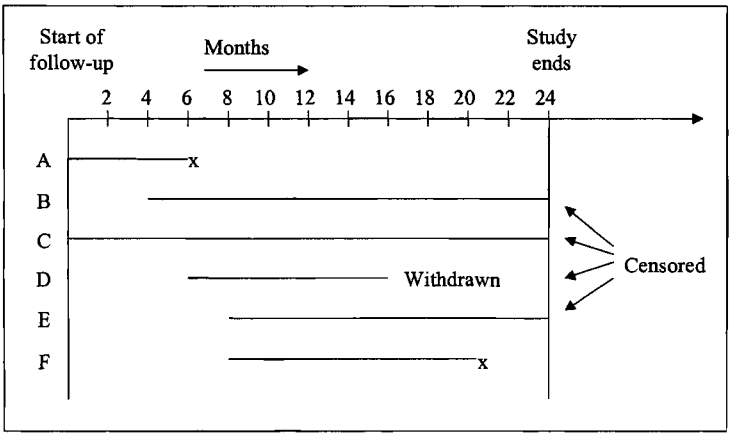
The problem is that survival proportions and complete cost histories are seldom available. In technical jargon, some patients are *censored* from the data. Censoring refers to situations where the exact survival time is not known. (Neither is the medical resource consumption in such cases). In medical studies *right-censoring* is most common, i.e., the complete survival time has been cut-off on the right side of the start of follow-up (see figure 5). This is the only kind of censoring that will be considered here.

Because of censoring, the proportion of patients surviving to the beginning of each time period is not known, and the average cost cannot be computed in the way outlined above. A solution would be to substitute the proportion of surviving patients $n_j/n$ with the probability of surviving to time period $j$ (Etzioni et al., 1996). In this way an estimate of the average cost can be obtained.

There are three main reasons why censoring may occur (Kleinbaum, 1996). One reason is that the patient does not experience the event of interest (e.g. death) before the study ends. This is common for clinical trials, which are often quite short, as well as for nation-wide registers for cancer and other diseases, where the cut-off point is the present time (or a little before, since it takes some time to assemble the data). The other two main reasons are that patients are lost to follow-up during the study period, or withdraw from the study for some other reason than the event of interest, e.g. because of an adverse drug reaction.

In figure 5, patients B, C, D, and E are censored. Patients A and F have died, so their survival times are known. Patient D has been withdrawn from the study, while the others are still alive at the end of follow-up. The only thing we can say for sure about the censored patients is that their survival time is at least as long as that recorded until censoring occurred.

**Figure 5.** *Censored cases in a medical study.*




### 4.7.2. The Kaplan-Meier method

Since there are censored data, we cannot calculate the average survival time simply by calculating average follow-up times for the patients, since this would underestimate the true survival time. In order to handle this problem, special statistical techniques for survival analysis have been developed. One of the most popular methods is the Kaplan-Meier product-limit estimator, which will be introduced by a concrete example.

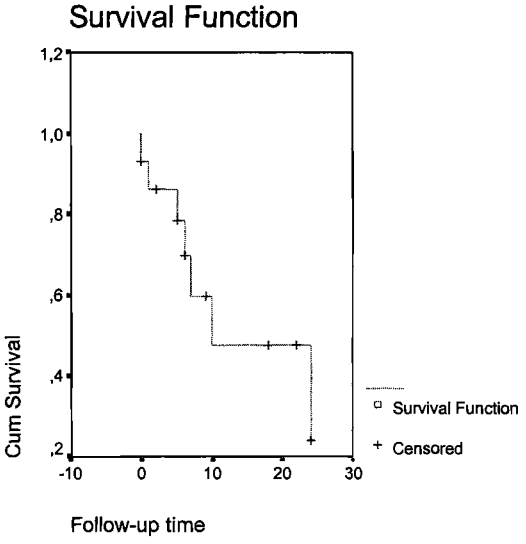
In table 2, a hypothetical sample of 15 patients is shown. The follow-up time (months) and the survival status for each patient are registered during the study (0 = survived, 1 = died).

**Table 2.** *Kaplan-Meier analysis of survival data.*

| Patient Id | Follow-up Time (months) | Survival Status | Number Alive Prior | Number Remaining Alive | Proportion Alive | Cumulative Survival Proportion |
|---|---|---|---|---|---|---|
| 01 | 0 | 1 | 15 | 14 | 14/15 | 14/15 = 0.93 |
| 02 | 0 | 0 | 14 | 13 | | |
| 03 | 1 | 1 | 13 | 12 | 12/13 | 0.93·12/13 = 0.86 |
| 04 | 2 | 0 | 12 | 11 | | |
| 05 | 5 | 1 | 11 | 10 | 10/11 | 0.86·10/11 = 0.78 |
| 06 | 5 | 0 | 10 | 9 | | |
| 07 | 6 | 1 | 9 | 8 | 8/9 | 0.78·8/9 = 0.70 |
| 08 | 6 | 0 | 8 | 7 | | |
| 09 | 7 | 1 | 7 | 6 | 6/7 | 0.70·6/7 = 0.60 |
| 10 | 9 | 0 | 6 | 5 | | |
| 11 | 10 | 1 | 5 | 4 | 4/5 | 0.60·4/5 = 0.48 |
| 12 | 18 | 0 | 4 | 3 | | |
| 13 | 22 | 0 | 3 | 2 | | |
| 14 | 24 | 1 | 2 | 1 | 1/2 | 0.48·1/2 = 0.24 |
| 15 | 24 | 0 | 1 | 0 | | |

In a Kaplan-Meier survival analysis, which is normally performed by a computer, the survival times are arranged in ascending order (as already happens to be the case in the table above). Each time an event occurs (here death is the event of interest), a survival probability is calculated for that point in time by dividing the number of patients remaining alive *after the event* with the number of patients alive *prior to the event*. The survival probabilities for each time an event occurs are then multiplied successively in order to obtain a cumulative survival proportion, which represents a non-parametric estimate of the survival function. The Kaplan-Meier method is non-parametric, since no distributional assumptions about the survival function are made. The resulting survival function is shown in figure 6.

**Figure 6.** *Kaplan-Meier survival function.*




### 4.7.3. The Kaplan-Meier sample average estimator

When a Kaplan-Meier estimate of the survival probabilities has been obtained, these probabilities can be substituted into the estimator of the average treatment costs:

$$AC = \hat{S}_1\bar{c}_1 + \hat{S}_2\bar{c}_2 + \hat{S}_3\bar{c}_3 + ... + \hat{S}_T\bar{c}_T = \sum_{j=1}^{T} \hat{S}_j\bar{c}_j, \qquad (19)$$

or in words: Average cost = Σ Probability(alive at j) * Mean (cost at j given alive at j).

This is called the Kaplan-Meier sample average estimator (or the KMSA estimator for short), since the Kaplan-Meier survival probability for each period of time is combined with the average cost in the sample for the same period of time. The KMSA estimator is a consistent estimator, as long as the patients are not censored because they are at an especially high or low mortality risk, or accrue especially high or low costs compared with the censored cases. Censoring should thus be *independent* of survival and costs. The independence of censoring and survival is satisfied under type I censoring, i.e. when follow-up ends at certain time and all surviving individuals are censored. The number of cases should also be sufficiently large.

In the *incidence approach* to measuring the costs of a disease, all costs are discounted back to the point in time when the disease is incident, i.e., at the time of diagnosis. Discounting can be easily incorporated in the KMSA estimator. Since the time intervals differ in length in a Kaplan-Meier analysis, continuous discounting is most practical:

$$AC = \hat{S}_1\bar{c}_1 + \hat{S}_2\bar{c}_2 \cdot e^{-rt_2} + \hat{S}_3\bar{c}_3 \cdot e^{-rt_3} + ... + \hat{S}_T\bar{c}_T \cdot e^{-rt_T}. \qquad (20)$$

For a small discount rate, e.g. $r \leq 0.03$, and a reasonably short time period, e.g. $t \leq 10$ years, the difference between continuous and annual compounding of interest rates is quite small. For $r = 3\%$, for example, $1/(1 + 0.03)^{10} = 0.744$, while $e^{-0.03 \cdot 10} = 0.741$.

### 4.7.4. Other approaches: Life-tables and parametric survival functions

In principle, any consistent estimator of the survival probabilities at different points in time could be used to estimate the average treatment cost. A follow-up life table could be used, in which the follow-up time is divided into intervals of equal size. Survival probabilities for each interval of time are then calculated by dividing the number of patients who died during the interval with the number of patients under observation. This estimate could then be combined with the average cost in the interval. However, the follow-up life table is less efficient than the Kaplan-Meier estimator, since we loose some information by dividing the follow-up period into arbitrary time intervals. (It should perhaps be mentioned that the Kaplan-Meier method is also essentially a life-table method, but the intervals of time are determined by the critical event rather than chosen in advance.)

A parametric approach to estimating the survival probabilities could also be used. In a parametric approach, we specify a certain functional form for the survival function, and then fit the parameters to the data at hand. The average cost also has to be expressed in parametric form. The parametric approach is a direct analogue of the KMSA method, but an integral is evaluated instead of a sum. The basic principle is the same: The average cost in a certain interval of time is multiplied with the probability of being alive in that interval. However, when an integral formulation is used, we have to work with the average cost per unit of time, since we are working with contiuous functions rather than

discrete steps as in the KMSA estimator. The total average cost ($AC$) can be estimated by an integral:

$$AC = \int_0^T \hat{S}(t)\,\bar{c}(t)\,e^{-rt}\,dt, \tag{21}$$

where $\hat{S}(t)$ is the parametric estimate of the survival function, $\bar{c}(t)$ the average cost per unit of time, $e^{-rt}$ is the discount factor, and $T$ is the maximum possible survival time.

To take a specific example, assume that the survival function can be expressed by an exponential function, and that the average cost per unit of time is constant. The survival function is then $S(t) = e^{-\lambda t}$, where the parameter $\lambda$ represents the hazard rate, which represents the proportion of individuals who dies per unit of time. In the exponential survival function, the hazard rate is assumed to be constant. The average cost per unit of time is $\bar{c}(t) = c$, where $c$ is a constant. We then obtain the following estimate of the average cost:

$$AC = \int_0^\infty e^{-\lambda t} \cdot c \cdot e^{-rt}\,dt = c\int_0^\infty e^{-(\lambda+r)t}\,dt = \frac{c}{\lambda + r}. \tag{22}$$

If 10% of the patients die per year, the average cost per year is SEK 52 000, and the costs are discounted at 3%, then the average present value of the total treatment cost is SEK 52 000/(0.10+0.03) = 400 000. (The upper integration limit is here infinity, which is not very realistic as a survival time. However, if we would limit $T$ to, say, 40 years, the average cost would be estimated to SEK 397 800, so infinity can in this case be used as an approximation).

## Summary of Studies II -VI

### Study II

**Consumption and production by age in Sweden: Basic facts and health economic implications.**

The main theme of Study II is a compilation of consumption and production figures by age in Sweden. The purpose of this is to use the difference between consumption and production in each age group as a measure of the average costs of added years of life in the general population.

What then are costs of added years of life, and why would one want to estimate them? In economic evaluations of health care interventions, only future costs for related illnesses have typically been included in the analysis. However, Meltzer (1997) has argued that for economic evaluations to be consistent with expected utility maximization, future costs for unrelated illnesses and general consumption should also be included. From a societal economic viewpoint, there is no reason to make a difference between various types of resource consumption. Ideally, Meltzer says, future costs (or costs of added years of life) should be estimated for the specific individuals likely to receive a particular health care intervention, but as an interim approach, average costs for the general population could be used.

Consumption by age was primarily drawn from the Family Expenditure Survey of Statistics Sweden (Hushållens utgifter, SCB). Earnings by age were also obtained from Statistics Sweden, but had to be adjusted by adding payroll taxes (arbetsgivaravgifter), and by taking account of labour force participation in the general population. Health care consumption by age was compiled in a more detailed fashion, primarily since it is interesting in its own right from a health economic point of view. Finally, a couple of applications in health economics are discussed, namely external costs for mortality changes and costs of added years of life in cost-effectiveness studies.

The results of the compilation of consumption and production by age are summarized in table 3. As can be seen in table 3, there are is a great shift in net consumption (consumption – production) around the age of 65. The net consumption increases significantly with age for the elderly. This may raise ethical concerns about the inclusion of costs of added year in health economic evaluations. However, if costs of added years of life are not included, treatments that extend the length of life may be given priority over treatments that increase the quality of life.

**Table 3.** Summary of consumption and production figures by age.

| ***Age*** | **00-19** | **20-34** | **35-49** | **50-64** | **65-74** | **75-84** | **85+** | **All** |
|---|---|---|---|---|---|---|---|---|
| ***Type of consumption*** | | | | | | | | |
| **Health care** | 5 914 | 7 529 | 9 652 | 13 623 | 20 395 | 26 732 | 27 601 | 11 449 |
| whereof | | | | | | | | |
| Pharmaceuticals | 539 | 795 | 1 349 | 2 425 | 3 485 | 3 946 | 3 324 | 1 627 |
| Primary and hospital care | 4 535 | 5 648 | 7 012 | 9 795 | 15 530 | 21 442 | 22 945 | 8 652 |
| Dental care | 840 | 1 086 | 1 291 | 1 403 | 1 380 | 1 344 | 1 332 | 1 171 |
| **Social services** | 2 138 | 3 417 | 3 417 | 3 417 | 8 159 | 46 113 | 149 219 | 9 486 |
| whereof | | | | | | | | |
| Elderly care | 0 | 0 | 0 | 0 | 7 186 | 44 690 | 146 510 | 6 740 |
| Services to impaired people | 2 097 | 3 376 | 3 376 | 3 376 | 710 | 710 | 710 | 2 600 |
| Transportation services | 41 | 41 | 41 | 41 | 263 | 713 | 1 999 | 147 |
| **Education** | 50 502 | 10 865 | 2 807 | 760 | 13 | 0 | 0 | 15 232 |
| whereof | | | | | | | | |
| Schools and child care | 49 962 | 0 | 0 | 0 | 0 | 0 | 0 | 12 181 |
| Universities | 403 | 8 274 | 1 555 | 283 | 13 | 0 | 0 | 2 152 |
| Adult schooling | 83 | 1 914 | 768 | 105 | 0 | 0 | 0 | 585 |
| Labour market training | 53 | 677 | 483 | 372 | 0 | 0 | 0 | 314 |
| **General public consumption** | 18 330 | 18 330 | 18 330 | 18 330 | 18 330 | 18 330 | 18 330 | 18 330 |
| **Other private consumption** | 56 406 | 87 300 | 80 721 | 105 942 | 95 523 | 71 909 | 49 219 | 80 596 |
| ***Total consumption*** | 133 290 | 127 442 | 114 927 | 142 074 | 142 420 | 163 084 | 244 369 | 135 093 |
| ***Total production*** | 2 750 | 148 140 | 227 115 | 202 079 | 9 101 | 1 033 | 169 | 113 168 |
| ***Consumption - Production*** | 130 540 | -20 698 | -112 188 | -60 005 | 133 319 | 162 051 | 244 200 | 21 925 |

**Study III**

**The possibility of predicting health care costs in the future from predicted changes in age structure and age specific mortality: The case of Sweden**

The issue of future health care costs has been a much discussed issue during the last few years (see e.g. Batljan & Lagergren, 2000). Changes in the age structure, especially the growing number of elderly people, have been at the center of this debate. However, as I hope my paper makes clear, the number of elderly *per se* is not the main problem, since the growing number of elderly people is a result of better health and hence lower mortality.

The main purpose of the paper is to investigate if future health care costs can be predicted based on predictions of future changes in age structure and mortality rates. A simple way of forecasting future health care costs is to take current age-specific health care costs as given, and apply these costs to demographic predictions of the future age structure. However, this will result in an overestimation, since the health care costs are a function of proximity to death rather than calendar age. The idea in this paper is to investigate the relationship between age-specific mortality and age-specific health care costs in order to see if this relationship can be used for improving predictions of future health care costs.

It is shown here that at least in Sweden and in the U.S., there is a linear relationship between age-specific mortality and age-specific health care costs. The close relationship between costs and mortality is hardly surprising, since the last months in life in general stand for a large proportion of the health care costs that an individual accumulates throughout his life. The linear relationship between age-specific mortality and age-specific health care costs in 1997 is combined with predictions for the age structure and the age-specific mortality rates in 2010 and in 2030 in order to predict the age-specific health care costs in these two future years. For example, by plugging in the age-specific mortality rates for 2010 into the cost-mortality relationship for 1997, predicted age-specific costs for 2010 are obtained. These cost are in turn multiplied with the predicted

number of people in each age group in 2010 in order to estimate the total health care costs.

This method of estimating the total health care costs in the future was tested by applying it retrospectively to old data on health care costs and mortality. A problem arises here, since health care costs for the elderly before the major Swedish health care reform of 1992 (Ädelreformen) was carried out, are not comparable with health care costs for the elderly in later years. I tried to compensate for this problem by calculating what the health care costs would have been in 1997, if the same cost items as before 1992 had been included. A linear relationship between age-specific mortality and age-specific health care costs in 1985 was then estimated, and this relationship was combined with the age structure and mortality rates in 1997 in order to predict the age-specific health care costs in the latter year. However, the method results in an underestimate of the health care costs, primarily since no account is taken of the real GDP growth per capita.

Against the background of international research on factors explaining differences in health care expenditures across countries and over time, the failure of the method for predicting future health care costs should not come as surprise. The research has shown that the age structure does not have a significant impact on the level of health care expenditures. The single most important factor for explaining the level of health care expenditures per capita is the level of GDP per capita. Health care expenditures tend to increase slightly more than the GDP. This does not mean that the exercise presented in the study is completely worthless. Even if the relationship between age-specific mortality and age-specific health care costs cannot be used to predict the level of the total health care expenditures in itself, it can still be used in order to making a prediction of how health care cost will be distributed among age groups. The results also corroborate the observation that the future age structure is not likely to have a great impact on the future health care costs. The financing side is of greater concern, since the ratio between the number of people in the workforce and the number of people in the total population will continue to decrease.

**Study IV**

**Cost effectiveness of bisoprolol in the treatment of chronic congestive heart failure in Sweden: Analysis using data from the Cardiac Insufficiency Bisoprolol Study II.** (Published in *Pharmacoeconomics* 19: 901-916. Co-authors: Niklas Zethraeus and Bengt Jönsson).

Treatment of heart failure with beta blockers was introduced in Sweden already in the 1970s, but it was not until the 1990s that large-scale clinical trials established the efficacy of this treatment in reducing morbidity and mortality (Swedberg, 1998; Krum, 1999). This study consists of a fairly straightforward economic evaluation of the beta blocker bisoprolol added to standard treatment of chronic heart failure, compared with placebo added to the same standard treatment. Although the economic evaluation is fairly straightforward, it raises a number of methodological issues. At the forefront are the inclusion of costs of added years of life and the question of how to model health outcomes that are not captured by the clinical trial on which the economic evaluation is based.

Data on survival and medical resource consumption for heart failure patients were taken from the clinical trial CIBIS II (The Cardiac Insufficiency Bisoprolol Study II), which comprised 2 647 patients from 18 European countries. In fact, only a small minority of the patients participating in the clinical trial came from Sweden.

The economic evaluation was performed as a cost-effectiveness analysis, which means that costs and health effects were compared between two different treatments. The treatment group received the beta blocker bisoprolol added to standard heart failure treatment with ACE inhibitors, diuretics, and digitalis. The control group received placebo in addition to the same standard treatment. For a disease like heart failure, which in severe stages has a very high mortality, the average number of gained years of life per patient is the obvious measure of health effects. The difference in health effects between bisoprolol and placebo was partly obtained from the clinical trial, and partly obtained by modelling of the expected remaining lifetime for the patients who were alive at the end of the clinical trial. However, in the base-case analysis the expected

survival after the end of the clinical trial was assumed to be identical for patients in the treatment and in the control group. Therefore it is the difference in mortality within the clinical trial that is behind also the difference in modelled survival after the end of the clinical trial. The expected lifetime after the end of the clinical trial was primarily based on results from previous clinical trials and epidemiological studies.

Resource consumption per patient in terms of hospital days, hospital admissions, and the number of days on a particular pharmaceutical was available from the clinical trial CIBIS II. In order to estimate the costs per patient, the resource consumption during the course of the clinical trial was combined with Swedish per diem and per admissions costs of hospitalisation, and average daily costs of pharmaceuticals. Costs and effects were then compared between the two treatments in order to investigate the cost-effectiveness of adding bisoprolol to the treatment of chronic heart failure. The results in table 4 indicate that treatment with bisoprolol is cost-effective, both with the costs of added years of life excluded and included, since the threshold value for the cost-effectiveness ratio is about SEK 450 000. The sensitivity analysis showed that the results are stable for reasonable variations in critical parameters, such as the expected additional lifetime after the end of follow-up.

**Table 4.** *Base-case results (1999 prices).*

| ***Cost items*** | ***Cost per patient (SEK)*** | | |
|---|---|---|---|
| | Bisoprolol | Placebo | Difference |
| Hospitalisations | 16 447 | 19 898 | -3 451 |
| Bisoprolol | 1 420 | 0 | 1 420 |
| Other medication | 6 777 | 6 730 | 47 |
| Dose titration | 5 795 | 0 | 5 795 |
| Added life years | 849 122 | 803 778 | 45 343 |
| Total | 879 560 | 830 406 | 49 155 |

| ***Effects*** | ***Life years per patient*** | | |
|---|---|---|---|
| | Bisoprolol | Placebo | Difference |
| Life years within study | 1.332 | 1.292 | 0.041 |
| Expected additional lifetime | 4.016 | 3.766 | 0.250 |
| Total | 5.348 | 5.057 | 0.291 |

| ***Cost-effectiveness*** | ***ΔCost/ΔEffect (SEK/gained life year)*** | |
|---|---|---|
| | Including costs of added life years | Excluding costs of added life years |
| Incremental cost-effectiveness ratio | 168 858 | 13 094 |

Source: Table VI in Ekman et al. (2001).

**Study V**

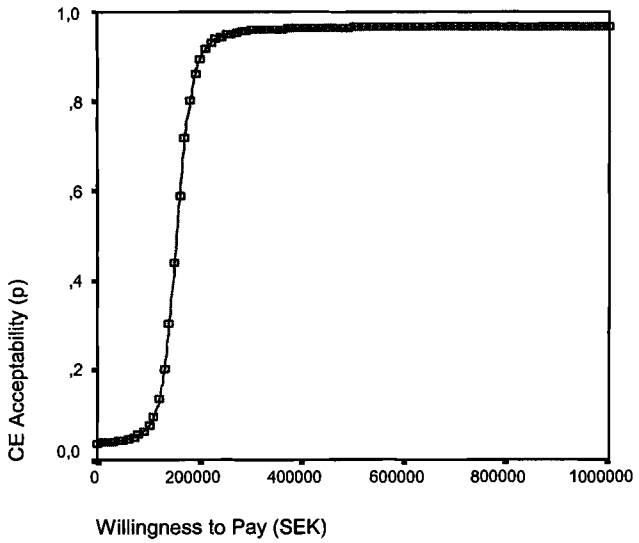
**Assessing uncertainty in cost-effectiveness analysis by combining resampling of clinical trial data with stochastic modelling: The economic evaluation of bisoprolol for heart failure revisited**

A drawback of the analysis in Study IV was that the expected survival after the end of follow-up was modelled in a deterministic way. This makes it impossible to assess the uncertainty of the cost-effectiveness estimate in a realistic way. In this study, resampling of the clinical trial data was combined with stochastic modelling of the expected survival after the end of follow-up in the clinical trial. The methodology is inspired by the bootstrap method, which is a simulation technique whereby various statistics, like the mean and variance, can be estimated through repeated resampling from the original sample. The difference from the traditional bootstrapping method is that resampling of observations from the data set (here clinical trial data) is combined with stochastic modelling of the expected remaining lifetime of the patients who were alive at the end of the clinical trial. Since the follow-up times in the clinical trial are rather short, modelling is necessary in order to obtain realistic results. Apart from the handling of uncertainty, a difference from the previous study is that the value-added taxes have been excluded from the private consumption figures in the costs of added years of life. This is more correct, since the value added taxes do not represent a resource consumption.

Since cost-effectiveness ratios have unfavourable statistical properties, the net benefit method was chosen as an alternative method. Given that the data set is large enough, both the difference in cost ($\Delta C$) and the difference in effect ($\Delta E$) between two treatments could be expected to be normally distributed according to the central limit theorem of probability theory. The cost-effectiveness ratio $R$ is a ratio of two normally distributed variables ($R = \Delta C/\Delta E$), which implies a tendency for extreme observations, and hence unstable mean and very wide variance. The net benefit ($NB$), in contrast, is a linear function of two normally distributed variables ($NB(p) = p \cdot \Delta E - \Delta C$), which implies that the net benefit is itself normally distributed. The net benefit method is inspired from cost-benefit analysis, but is a simplification in the sense that a constant value $p$ per unit of health effect is used.

A striking, but not surprising, conclusion is that the confidence interval obtained by combining resampling and stochastic modelling is much wider than the variation obtained from the conventional sensitivity analysis in Study IV. This indicates that a sensitivity analysis of deterministic modelling parameters is insufficient as a way of representing uncertainty. Cost-effectiveness acceptability curves were constructed on the basis of the empirical simulation distributions of costs and health effects. The cost-effectiveness acceptability curve shows the proportion of the simulated values of the net benefit that is larger than zero for various values of the threshold value *p* per gained year of life. In figure 7, the cost-effectiveness acceptability curve (with costs of added years of life included) is displayed. On the horizontal axis, the willingness to pay per gained year of life is shown, and on the vertical axis the cost-effectiveness acceptability as a function of the willingness to pay is shown.

**Figure 7.** *Cost-effectiveness acceptability curve with costs of added years of life included.*




In the base-case analysis, with a value of *p* equal to SEK 450 000, the mean net benefit is equal to SEK 101 400 with costs of added years of life included. The mean net

benefit is significantly larger than zero according to a one-sided confidence interval at the 5% level.

**Study VI**

**Survival analysis techniques for estimating the costs attributable to head and neck cancer in Sweden**

The sixth and final study concerns the estimation of the average treatment cost attributable to a disease when the data contain censored, i.e. incomplete, observations. For various reasons, censored observations are common in medical and epidemiological studies. A common reason is simply that the follow-up time is limited. As a result, it is not known how long the survival time for those who are alive at the end of follow-up really is. The only thing that is known with certainty is that it is at least as long as the follow-up time. This is of course problematic if we want to estimate the average survival time or the average resource utilization for all patients, both survivors and non-survivors included.

The purpose of the study is to estimate the average inpatient treatment cost per patient from diagnosis to death for head and neck cancer in Sweden. The method chosen for this purpose is the Kaplan-Meier sample-average (KMSA) estimator, which is a method that has been proposed specifically for handling censored cost data. The KMSA estimator builds on the non-parametric Kaplan-Meier method of estimating the survival function. The database that was used for the study was obtained from the national Swedish cancer registry. It includes all patients diagnosed with head and neck cancer in Sweden from 1986 to 1996.

In the KMSA estimator, the expected average cost is calculated by multiplying the probability of being alive in a certain interval of time $i$ with the average cost for those who are alive in that interval, and then summing up the products between survival probability and average cost for all intervals within the follow-up time:

Average treatment cost = $\Sigma$ (Probability of being alive at time $i$ * Average cost at time $i$).

As an alternative method, a parametric analogue of the KMSA estimator is presented. Finally, advantages, disadvantages, and possible refinements of the methodology are discussed. For example, there is a possibility of refining the analysis by taking account of explanatory variables such as age, sex, and severity of disease in a regression model. Regression-based methods for censored cost data would add further insights, but are technically demanding, and still very much under development. See Heyse et al. (2001) for a survey.

As for the results, the analysis presented in the study suggests that the average inpatient cost attributable to head and neck cancer in Sweden is about SEK 260 000 per patient from diagnosis to death (2001 prices). The result can serve as a building block in a subsequent economic evaluation of a new treatment for head and neck cancer. The result can also be used as a step in an economic evaluation of preventive measures aimed at reducing the number of new cases or detecting them at an earlier stage by a screening program.

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# Consumption and Production by Age in Sweden: Basic Facts and Health Economic Implications

By Mattias Ekman

**Abstract**

For cost-effectiveness analysis to be consistent with expected utility maximization, David Meltzer has proposed that the difference between consumption and production should be included as costs in added years of life. In order to obtain an estimate of these costs, average production and consumption figures by age for the general population in Sweden were compiled. Production is here defined as the total labour cost, including pre-tax income and pay-roll taxes, but excluding transfer payments such as paid sick-leave. Private consumption was mainly estimated from a consumer expenditure survey. Public consumption was estimated from the Swedish national accounts and other government sources. Health care consumption by age was given particular consideration, since these costs are interesting in their own right from a health economic viewpoint. Towards the end of the paper, the reliability and validity of the age distribution of consumption and production is discussed, as well as applications to health economic evaluations.

Key words: Production and consumption by age, costs in added years of life, health care expenditures.

# 1. Introduction

Knowledge of consumption and production patterns by age is useful for health economic evaluations, not the least since such figures can make it possible to include future costs in health economic analyses. Meltzer (1997) has argued that existing approaches to medical cost-effectiveness analysis are biased to favour interventions that extend the length of life over interventions that improve the quality of life. As a way of overcoming this problem, he proposes a life-time expected utility approach to cost-effectiveness, where not only medical expenditures but also future consumption and earnings are considered. Meltzer (1997) and Johannesson, Meltzer and O'Conor (1997) have provided examples of the consequences of excluding future costs from health economic analyses.

The structure of the paper is as follows. Method and data sources are discussed in section 2. In section 3, I will begin the compilation of consumption and production figures by displaying the production in different age groups. The value of production associated with an individual is here defined as the total labour cost, i.e. the sum of take-home income, taxes and compulsory National Insurance contributions. In section 4, I then go on to discuss private and public consumption, with particular emphasis on health care consumption.

The consumption expenditures have been classified into five major categories:

1. Health care expenditures, both private and public, including pharmaceuticals, primary and hospital care, and dental care.
2. Social services, including elderly care, services to impaired people, and transportation services for elderly and impaired people.
3. Education, including child care, schools, universities, and labour market training programmes for the unemployed.
4. Other public consumption including, e.g., defence, and public order and safety.
5. Other private consumption.

Finally, I put it all together and show how average production and consumption vary with age in Sweden. The difference between consumption and production is calculated for each age group. I also look at the relation between private and public health care costs, and discuss how production net of consumption data can be used for health economic calculations.

A couple of limitations of this study should be pointed out at the start. First, only aggregate numbers for each age group will be presented. I will not discuss the variability of income or consumption within each age group. Second, the study is limited to one single year, namely 1997. At the time when the figures were compiled, this was the most recent year for which it was possible to obtain a complete and reasonably reliable estimate of consumption and production patterns by age in Sweden.

## 2. Method and data sources

Aggregate figures on production and consumption have mostly been compiled from the Swedish national accounts, published by Statistics Sweden. These figures are generally not distributed by age, or at least not distributed according to the age groups used in this paper. The age distribution very often had to be based on survey results. However, it seems that many of the surveys that I consulted had a tendency of slightly underestimating the actual consumption. I have in general solved this problem by combining the figures on total consumption from a source that was deemed to be more reliable, e.g. the national accounts, with the age distribution according to a corresponding survey. As it turned out, accurate estimates of the consumption expenditures among the elderly were most difficult to obtain. Here, I relied on various sources, mostly from Statistics Sweden, the Swedish Association of Local Authorities (Svenska Kommunförbundet), and the Federation of Swedish County Councils (Landstingsförbundet).

Since many of the figures concerning consumption and production appear in the national accounts, it can be illustrative to relate them to the GDP. The two most common ways to measure the GDP are the expenditure method and the income method (Lipsey & Chrystal, 1995; Beckerman, 1976). These two methods are illustrated in table 1. The

expenditure method consists of estimating the national product by adding up all the components of final demand, and the income method consists of adding up all the incomes received by the factors of production. A third way of measuring the GDP is the output method, which is based on value added by industry of origin, but this approach is of less interest here.

**Table 1.** *Two ways of measuring the GDP.*

| ***Expenditure method*** | ***Income method*** |
|---|---|
| **1. Consumption expenditure** | **1. Factor payments** |
| • Goods and services sold to final users. | • Income from employment. |
| **2. Investment expenditure** | • Income from self-employment. |
| • Stockbuilding. | • Rent. |
| • Fixed-capital formation and residential investment. | • Profits (dividends and retained earnings). |
| **3. Government expenditure** | **2. Non-factor payments** |
| **4. Net exports** (exports - imports) | • Indirect taxes net of subsidies. |

In table 1 we can see that, apart from income, the GDP at market prices consists of rents (including payments for rental housing and imputed rents for the use of owner-occupied housing), profits and indirect taxes net of subsidies. If the indirect taxes net of subsidies are excluded, we obtain the GDP at factor prices, which in 1997 was SEK 1 596 billion. From the composition of the GDP by the two measures in table 1 it is clear that there is no direct link between production as measured by personal income and labour taxes, and consumption as measured by private and public consumption.

## 3. Production

The value of production for each individual is here defined as the total labour cost of the employee from the employer's point of view. Data on production in different age groups has been obtained from Statistics Sweden. However, the data from Statistics Sweden was not entirely complete, since it only included the take-home pay received by the employee plus taxes withheld. In addition, the employer has to pay payroll taxes, and national insurance and pension fund contributions on behalf of the employee. Thus, I had to adjust the data to account for this. I calculated the total labour cost by

increasing the sum of per capita income and taxes withheld for each age group by 32.92% for employees, and by 31.25% for self-employed. For people over 65 years of age, a payroll tax of 22.42% applies, since employees or self-employed who are older than the official retirement age need not make any national insurance or pension fund contributions. The results of these calculations are presented in table 2. The tax rates were obtained from the National Swedish Tax Authorities (Riksskatteverket).

According to my calculations, the sum of payroll taxes, national insurance contributions and pension fund contributions was SEK 247.7 billion in 1997. At least on the aggregate level, adding those items by multiplying the pre-tax income with the tax rate seems to work out well. According to the Tax Statistical Yearbook of Sweden the actual figure for 1997 was SEK 247 billion, i.e. practically the same amount.

The choice of age groups may perhaps require an explanation. Since the figures are meant to be used for health economic calculations, the choice of age groups has been made to harmonise with economic models that have been used at the Centre for Health Economics at the Stockholm School of Economics.

**Table 2.** *Production in different age groups in 1997.*

| *Age* | *Sex* | *Production in MSEK* | *Number of people* | *Average production in SEK* |
|---|---|---|---|---|
| **00-15** | Men | 342 | 900 305 | 380 |
| | Women | 276 | 853 565 | 323 |
| | Total | 618 | 1 753 870 | 352 |
| **16-19** | Men | 2 942 | 206 330 | 14 258 |
| | Women | 2 371 | 196 877 | 12 044 |
| | Total | 5 313 | 403 207 | 13 177 |
| **20-34** | Men | 166 149 | 923 173 | 179 976 |
| | Women | 101 361 | 882 618 | 114 841 |
| | Total | 267 510 | 1 805 791 | 148 140 |
| **35-49** | Men | 245 394 | 909 539 | 269 801 |
| | Women | 160 595 | 878 058 | 182 898 |
| | Total | 405 990 | 1 787 597 | 227 115 |
| **50-64** | Men | 189 243 | 780 458 | 242 477 |
| | Women | 124 947 | 774 328 | 161 361 |
| | Total | 314 190 | 1 554 786 | 202 079 |
| **65-74** | Men | 4 961 | 356 758 | 13 906 |
| | Women | 2 058 | 414 451 | 4 965 |
| | Total | 7 019 | 771 209 | 9 101 |
| **75-84** | Men | 441 | 236 311 | 1 865 |
| | Women | 157 | 342 102 | 458 |
| | Total | 597 | 578 413 | 1 033 |
| **85+** | Men | 24 | 59 039 | 401 |
| | Women | 9 | 133 713 | 67 |
| | Total | 33 | 192 752 | 169 |
| **20-64** | Total | 987 689 | 5 148 174 | 191 852 |
| **All** | Total | 1 001 269 | 8 847 625 | 113 168 |

Source: Statistics Sweden and my own estimations.

It could be of interest to compare the aggregate production with the GNP figures for Sweden in 1997. In 1997, the GNP as measured in current market prices amounted to SEK 1 805 billion (Statistical Yearbook of Sweden 2000, Table 321). We see that the total production, i.e. about SEK 1 000 billion, is much lower than the GDP. What accounts for the difference?

In table 1 above we can see that, apart from income, the GDP at market prices consists of rents (including payments for rental housing and imputed rents for the use of owner-

occupied housing), profits and indirect taxes net of subsidies. If the indirect taxes net of subsidies are excluded, we obtain the GDP at factor prices, which in 1997 was SEK 1 596 billion. From the composition of the GDP by the two measures in table 1 it is clear that there is no direct link between production as measured by personal income and labour taxes, and consumption as measured by private and public consumption.

The average production of about SEK 113 000 per capita may seem a bit low. This is partly due to the inclusion of children and retired people and partly due the fact that far from all people between the ages of 20 and 64 are working. Only about 77% of those who were between 16 and 64 were participating in the workforce in 1997. Of those people who were working, nearly a fourth worked less than 35 hours per week (Statistical Yearbook of Sweden 1999, Tables 196 and 198).

# 4. Consumption

## 4.1. Health care

### 4.1.1. Pharmaceutical expenditures

The per capita sales of prescription pharmaceuticals in 1997 were obtained from the National Corporation of Swedish Pharmacies (Apoteket AB).

**Table 3.** *Per capita costs for prescription pharmaceuticals in 1997 (SEK).*

| *Age* | *Men* | *Women* | *Total* |
|---|---|---|---|
| 00-19 | 623 | 451 | 539 |
| 20-34 | 615 | 983 | 795 |
| 35-49 | 1 127 | 1 578 | 1 349 |
| 50-64 | 2 171 | 2 682 | 2 425 |
| 65-74 | 3 606 | 3 381 | 3 485 |
| 75-84 | 4 252 | 3 734 | 3 946 |
| 85+ | 3 800 | 3 113 | 3 324 |

Source: Swedish Pharmaceutical Statistics 1997, and my own calculations.

### 4.1.2. Primary and hospital care

For the country as a whole, age-related general health care costs for physician and hospital services are not available, but such data exist for Region Skåne in southern

Sweden, as shown in table 4a. Because of different cost definitions, it is not entirely clear how the data from Region Skåne should be compared with aggregate figures for the whole country, but they seem to be representative. Based on similar cost definitions, the average health care costs per capita in Region Skåne are only about 2% higher than the average costs for entire Sweden (Yearbook of Health and Medical Care 1999, table 5.8). I have therefore decided to use the costs from Region Skåne without any adjustments other than those concerning the age groups.

**Table 4a.** *Health care costs in Region Skåne in 1997.*

| *Age* | 0-4 | 5-14 | 15-44 | 45-64 | 65-74 | 75-84 | 85+ | All |
|---|---|---|---|---|---|---|---|---|
| *Per capita cost* | 7 409 | 3 487 | 5 941 | 8 899 | 15 530 | 21 442 | 22 945 | 8 732 |

Source: Kostnader 1997 för hälso- och sjukvård för befolkningen i Skåne. Region Skåne.

As can be seen above, the age groups used in the data from Region Skåne are somewhat different from those that I have used throughout this paper. Unfortunately, the Skåne data were not available in 5-year classes, but I transformed the data to fit the age groups used here by interpolation. Fortunately, the age groups are the same for people over 65 years of age.

**Table 4b.** *Health care costs in Region Skåne in 1997.*

| *Age* | 0-19 | 20-34 | 35-49 | 50-64 | 65-74 | 75-84 | 85+ | All |
|---|---|---|---|---|---|---|---|---|
| *Per capita cost* | 4 535 | 5 648 | 7 012 | 9 795 | 15 530 | 21 442 | 22 945 | 8 732 |

Source: Kostnader 1997 för hälso- och sjukvård för befolkningen i Skåne. Region Skåne, and my own calculations.

### 4.1.3. Dental care

The statistics on dental care are unfortunately not very extensive. However, in a report from the National Social Insurance Board (RFV Anser 2000:3) there is an age distribution of average out-of-pocket costs for dental care in different age groups in 1998, based on data from the county of Södermanland.

**Table 5.** *Average out-of-pocket costs for dental care in the county of Södermanland in 1998.*

| *Age* | 20-29 | 30-39 | 40-49 | 50-59 | 60-69 | 70-79 | 80+ | All |
|---|---|---|---|---|---|---|---|---|
| ***Men*** | 604 | 695 | 759 | 804 | 829 | 793 | 760 | 731 |
| ***Women*** | 581 | 662 | 737 | 783 | 760 | 747 | 749 | 703 |
| ***Total*** | 593 | 678 | 748 | 793 | 792 | 767 | 753 | 717 |

Source: RFV Anser 2000:3.

However, these costs cannot be used directly. First, the age groups have to be adjusted. This was done through linear interpolation. Second, the above costs concern 1998. Third, the figures are taken from the National Dental Service (Folktandvården) and do not take account of privately provided dental care. Fourth, the figures are taken from only one county, and may not be representative for the nation as a whole. My (partial) solution to these problems is to use the total out-of-pocket costs for dental care from the national accounts and then apply the age distribution in table 5 to these costs. The total out-of-pocket costs for dental care in Sweden were MSEK 6 528 in 1997 (Yearbook of Health and Medical Care 1999). On a per capita basis, these costs are somewhat higher than those based on the Södermanland data. There are two likely explanations for this. One factor is that the patients' out-of-pocket costs are on average about 15% higher for the nation as a whole than for the county of Södermanland (RFV Anser 2000:3), but this does not explain the whole difference. One possible further explanation for the difference is that the out-of-pocket costs for National Dental Service are on average lower than the costs for privately provided dental care. If that were true, the Södermanland figures would be an underestimation of the total figures. Hopefully, the age distribution would then still be applicable. This is far from certain, of course, but the Södermanland data seem to be the best available.

**Table 6.** *Interpolated and adjusted average out-of-pocket costs for dental care based on data from county of Södermanland.*

| *Age* | 20-34 | 35-49 | 50-64 | 65-74 | 75-84 | 85+ |
|---|---|---|---|---|---|---|
| ***Out-of-pocket costs, interpolated data*** | 614 | 730 | 793 | 780 | 760 | 753 |
| ***Out-of-pocket costs, interpolated and adjusted data*** | 829 | 986 | 1 071 | 1 054 | 1 027 | 1 017 |

Source: RFV Anser 2000:3, and my own calculations.

There are figures for the whole country for 1999, but since a dental-care-finance reform took effect on 1 January 1999, these figures are not applicable to the situation in 1997. From January 1, 1999, and onwards, the dental care patients have had to pay a larger part of the costs themselves, especially for costly interventions. There are also data on out-of-pocket expenditures for dental care available from the Income Distribution Survey for 1994 and 1998 (Yearbook of Health and Medical Care 2000). However, the expenditures are not registered as averages in the Income Distribution Survey, since the respondents only indicate within what range the expenditures are lying, i.e., No expenditures, SEK 1-500, SEK 501-1 000, SEK 1 001-2 000, SEK 2 001-3 000, and SEK 3 001 and over. Given certain assumptions, it is possible to estimate average out-of-pocket expenditures based on these data, and the resulting figures are in general quite close those obtained from the Södermanland data. I have therefore decided to use the Södermanland data as an approximation for the age distribution of dental care costs for the whole country.

The part of the dental care costs that are reimbursed by the government is available in the National Insurance statistics. The total dental reimbursement costs in Sweden were MSEK 2 021 in 1997. In the absence of better information, I have used the out-of-pocket costs to distribute these costs into different age groups. For children and young people under the age of 20, dental care is free of charge in Sweden. The average cost does not seem to be available for the whole country, but according to a government report (SOU 1998:2) the average cost in Stockholm for those under the age of 20 was SEK 840 in 1996. The report claims that this cost is representative for the whole country.

**Table 7.** *Estimated average costs for dental care in Sweden in 1997.*

| ***Age*** | **00-19** | **20-34** | **35-49** | **50-64** | **65-74** | **75-84** | **85+** |
|---|---|---|---|---|---|---|---|
| ***Average national insurance costs**** | 840 | 257 | 305 | 332 | 326 | 318 | 315 |
| ***Out-of-pocket costs*** | 0 | 829 | 986 | 1 071 | 1 054 | 1 026 | 1 017 |
| ***Total dental care costs per capita*** | 840 | 1 086 | 1 291 | 1 403 | 1 380 | 1 344 | 1 332 |

* Costs for people under 20 are covered by the county councils, not the National Insurance.

## 4.2. Social services

### 4.2.1. Elderly care

The costs for elderly care, and other social services mainly concerning people with handicap, are in fact quite important. With statistics from the Finance department of the Swedish Association of Local Authorities (Svenska Kommunförbundet), estimates of the costs for elderly care in different age groups have been compiled. These are shown in table 8.

**Table 8.** *Average costs for elderly care in different age groups (SEK).*

| *Age* | *Men* | *Women* | *Total* |
|---|---|---|---|
| **65-74** | 6 519 | 7 761 | 7 186 |
| **75-84** | 36 642 | 50 248 | 44 690 |
| **85+** | 124 627 | 156 198 | 146 510 |

Source: Swedish Association of Local Authorities.

### 4.2.2. Social services to impaired people

According to statistics from the Swedish Association of Local Authorities, the costs for elderly care and social services to handicapped people were on average SEK 8 748 per capita in Sweden in 1997 ("Vad kostar verksamheten i din kommun? 1997"). This gives a total cost of SEK 8 748 · 8 847 625 = 77.4 billion. The costs elderly care amounted to SEK 59.3 billion, and consequently the costs of social services to handicapped were about 18.1 billion SEK in 1997. The average cost per capita for social services to the handicapped was thus SEK 18 100/8.848 = 2 050. There were also some extra costs for personal assistance that were paid by central government. These costs amounted to MSEK 4 496 in 1997. The number of handicapped is distributed fairly evenly in different age groups. However, the intensity and the nature of the aid that they receive are contingent upon age. The following estimate of the costs per capita in different age groups was based on statistics concerning care and services to impaired people. The reason why the per capita cost is lower for those under 20 years of age is probably that children get a lot of help from their parents. The elderly have a lower per capita cost since they get help within the framework of elderly care instead.

**Table 9.** *Per capita costs for assistance to impaired people.*

| *Age* | *Cost* |
|---|---|
| **00-19** | 2 097 |
| **20-64** | 3 376 |
| **65+** | 710 |
| **All** | 2 554 |

Source: Insatser för personer med funktionshinder 1998. Statistik Socialtjänst. Socialstyrelsen, and my own estimations.

### 4.2.3. Transportation services

There are also costs for publicly provided taxi services (Färdtjänst) to elderly and handicapped people. These costs amounted to MSEK 1 300 in 1997. In order to use the publicly provided taxi services, you need a licence. Licences are granted to handicapped or elderly people with disabilities that make it difficult for them to use other means of public transport, such as buses and commuter trains.

According to a Social Services survey reported by Statistics Sweden, handicapped people between 0-64 on average use taxi services for a value of about SEK 350 per month. Since there are 71 040 licences in this age group, this amounts to SEK 350 · 12 · 71 040 = MSEK 298 for the group as a whole on a yearly basis, i.e. SEK 41 per capita. For people aged 65 and over, I assumed that the costs are directly proportional to the number of licences in each age group, and that there are no differences between different age groups in terms of how often they use the taxi services. The data on the number of licences concern the age groups 0-64 (71 040 licences), 65-79 (126 434 licences), and 80+ (221 199 licences). Interpolation was used in order to get estimations for the age groups 65-74, 75-84, and 85+. The results are displayed in table 10.

**Table 10.** *Calculation of costs for taxi services by age.*

| Age | Per capita cost (SEK) |
|---|---|
| **0-64** | 41 |
| **65-74** | 263 |
| **75-84** | 713 |
| **85+** | 1 999 |

Source: Statistik socialtjänst 1998:3. Färdtjänst och riksfärdtjänst 1997, and my own calculations.

### 4.3. Education

#### 4.3.1. Schools and child care

I regard consumption of childcare and school education as consumption by the child or adolescent and not by the parents. While I think it is natural to regard school education as a service consumed by the adolescents themselves, childcare could perhaps equally well be seen as consumption of a service by the parents. However, since the children also receive some training and social skills at day-care centres, I think that it is not unfair to allocate these costs to them, even if the parents are responsible for putting them there in the first place.

The costs for day-care centres and for schooling are shown in table 11. Only the net cost is displayed, i.e. the cost net of revenues from fees. These revenues are typically low in Sweden, and are practically relevant only for day care centres, where the revenues are equivalent to 16% of the total costs.

**Table 11.** *Educational expenditures for day care centres and schools in 1997.*

| ***Type of school*** | ***Costs (MSEK)*** |
|---|---|
| Day care centers | 35 512 |
| Comprehensive schools | 49 378 |
| Special schools | 3 101 |
| Upper secondary schools | 19 782 |
| Total | 107 772 |
| | |
| ***Number of children and young people (0-19)*** | 2 157 077 |
| | |
| ***Costs per capita (SEK)*** | 49 962 |

Source: Statistical Yearbook of Swedish Education in 1998.

#### 4.3.2. University education

The age distribution of university students is shown in table 12. I have distributed the total costs for university education directly according to the percentage of students in each age group. The total costs were calculated by subtracting the estimated costs for university research from the total costs for the universities, i.e. MSEK 30 404 – 11 363 = 19 041.

**Table 12.** *Age distributed costs for college and university students in 1997.*

| Age | Number of students | Percentage of students | Per capita cost (SEK) |
|---|---|---|---|
| 0-19 | 12 174 | 4,6% | 403 |
| 20-34 | 209 014 | 78,5% | 8 274 |
| 35-49 | 38 896 | 14,6% | 1 555 |
| 50-64 | 6 159 | 2,3% | 283 |
| 65-74 | 137 | 0,1% | 13 |

Sources: Årsrapport för universitet och högskolor 1998, Högskoleverkets rapportserie 1999: 11R, Statistiska meddelanden U20 SM9901, SCB, and my own calculations.

The numbers of students under the age of 20 and over the age of 65 were not explicitly stated in the statistics, but could be estimated from the statistics on the age of newly registered students, and by the number of degrees taken in different age groups. Actually, there are even some students aged 75 and over, but these are only a handful. Perhaps a more serious problem is that I found no statistics on the intensity of the studies, i.e. if the students were studying on a full-time or part-time basis. One would suspect that older students are part-time students to a greater extent than younger ones. Furthermore, younger students are perhaps more often studying for degrees in fields such as science, engineering, and medicine, where the costs per student are higher than for humanities and social sciences. However, in the absence of more detailed information I assumed that the intensity of study and cost of study are the same for younger and older students. This may result in an overestimation for the older age groups.

### 4.3.3. Adult school education

Average costs for adult school education have been estimated in a similar way. In this case, it was possible to take account of differences between age groups concerning full-time and part-time studies. This is reflected in table 13, where there is a difference between the percentage of students and the percentage of education, the latter being a percentage of students weighted by the intensity of study. (Weights: full-time = 1, half-time = ½, part-time = ¼). However, the difference between the two types of percentage is not large. In the absence of better information, I have assumed that no one is over 65 years of age in the adult school education.

**Table 13.** *Age distributed costs for adult school education in 1997.*

| Age | Number of students | Percentage of students | Percentage of education | Per capita cost (SEK) |
|---|---|---|---|---|
| 0-19 | 9 165 | 4,1% | 3,5% | 83 |
| 20-34 | 139 255 | 63,0% | 66,8% | 1 914 |
| 35-49 | 63 172 | 28,6% | 26,6% | 768 |
| 50-64 | 9 453 | 4,3% | 3,2% | 105 |

Source: Statistical Yearbook of Swedish Education 1998, Stockholm: Statistics Sweden, and my own calculations.

### 4.3.4. Labour market training courses

There are also some costs for labour market training for the unemployed. These costs have been distributed by age by using the estimated number of unemployed in each age group, as shown in table 14.

**Table 14.** *Age distributed costs for labour market training in 1997.*

| Age | Unemployed (thousands) | Cost per age group (MSEK) | Cost per capita (SEK) |
|---|---|---|---|
| 0-19 | 14 | 114 | 53 |
| 20-34 | 150 | 1 223 | 677 |
| 35-49 | 106 | 864 | 483 |
| 50-64 | 71 | 579 | 372 |
| All 0-64 | 341 | 2 780 | 381 |

Source: Statistical Yearbook of Sweden 1999, and my own calculations.

## 4.4. Other public consumption

Statistics on the general public consumption are available from Statistics Sweden. In table 15, I have excluded costs with a clear age dependency, such as costs for health care, elderly care, childcare and education.

**Table 15.** *Public consumption in 1997.*

| *Public Consumption** | *MSEK* | *SEK per capita* |
|---|---|---|
| General public services | 39 794 | 4 498 |
| Defence | 39 234 | 4 434 |
| Public order and safety | 22 884 | 2 586 |
| University research | 11 363 | 1 284 |
| Housing and community amenity services | 5 031 | 569 |
| Recreation, culture and religion | 25 361 | 2 866 |
| Agriculture, forestry, hunting and fishing | 1 097 | 124 |
| Mining and quarrying, manufacturing and construction | 544 | 61 |
| Transportation and communication | 11 137 | 1 259 |
| Other economic affairs and services | 4 265 | 482 |
| Expenditure not classified by major group | 1 469 | 166 |
| Total | 162 179 | 18 330 |

* Education, health care, and social security and welfare not included.

Source: Statistics Sweden.

## 4.5. Other private consumption

### 4.5.1. Elderly care fees and disposable incomes for the elderly

The consumption for people over 75 years of age does not seem to be readily available in any published source. Instead, their consumption possibilities have been estimated indirectly, based on their total income in terms of pensions, allowances, labour income and net capital returns. For the elderly, who do not have children living at home, consumption and disposable income could be expected to be pretty close, since consumption plus savings equal disposable income, and the savings are on average quite low in Sweden. Pensions, allowances, labour incomes, and net capital incomes for people over the age of 65 were obtained from Statistics Sweden (Incomes, taxes and allowances in 1997, Tables 4.3, 6.2, and 23). No age-distributed figures on net capital incomes were available specifically for people over 85 years of age, but I assumed that all people over the age of 75 have the same average income from capital.

The only major type of allowance that I have identified for the elderly is the housing allowance. In the report "Incomes, taxes and allowances in 1997" the sums and the number of persons in different age groups receiving housing allowances are available. By using the population statistics, these numbers were transformed to the per capita figures that are shown in table 16a.

**Table 16a.** *Housing allowances for the elderly (SEK).*

| Age | Housing allowance |
|---|---|
| 65-69 | 1 751 |
| 70-74 | 2 521 |
| 75-79 | 3 888 |
| 80+ | 9 278 |

Source: Incomes, taxes and allowances in 1997.

The average housing allowance for those over 80 is in fact quite large. The explanation for this is that the housing allowances have been relatively generous for elderly people with low incomes ("Taxor för vård och omsorg – ett hjälpmedel"). By using curve fitting of the data in table 16a, the housing allowance for the age group 80-84 was estimated to be SEK 6 673 per year. The housing allowances were then calculated for the usual age groups used in this paper. The results are shown in table 16b.

**Table 16b.** *Housing allowances for the elderly (SEK). Estimated results.*

| Age | Housing allowance |
|---|---|
| 65-74 | 2 130 |
| 75-84 | 5 018 |
| 85+ | 12 450 |

Source: Incomes, taxes and allowances in 1997, and my own estimations.

Pre-tax incomes were available in the statistics. Tax payments were not directly available, but I have calculated these by applying the appropriate tax rate to the average income of each age group. This is an approximation, since the income distribution will affect the average tax rate in each age group. However, the approximation seems to be a fairly good one. According to Statistics Sweden (Incomes, taxes and allowances in 1997), the sum of the taxes paid by people over 65 amounted to SEK 39.5 billion in 1997, while my calculation gives an estimated sum of SEK 39.9 billion. The resulting incomes, taxes and allowances are displayed in table 17.

**Table 17.** *Incomes, taxes and allowances for the elderly.*

| Age | Average income | Income tax | Housing allowance | Disposable income |
|---|---|---|---|---|
| **65-74** | 155 169 | 45 215 | 2 130 | 112 084 |
| **75-84** | 127 204 | 36 961 | 5 018 | 95 261 |
| **85+** | 98 855 | 28 031 | 12 450 | 83 274 |

Source: Incomes, taxes and allowances in 1997, and my own estimations.

I made separate calculations for capital incomes and for incomes from pensions and work. For capital incomes, a flat tax of 30% applies. The decomposition of earnings and taxes is shown in table 18.

**Table 18.** *The composition of incomes and taxes.*

| Age | Earnings | Earnings tax | Capital income | Capital income tax |
|---|---|---|---|---|
| **65-74** | 139 843 | 40 617 | 15 326 | 4 598 |
| **75-84** | 111 107 | 32 132 | 16 097 | 4 829 |
| **85+** | 82 758 | 23 202 | 16 097 | 4 829 |

Source: Incomes, taxes and allowances in 1997, and my own estimations.

The next step is to calculate the adjusted disposable income, i.e. the amount that is left after the elderly care fees for nursing homes and home help services have been paid. The elderly care fees have been obtained from a survey performed by Statistics Sweden.

**Table 19.** *Elderly care fees for home help and nursing homes.*

| Age | Income | Home help | Nursing home |
|---|---|---|---|
| **65-79** | 148 467 | 6 252 | 68 340 |
| **80+** | 109 556 | 5 424 | 61 848 |

Source: Statistics Sweden. Avgifter inom kommuner och landsting 1997.

The level of the elderly care fee is related to the income of the individual. For simplicity, I assumed that incomes and elderly care fees are linearly related. I calculated a linear relationship between the average incomes and the average fees for the two age groups in table 19. I then applied this relationship to the average income for each age group. Finally, the estimated home help and nursing home fees were multiplied with the proportion in each age group that uses each type of elderly care. The resulting average total fees are displayed in table 20.

**Table 20.** *Estimated average elderly care fees.*

| Age | Income | Home help fee | Proportion with fee | Nursing home fee | Proportion with fee | Average total fee |
|---|---|---|---|---|---|---|
| **65-74** | 155 200 | 6 395 | 0,032 | 69 463 | 0,011 | 972 |
| **75-79** | 133 400 | 5 931 | 0,086 | 65 826 | 0,071 | 5 197 |
| **80-84** | 118 200 | 5 608 | 0,189 | 63 290 | 0,132 | 9 437 |
| **85-89** | 103 700 | 5 299 | 0,315 | 60 871 | 0,286 | 19 074 |
| **90+** | 88 100 | 4 967 | 0,400 | 58 268 | 0,487 | 30 335 |

Source: Statistics Sweden and my own estimations.

The results from table 20 can now be combined with the disposable incomes from table 17. The adjusted disposable income is defined as the difference between disposable income and elderly care fees. It is the adjusted disposable income that is available for private consumption.

**Table 21.** *Estimated disposable income and elderly care fees.*

| Age | Disposable income | Elderly care fee | Adjusted disposable income |
|---|---|---|---|
| **65-74** | 112 084 | 972 | 111 111 |
| **75-84** | 95 261 | 6 918 | 88 343 |
| **85+** | 83 274 | 22 425 | 60 848 |

The adjusted disposable income for the age group 65-74 was in a sense unnecessary to calculate, since the consumption for this group is already included in the Family Expenditure Survey. Yet it is interesting to compare the figure with that based on the Family Expenditure Survey (SEK 117 165), which is higher than the other figure by several thousands of SEK. This difference shows that the figures are somewhat uncertain. The Family Expenditure Survey has a sampling error, and furthermore I did not take account of savings when I estimated consumption from disposable income. Since the consumption figures for the younger age groups come from the Family Expenditure Survey, I have for reasons of uniformity decided to retain the figure based on the Family Expenditure Survey for the age group 65-74 in the final results.

When calculating the elderly care fees above, I did not take into account that these mostly consist of fees concerning meals and housing rents. Only a minor part of the fees seems to concern care. The fees for meals are available from "Taxor för vård och omsorg – ett hjälpmedel." ("Health and elderly care fees – a reference guide"). However, some municipalities report the monthly fee, while others report the daily fee or,

most often, the fee per meal. Assuming 30 days in a month and 2 meals per day, I transformed all figures to monthly fees. For the municipalities where fees are available, i.e. for 279 out of 288, the average monthly fee is SEK 2 150.

The average was not weighted to take account of the size of the population in each municipality. To make an assessment of this, I calculated the average population-weighted fee for Sweden's ten largest municipalities, together representing 2.3 million inhabitants, or 27% of the Swedish population.[1] The average fee in these municipalities was SEK 2 159. Size does not seem to matter much in this case, and there is no reason to modify the average fee of SEK 2 150 calculated above.

The next step is to calculate the housing fees. Here I have relied on a survey performed by the National Board of Health and Welfare (Äldreuppdraget 97:8). The report includes figures given by the elderly themselves, as well as figures stated by the municipalities. The author of this report claims that the figures reported by the elderly themselves are trustworthier, but I find that these figures are perhaps too high. The average yearly total fees, which are available from another source (Avgifter inom kommuner och landsting 1997), set a limit on how high the housing fees can be. For those over 80 years of age, the monthly housing fees can be SEK 61 848/12 – 2 150 = 3 004 at the highest, if no room is left for fees for personal aid and care. As a compromise, I took the average of the average fees reported by the municipalities and the elderly themselves. This resulted in an average housing fee of SEK 2 678 per month, implying a total average fee for meals and housing of SEK 2 150 + 2 678 = 4 828. Since the total average monthly elderly care fee was SEK 5 545, only SEK 717 concerned personal aid and care. The fees for meals and housing were subtracted from the nursing home fees in table 19, and then distributed by age in the same way as in table 20 (by linear relationships). It was assumed that the fees for meals and housing are age-distributed in the same way as the total fees. The average fee for care and personal aid is shown in table 22. These are the figures that I used for estimating the consumption of the elderly. The meals and the housing are publicly provided, but must nevertheless be classified as private consumption.

**Table 22.** *The part of the yearly fee that concerns personal aid and care.*

| Age | Average fee | Disposable income | Adjusted disposable income |
|---|---|---|---|
| 65-74: | 301 | 112 084 | 111 783 |
| 75-84: | 1 532 | 95 261 | 93 729 |
| 85+: | 4 437 | 83 274 | 78 837 |

It should be noted that the fees displayed in table 22 are quite sensitive to the assumptions that I have made, in particular with regard to the housing fees. If I use the figures stated by the elderly themselves, SEK 2 980, I get fees of about SEK 260 for the age group 65-74, about SEK 1 200 for the age group 75-84, and about SEK 3 300 for the those over the age of 85. If instead I use the average housing fee according to the municipalities (SEK 2 380), the figures become SEK 340, 1 870 and 5 560 respectively.

### 4.5.2. The Family Expenditure Survey

The age-related data on private consumption has primarily been obtained from the Family Expenditure Survey of Statistics Sweden. It was carried out most recently in 1996. There are several problems with the data from this survey. First, taxes on goods and services are included. This is a potential problem, since these taxes can be used to finance government consumption. If the taxes on private consumption in a country are high, and these taxes are then spent on government consumption, this will increase the sum of private and public consumption at market value without increasing the total consumption at factor cost. This is shown in appendix 4. I have tried to take account of this problem by estimating private consumption with net indirect taxes both included and excluded. However, I will base my main results on the consumption figure with indirect taxes excluded, since this represents the cost of consumption at factor prices. This cost is deemed to be most correct as an opportunity cost in health economic evaluations.

Second, according to estimates in the Family Expenditure Survey, the consumption as measured by the survey usually has been only about 94% of the actual consumption as measured by total sales. This is probably due to the fact that the households participating in the survey register their expenses by bookkeeping, and in practice the house-

[1] Stockholm, Göteborg, Malmö, Uppsala, Linköping, Västerås, Norrköping, Örebro, Jönköping, and Helsingborg (Table 35 in the Statistical Yearbook of Sweden 1999).

holds tend not to account for all of their expenses. I have tried to take account of this deviation by using figures on total consumption from the national accounts, and then make a distribution according to the age structure of consumption reflected by the Family Expenditure Survey of 1996. In 1997, the total consumption was about SEK 920 billion (Statistical Yearbook of Sweden 2000, Table 322). According to the Family Expenditure Survey, the total consumption in the ages between 0 and 74 was about SEK 743 billion. These figures are of course not directly comparable, partly since the years are not the same, and partly since people over the age of 75 have not been included in the survey. This problem has been tackled by separately estimating the 1997 consumption of people over 75 years of age, and then subtracting their consumption from the total figure for 1997. The figures in table 23 are based on disposable incomes for the elderly, which have been taken from table 22. A compensating factor, by which I scaled up the figures in the Family Expenditure Survey, was then calculated by dividing the estimated total consumption of people between 0 and 74 in 1997 with the total consumption for people between 0 and 74 as given by the Family Expenditure Survey.

**Table 23.** *Estimated consumption expenditures for people over 75 in 1997.*

| Age | 75-84 | 85+ | 75+ |
|---|---|---|---|
| Per-capita consumption (SEK) | 93 729 | 78 837 | 90 007 |
| Number of people | 578 413 | 192 752 | 771 165 |
| Total consumption (MSEK) | 54 214 | 15 196 | 69 410 |

Source: Statistics Sweden and my own estimations.

The estimated consumption of people between 0 and 74 in 1997 was calculated by subtracting the consumption of people over the age 75 from the total consumption, MSEK 919 975 - 69 410 = 850 565. This figure was divided by the total consumption of people between 0 and 74 according to the Family Expenditure Survey to give what I have called compensating factor 1, which is equal to 850 565/742 737 = 1.145. The results are shown in table 24.

**Table 24.** *Consumption in 1997 (MSEK).*

| | |
|---|---|
| Total consumption in 1997 | 919 975 |
| - Estimated consumption for those over the age of 75 in 1997 | -69 410 |
| = Estimated consumption 0-74 in 1997 | 850 565 |
| Consumption 0-74 according to the Family Expenditure Survey 96 | 742 737 |

Source: Statistics Sweden and my own calculations.

Taking taxes on goods and services net of subsidies into account, I have also calculated an additional compensating factor, called compensating factor 2. The calculation of the net indirect taxes are shown in table 25.

**Table 25.** *Indirect taxes 1997 (MSEK).*

| | |
|---|---|
| Value-added taxes | 97 827 |
| Excise taxes | 62 629 |
| Net indirect taxes | 160 456 |

Source: Statistics Sweden.

The sum of the value added taxes on the households' consumption, including the households' non-profit associations, was MSEK 97 827 in 1997 (see appendix 2). Other consumer taxes on goods and services must be added to this figure, such as the special excise taxes on alcoholic beverages, tobacco, energy, and road vehicles. In total, these taxes amounted to MSEK 62 629 in 1997 (Tax Statistical Yearbook of Sweden 1999, Table 1.2). The net indirect taxes must also be subtracted from the estimated consumption of people over 75. In the absence of better information, I have assumed that the ratio between net indirect taxes and consumption is the same for those over 75 as for the population as a whole. The compensating factor 2 is thus (919 975 – 160 456 – 69 410 · (1 – 160 456 /919 975))/ 742 737 = 0.945. A potential problem here is that I have not compensated for different consumption patterns in different age groups. For example, if people in certain age groups tend to consume relatively more tobacco, alcoholic beverages and gasoline, the results of my calculations will be slightly inaccurate, since these goods have particularly high tax rates.

The compensating factors are used in table 26 below to calculate the consumption figures for 1997, with and without net taxes on goods and services.

**Table 26.** *Consumption expenditures per adult in 1996 and in 1997.*

| Age | 0-19 | 20-34 | 35-49 | 50-64 | 65-74 | 0-74 |
|---|---|---|---|---|---|---|
| Health care | 1 377 | 1 754 | 1 580 | 3 052 | 3 337 | 2 073 |
| whereof | | | | | | |
| Medicines | 291 | 306 | 352 | 593 | 900 | 444 |
| Physician and hospital care | 325 | 604 | 321 | 514 | 1 066 | 499 |
| Total expenditures (96) - unadjusted | 60 131 | 93 925 | 86 932 | 114 026 | 103 655 | 88 606 |
| Total expenditures (97) - adjusted | 68 861 | 107 561 | 99 552 | 130 580 | 118 703 | 101 470 |
| Total expenditures* (97) | 68 376 | 106 847 | 99 021 | 129 705 | 117 154 | 100 727 |
| Total expenditures excluding net taxes on goods and services* (97) | 56 406 | 88 129 | 81 707 | 107 013 | 96 577 | 83 091 |

* 70% of pharmaceutical costs deducted as well as estimated costs for medical consultations.

In table 26 most health care expenditures have been excluded, since these expenditures have been estimated separately. For example, the out-of-pocket expenditures for pharmaceuticals are included in table 3. However, according to the Swedish Pharmaceutical Statistics, people paid on average 27% of their pharmaceutical prescription bills privately in 1997. The government reimbursed the rest. Since the total value of prescription sales in 1997 was MSEK 14 392, the privately paid costs amounted to about MSEK 3 886. The total costs for OTC pharmaceuticals were MSEK 1 695 in 1997. Assuming that the same ratio is applicable to all age groups, this means that the costs for prescription pharmaceuticals were about 70% of the total private medical costs. Thus, I have kept only 30% of the costs for medicines in the total consumption figures in table 26 above, and subtracted the rest in order to avoid double counting.

The average out-of-pocket costs for dental care from the Family Expenditure Survey are somewhat lower than the average costs from the figures in table 7, namely about SEK 840 as compared to SEK 976, but this may very well be due to the sampling error.

It should also be noted that the per capita consumption figures in table 26 are not directly found in the Family Expenditure Survey, since the survey measure the consumption of *households*, not individuals. In order to obtain estimates of the per capita consumption, the consumption of children had to be factored out. For this purpose, so-called consumption units were used. These are presented in appendix 3, together with some original data from the Family Expenditure Survey.

## 5. Private health care expenditures

Private fees for medical consultations paid by people under the age of 75 are available in the Family Expenditure Survey, but these figures also involve fees to chiropractors and massage therapist. For people over the age of 65, survey data are available from the Yearbook of Health and Medical Care 1999. Unfortunately, the figures from the Family Expenditure Survey and the Yearbook are not compatible. The survey figures in the Yearbook are almost certainly too low, since they give aggregate figures that are significantly lower than would be expected from both the pattern in the Family Expenditure Survey, and the total private health care expenditures available elsewhere in the Yearbook. On the other hand, the figures in the Family Expenditure Survey are probably too high, since they also include fees to chiropractors, massage therapist etc.

**Table 27.** *Private fees for medical visits in SEK in 1997, according to data from the Income Distribution Survey.*

| *Age* | *Average fee Men* | *Number of men* | *Average fee Women* | *Number of women* | *Average fee Total* |
|---|---|---|---|---|---|
| **65-74** | 503 | 356 758 | 523 | 414 451 | 513 |
| **75-84** | 578 | 236 311 | 564 | 342 102 | 570 |
| **85+** | 528 | 59 039 | 525 | 133 713 | 526 |
| **All 65+** | 532 | 652 108 | 539 | 890 266 | 536 |

Source: Yearbook of Health and Medical Care 99, table 5:14, and my own calculations.

I have tried to reconcile the different figures by taking the age distribution in the Family Expenditure Survey as a basis, and then scale the fees for those over 65 with the help of the age distribution for people over 65 from the Yearbook. Since the fee for people over 65 is SEK 1 066 according to the Family Expenditure Survey, the estimated fee for the age group 75-84 becomes SEK 570/513 · 1 066 = 1 183, and the estimated fee for those over 85 years of age becomes SEK 526/513 · 1 066 = 1 092. The next step is to use these figures (called Per capita 1 in table 28) to calculate the total private fees. The sum is MSEK 4 882, which is too high if we compare with the total fees according the Yearbook of Health and Medical Care 99. The final step is to scale down the fees so that they become compatible with the total sum of MSEK 3 788 (Sum 2). From these sums the average fees per capita in each age group are calculated (Per capita 2 in table 28). The caveat here is that this scaling exercise presupposes that the fees for chiropractors

and massage therapists are age distributed in the same proportion as ordinary medical consultations.

**Table 28.** *Estimation of private fees for medical visits in 1997.*

| Age | 0-19 | 20-34 | 35-49 | 50-64 | 65-74 | 75-84 | 85+ | Sum |
|---|---|---|---|---|---|---|---|---|
| Per capita 1 (SEK) | 325 | 604 | 321 | 514 | 1 066 | 1 183 | 1 092 | |
| Number of people | 2 157 077 | 1 805 791 | 1 787 597 | 1 554 786 | 771 209 | 578 413 | 192 752 | 8 847 625 |
| Sum 1 (MSEK) | 701 | 1 091 | 574 | 799 | 822 | 684 | 211 | 4 882 |
| Percentage | 14,4% | 22,3% | 11,8% | 16,4% | 16,8% | 14,0% | 4,3% | 100,0% |
| Sum 2 (MSEK) | 544 | 846 | 445 | 620 | 638 | 531 | 163 | 3 788 |
| Per capita 2 (SEK) | 252 | 469 | 249 | 399 | 827 | 918 | 848 | |

An unexpected result in table 28 is that the fee is very high for the age group 20-34. In most cases, health care fees seem to increase rather smoothly with age, except perhaps for the oldest (75+), where the fees and costs often seem to level out. I do not know whether or not there is a plausible explanation for this result. Perhaps the anomaly is caused by the sampling error in the Family Expenditure Survey.

The costs for eyeglasses and medical articles (other than pharmaceuticals) were distributed according to age with the total private health care costs in the Family Expenditure Survey used as a basis (Per capita 1 in table 29). It was assumed that the health care consumption of people over 75 is the same as for those between 65-74 years of age. The resulting average fees are shown as Per capita 2 in table 29.

**Table 29.** *Estimation of private costs for eyeglasses and medical articles in 1997.*

| Age | 0-19 | 20-34 | 35-49 | 50-64 | 65-74 | 75-84 | 85+ | Sum |
|---|---|---|---|---|---|---|---|---|
| Per capita 1 (SEK) | 1377 | 1754 | 1580 | 3052 | 3337 | 3337 | 3337 | |
| Number of people | 2 157 077 | 1 805 791 | 1 787 597 | 1 554 786 | 771 209 | 578 413 | 192 752 | 8 847 625 |
| Sum 1 (MSEK) | 2 970 | 3 167 | 2 824 | 4 745 | 2 574 | 1 930 | 643 | 18 854 |
| Percentage | 15,8% | 16,8% | 15,0% | 25,2% | 13,6% | 10,2% | 3,4% | 100,0% |
| Sum 2 (MSEK) | 559 | 597 | 532 | 894 | 485 | 364 | 121 | 3 551 |
| Per capita 2 (SEK) | 259 | 330 | 298 | 575 | 628 | 628 | 628 | |

The private pharmaceutical costs have been estimated from table 3 and from the Family Expenditure Survey. In the first round, the pharmaceutical expenditures were estimated by combining the privately paid part of the prescription pharmaceuticals with the estimated expenses on OTC pharmaceuticals taken from the Family Expenditure Survey (about 30% of the costs concern OTC pharmaceuticals). When these costs are added (Privately paid + OTC pharma = Per capita 1) and summed up, we arrive at Sum 1 in table 30. However, this sum (MSEK 5 330) is lower than the sum in the Yearbook of

Health and Medical Care 1999 (MSEK 5 842). A plausible explanation for the deviance is that I have underestimated the costs for OTC pharmaceuticals by relying on the Family Expenditure Survey. If the larger sum is distributed according to the same age distribution as Sum 1, we get Per capita 2 in table 30.

**Table 30.** *Estimation of private costs for pharmaceuticals in 1997.*

| *Age* | 0-19 | 20-34 | 35-49 | 50-64 | 65-74 | 75-84 | 85+ | Sum |
|---|---|---|---|---|---|---|---|---|
| Prescription pharma | 539 | 795 | 1 349 | 2 425 | 3 485 | 3 946 | 3 324 | |
| Privately paid | 170 | 285 | 380 | 625 | 815 | 978 | 979 | |
| OTC pharma | 100 | 105 | 121 | 204 | 309 | 309 | 309 | |
| *Per capita 1 (SEK)* | 270 | 390 | 501 | 829 | 1 124 | 1 287 | 1 288 | |
| *Number of people* | 2 157 077 | 1 805 791 | 1 787 597 | 1 554 786 | 771 209 | 578 413 | 192 752 | 8 847 625 |
| *Sum 1 (MSEK)* | 582 | 704 | 895 | 1 289 | 867 | 744 | 248 | 5 330 |
| *Percentage* | 10,9% | 13,2% | 16,8% | 24,2% | 16,3% | 14,0% | 4,7% | 100,0% |
| *Sum 2 (MSEK)* | 638 | 772 | 981 | 1 413 | 950 | 816 | 272 | 5 842 |
| *Per capita 2 (SEK)* | 296 | 427 | 549 | 909 | 1 232 | 1 411 | 1 412 | |

Out-of-pocket costs for dental care are available in table 7. The patient fees for medical care were deducted from the figures in the family expenditure survey. Putting it all together, we get the out-of-pocket health care costs shown in table 31.

**Table 31.** *Estimated out-of-pocket health care costs in 1997.*

| *Age* | 0-19 | 20-34 | 35-49 | 50-64 | 65-74 | 75-84 | 85+ | All |
|---|---|---|---|---|---|---|---|---|
| *Pharmaceuticals* | 296 | 427 | 549 | 909 | 1 232 | 1 411 | 1 412 | 660 |
| *Eyeglasses and medical articles* | 259 | 330 | 298 | 575 | 628 | 628 | 628 | 401 |
| *Patient fees* | 252 | 1 298 | 1 235 | 1 470 | 1 881 | 1 944 | 1 865 | 1 166 |
| Dental care | 0 | 829 | 986 | 1 071 | 1 054 | 1 026 | 1 017 | 738 |
| Medical care | 252 | 469 | 249 | 399 | 827 | 918 | 848 | 428 |
| *Total health care* | 807 | 2 055 | 2 082 | 2 953 | 3 741 | 3 983 | 3 905 | 2 228 |
| | | | | | | | | |
| *Sum (MSEK)* | 1 742 | 3 712 | 3 721 | 4 592 | 2 885 | 2 304 | 753 | 19 708 |

## 6. Consumption and production

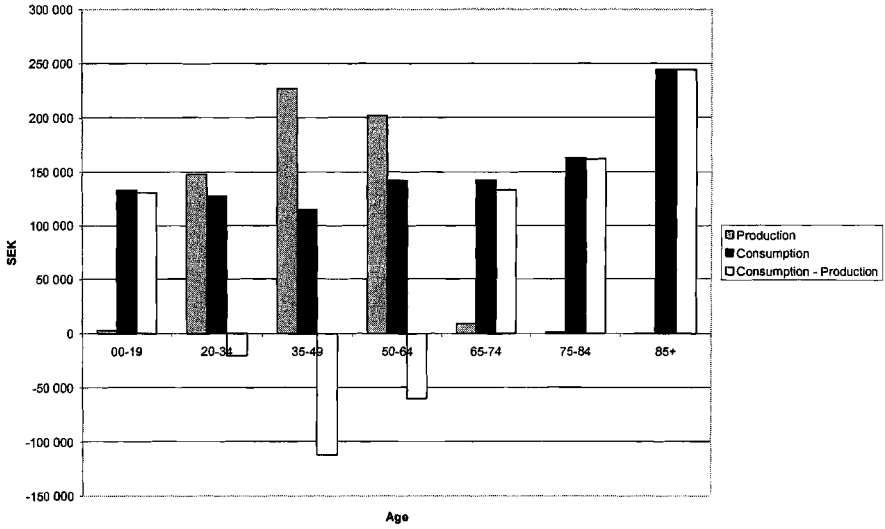
Putting it all together, we get the following table:

**Table 32.** *Consumption and production in different age groups.*

| *Age* | 00-19 | 20-34 | 35-49 | 50-64 | 65-74 | 75-84 | 85+ |
|---|---|---|---|---|---|---|---|
| ***Consumption*** | 133 290 | 127 442 | 114 927 | 142 074 | 142 420 | 163 084 | 244 369 |
| Health care | 5 914 | 7 529 | 9 652 | 13 623 | 20 395 | 26 732 | 27 601 |
| Social services | 2 138 | 3 417 | 3 417 | 3 417 | 8 159 | 46 113 | 149 219 |
| Other public consumption | 68 832 | 29 195 | 21 137 | 19 090 | 18 343 | 18 330 | 18 330 |
| Other private consumption | 56 406 | 87 300 | 80 721 | 105 942 | 95 523 | 71 909 | 49 219 |
| ***Production*** | 2 750 | 148 140 | 227 115 | 202 079 | 9 101 | 1 033 | 169 |
| ***Consumption - Production*** | 130 540 | -20 698 | -112 188 | -60 005 | 133 319 | 162 051 | 244 200 |

Since the intention is to use the figures as an estimate of costs of added years of life, the difference between consumption and production has been calculated. A positive difference indicates a cost in this context. The results are also displayed graphically in figure 1 below.

**Figure 1.** *Consumption and production in different age groups.*



## 7. Reliability and uncertainty

An important topic that I have as yet barely touched upon is the accuracy of the underlying data. In some cases, such as the income figures for example, I think that it is reasonable to expect the data to be fairly reliable. However, since the age-related income figures are based on income reported to the tax authorities, there is probably some underreporting due to illicit work. By their very nature, illicit earnings are difficult to estimate, but they seem to be far from negligible. According to estimations by the Swedish National Audit Office, illicit earnings correspond to about 5 % of total work hours or 3% of the GDP (Tax Statistical Yearbook of Sweden). However, I have not made any attempt to take account of possible underreporting of income.

On the consumption side, the age distributions almost always have been based on sampling surveys. Unfortunately, the sampling error was often not displayed in the sources. However, based on the data in the original Family Expenditure Survey, I estimate that at the 95% confidence level, the margin of error for the total consumption is about SEK 5 000 to 10 000 for each age group. For example, this range of uncertainty means that results that the consumption expenditure is larger for those aged 20-34 than for those aged 35-49 may very well be due to the sampling error. We can also compare the consumption for the age group 65-74 as reflected in the data based on the Family Expenditure Survey (SEK 117 154) with the consumption based on the estimated disposable income (SEK 112 084). The difference between these figures could possibly also be due to the sampling error of the Family Expenditure Survey. In addition, it should be noted that the latter figure ignores that the elderly perhaps use some of their savings for consumption expenditures.

From an intuitive viewpoint, some results seem to be unreliable. For example, it is a bit strange that the private costs concerning physician and hospital care for the age group 20-34 are higher than for those aged 35-65, in spite of the fact that the public spending is lower for the former age group. However, I have resisted from tampering with this figure, although I find it likely that the sampling error is to blame for the surprising result. For small subcategories of the Family Expenditure Survey, like this one, the sampling error can probably be quite large, but it is not explicitly stated in the survey. For the

total private health care expenditure, the sampling error may be as large as ±50%, and may thus be even higher for smaller subcategories of consumption.

Apart from the sampling error, there may also be systematic errors in the surveys. The Family Expenditure Survey, for example, is known to underestimate the total consumption somewhat. I compensated for this by using the total expenditures from the national accounts and then distributing these according to the age distribution of expenditures found in the survey. The motivation for this is that the total figures seem to be more reliable than the aggregated survey figures. The total consumption can, for example, be estimated from the total sales to private consumers in the economy. This figure can be estimated with a better degree of accuracy than the survey data. Except for the Family Expenditure Survey, the same method had to be applied to the private dental care expenditures and the private health care expenditures of elderly people. There may be other systematic errors as well. In the Family Expenditure Survey, for example, the respondent families had more children than the average Swedish family. It is hard to say how this affects the level of expenditure, but in any case it shows that the families participating in the survey are not entirely representative for the population at large.

For the elderly it might in fact be better to estimate the consumption indirectly based on the disposable income rather than estimating the consumption directly by way of a survey. The same is perhaps true for younger people, but you would then still have to use consumption units[2] to separate the consumption of the children from the consumption of the parents. Of course, the result would then be contingent on the accuracy of the consumption units, but this caveat applies to the results from the Family Expenditure Survey as well. If the consumption units do not correctly reflect the consumption for children and adults, then an age distribution based on the Family Expenditure Survey will also be inaccurate.

The most serious drawback of the disposable income approach for estimating the age distribution of consumption is that no information is obtained about the composition of the consumption in terms of expenditure for health care, housing, cloths etc. However,

[2] See appendix 3.

most of the health care consumption, with the exception of chiropractors, massage therapist etc, can be estimated from other sources.

## 8. Validity

The purpose of compiling these figures on production net of consumption for different age groups has primarily been to use them for health economic calculations. A particular problem in this context is that the figures represent average consumption and production for the whole population. These figures are not necessarily applicable to subpopulations affected by specific diseases. The fact that health is correlated to income poses problems. If you are suffering from poor health, then you are likely to be poorer than average in economic terms as well. Not surprisingly, health and elderly care expenditures are strongly correlated with the health status. To take a concrete example, the Swedish government has calculated so-called norm costs as a basis for distributing subsidies between municipalities. Among other things, norm costs correlate with health status, socio-economic status, marital status and sex to elderly care costs. Calculations show that within each age group, the average costs for elderly care varies widely depending on health status. For example, men aged 65-74 with full health had average elderly care costs of SEK 14 per year, whereas those with severe health problems had average costs of SEK 110 009 per year. For men over 85 years of age, the average costs were SEK 3 164 for those with full health, whereas those with severe health problems had average costs of SEK 226 657 (Batljan and Lagergren, 2000, Table 3.2). For women, there are similar patterns.

Ideally, income and consumption figures for the group under study should be used. However, in a health economic study, patient specific data on income and consumption are usually not readily available. For prevention studies, the average figures compiled here would probably often be suitable, but for specific diseases the applicability would have to be evaluated from case to case.

Another major problem concerns the extension of the production and consumption figures into the future. Often a health economic evaluation includes health effects and

economic consequences that carry on for many years. The output of the economy as well as the demographic patterns are changing over time, which means that extrapolations of current data into the future are likely to end up in unreliable results. For example, the Swedish baby-boom generation born in the 1940's is better educated and has a higher average income than previous generations. As this generation goes into retirement, the incomes and probably also the consumption expenditures of the elderly will become higher than today, both in absolute terms and relative to younger generations. The health status of the baby-boom generation is also likely to be better than for the current generation of elderly people. In Sweden the percentage of the elderly with poor or severely poor health has diminished considerably during the last decades, particularly for the younger old (65-84) (Batljan and Lagergren, 2000).

# 9. Applications

## 9.1. Resource consequences of mortality changes

One application of the figures on consumption net of production is the calculation of resource consequences of mortality changes. In this context, figures on consumption and production by age can be used to estimate what Johannesson (1994; 1996) calls the external costs, i.e. the effect on other people's consumption as a consequence of the health care program.

A simplified cost-benefit framework for an individual is shown in figure 2. Here, the benefits and costs of a prolonged life for the individual as well as for the rest of society are shown. I have disregarded certain aspects, such as the value other individuals in society may put on the individual's life (altruistic externality). The presence and severity of disease affect both income and willingness to pay (WTP), so a more complicated model such as the one presented by Meltzer (1997) is needed for all full analysis. However, the purpose of the present discussion is only to illustrate the general principles of what costs to include.

**Figure 2.** *Benefits and costs of prolonged life attributable to an individual.*

| | Benefits | Costs |
|---|---|---|
| Individual himself | • WTP for private consumption<br>• WTP for public consumption | • Cost of private consumption |
| Rest of society | • Taxes (paid by the individual) | • Cost of public consumption |
| Total | • WTP of consumption + Taxes | • Cost of total consumption |

Disregarding savings and investments, Taxes = Production – Net income. We also have that Net income = Cost of private consumption. From these relations it follows that Taxes = Production – Cost of private consumption. This in turn means that we can write the benefits as

Benefits = WTP for consumption + Production – Cost of private consumption,

and the costs as

Costs = Cost of total consumption.

In both cost-benefit and cost-effectiveness analysis, Production usually appears on the cost side (production losses are defined as indirect costs). We can thus move Production from the benefit side to the cost side:

Benefits = WTP for consumption – Cost of private consumption =
= Consumer surplus + WTP for public consumption.

and

Costs = Cost of total consumption – Production.

Presumably, when the WTP for a life-saving treatment is measured, the individual takes into account all benefits of consumption during the additional lifetime, whether private or public. The consumer surplus is defined as the difference between what a consumer is willing to pay and what he actually has to pay (Katz & Rosen, 1998, p.110). This is the net monetary value of the individual's private consumption. Since I have assumed that the public consumption is entirely tax financed, its value for the individual is equal to the WTP.

There is a saying that the best things in life are free, so the question is if the above measure captures all the benefits. Perhaps not, but tangible and intangible benefits are often hard to disentangle. If we buy food, for example, we may invite friends for dinner, thus combining the pleasure of a tasty meal with stimulating conversation. One would therefore expect that the WTP for tangible goods to some extent takes into account interactions with intangible benefits like love and friendship. Let us leave the discussion there, since the purpose of this paper is not to discuss the proper measurement of benefits.

As for the costs, we can see that the proper measurement of costs in cost-benefit analysis is the change in consumption minus production for the treated individual. All costs in added years of life are included, whether medical or non-medical. From the above reasoning, we can see that these costs could also have been defined as Cost of public consumption – Taxes, i.e., net public transfers to the individual. This follows from the fact that Cost of total consumption = Cost of private consumption + Cost of public consumption, and that Production = Taxes + Cost of private consumption.

In a cost-effectiveness analysis, the conclusions are similar. In a cost-effectiveness analysis, we measure the WTP for a gained life year, or a gained quality-adjusted life year (QALY). As shown by Johannesson (1994; 1996), all costs that are not included in the measurement of the WTP for the gain in life years or QALY:s should be included as costs. If an individual is fully insured, which is usually the case in the western world, the consequence for the rest of society of an extended lifetime is a net consumption

externality, which is also here measured as the difference between consumption and production during the extended lifetime.

### 9.2. Reassessment of previous studies

The figures on consumption net of production can be used in retrospective reassessments of earlier studies that did not take costs in added years of life into account. Meltzer (1997) discusses a simplified approach to estimating the effect of including the costs of added years of life. This approach assumes that the mortality changes (ΔLE) are concentrated at the time of the intervention and that annual future costs (*C*) are roughly constant. Then the cost-effectiveness ratio (*CE*) can be expressed as

$$CE = \frac{\Delta\text{cost}}{\Delta\text{QALY}} = \frac{\Delta\text{present cost}}{\Delta\text{QALY}} + \frac{\Delta\text{future cost}}{\Delta\text{QALY}} = \frac{\Delta\text{present cost}}{\Delta\text{QALY}} + C \cdot \frac{\Delta\text{LE}}{\Delta\text{QALY}} \qquad (1)$$

Since the mortality change is available from many existing cost-effectiveness studies, and the future costs can be approximated by figures for the general population, the above formula can be used for retrospective estimates of the bias of not including future costs from studies that have been performed along traditional lines. Johannesson, Meltzer, and O'Conor (1997) studied the effect of incorporating future costs in the treatment of hypertension. They showed that the cost-effectiveness ratios can often differ considerably depending on whether future costs are included or not, especially for older patients.

Here I will look at a study that actually included cost in added years of life, but I will disregard this fact and make a reassessment as if these costs had not been included. In fact, this will also add some additional insights. The study concerned an economic evaluation of the beta blocker bisoprolol in heart failure (Ekman et al., 2001). A striking feature of that evaluation was that the cost-effectiveness ratios that included costs of added years of life were more stable for variations in critical parameters than the cost-effectiveness ratios that excluded those costs. How can this difference be explained? To

answer that question, a modified version of Meltzer's formula can be used. The cost-effectiveness ratio $R$ is written as

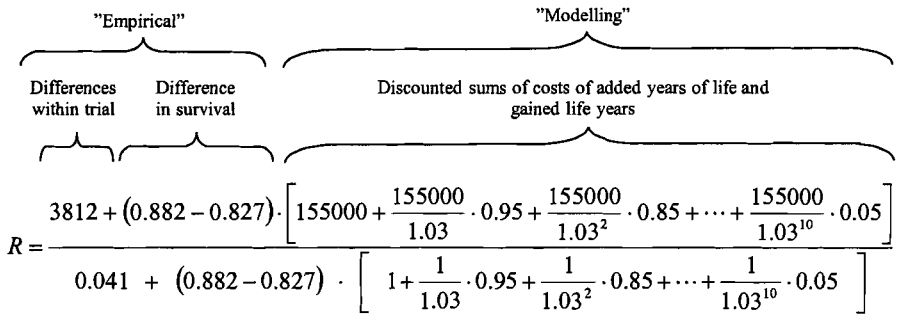
$$R = \frac{\Delta C_{trial} + \Delta S_{trial} \cdot C \cdot LE_{post-trial}}{\Delta LE_{trial} + \Delta S_{trial} \cdot LE_{post-trial}}, \quad (2)$$

where $\Delta C_{trial}$ is the cost difference per patient between bisoprolol and placebo within the clinical trial, $\Delta S_{trial}$ is the mortality difference within the clinical trial, $C$ is the cost per added year of life (assumed to be constant), $\Delta LE_{trial}$ represents the difference in lifetime within the trial, and $LE_{post-trial}$ represents the expected lifetime after the trial. In the base-case analysis, it was cautiously assumed that the mortality equalizes immediately after the end of the clinical trial. $\Delta LE$ in Meltzer's expression can therefore be separated into $\Delta S \cdot LE$, where $LE$ is the same for both the bisoprolol group and the placebo group.

The difference in treatment cost between bisoprolol and placebo within the clinical trial was SEK 3 812. The difference in survival in terms of life years within the trial was 0.041 years. During the clinical trial, the survival in the bisoprolol group was 88.2%, compared to 82.7% in the placebo group. This information was combined with an estimate of the expected additional lifetime after the end of the clinical trial, in order to create an estimate of the total difference in terms of gained life years: Incremental effect = 0.041 + (0.882 – 0.827) · Expected lifetime after the end of the clinical trial.

In the actual economic evaluation, the costs of added years of life were age dependent. For simplicity, the same value is here used for all cases, in spite of the age dependence. However, the amount of SEK 155 000 is fairly representative of the average costs of added years of life. In the economic evaluation reported in Ekman et al. (2001), the average costs of added years of life were somewhat higher than this amount, about SEK 175 000 on average, since the consumption expenditures included value-added taxes in that analysis. Costs and health effects were discounted at a rate of 3% (Lipscomb et al, 1996).

If the figures above are introduced in the modified formula (2), the following expression is obtained:




The discounted sum in the numerator represents the total costs of added life years and the discounted sum in the denominator represents the gained life years. The factors 0.95; 0.85 etc represent survival probabilities, which are used for estimating the expected remaining lifetime after the end of follow-up of the clinical trial. The timing of the discounting has also been simplified in order to get a simple algebraic expression. If we move the constant costs of added years of life out of the bracket in the numerator and calculate the sum, then we get the following result:

$$R = \frac{3812 + 0.055 \cdot 155000 \cdot 5.47}{0.041 + 0.055 \cdot 5.47} = 147600.$$

By studying the structure of this formula, we can see why the results including costs of added years of life were so stable for changes in, for example, the modelling of the survival after the trial. If we change the survival or the discount rate, the sums (here equal to 5.47) in both the numerator and denominator will change by equal amounts.

If costs of added years of life are ignored, the corresponding value of the cost-effectiveness ratio $R$ is

$$R = \frac{3812}{0.041 + 0.055 \cdot 5.47} = 11150.$$

Here, changes in the modelling of survival have a much greater effect, since the life-expectancy sum only appears in the denominator.

## 10. Summary of results and concluding remarks

The main contribution of this paper is a detailed compilation of consumption and production figures by age. The results are summarized in table 33.

**Table 33.** *Summary of consumption and production figures by age.*

| *Age* | 00-19 | 20-34 | 35-49 | 50-64 | 65-74 | 75-84 | 85+ | All |
|---|---|---|---|---|---|---|---|---|
| ***Type of consumption*** | | | | | | | | |
| **Health care** | 5 914 | 7 529 | 9 652 | 13 623 | 20 395 | 26 732 | 27 601 | 11 449 |
| whereof | | | | | | | | |
| Pharmaceuticals | 539 | 795 | 1 349 | 2 425 | 3 485 | 3 946 | 3 324 | 1 627 |
| Primary and hospital care | 4 535 | 5 648 | 7 012 | 9 795 | 15 530 | 21 442 | 22 945 | 8 652 |
| Dental care | 840 | 1 086 | 1 291 | 1 403 | 1 380 | 1 344 | 1 332 | 1 171 |
| **Social services** | 2 138 | 3 417 | 3 417 | 3 417 | 8 159 | 46 113 | 149 219 | 9 486 |
| whereof | | | | | | | | |
| Elderly care | 0 | 0 | 0 | 0 | 7 186 | 44 690 | 146 510 | 6 740 |
| Services to impaired people | 2 097 | 3 376 | 3 376 | 3 376 | 710 | 710 | 710 | 2 600 |
| Transportation services | 41 | 41 | 41 | 41 | 263 | 713 | 1 999 | 147 |
| **Education** | 50 502 | 10 865 | 2 807 | 760 | 13 | 0 | 0 | 15 232 |
| whereof | | | | | | | | |
| Schools and child care | 49 962 | 0 | 0 | 0 | 0 | 0 | 0 | 12 181 |
| Universities | 403 | 8 274 | 1 555 | 283 | 13 | 0 | 0 | 2 152 |
| Adult schooling | 83 | 1 914 | 768 | 105 | 0 | 0 | 0 | 585 |
| Labour market training | 53 | 677 | 483 | 372 | 0 | 0 | 0 | 314 |
| **General public consumption** | 18 330 | 18 330 | 18 330 | 18 330 | 18 330 | 18 330 | 18 330 | 18 330 |
| **Other private consumption** | 56 406 | 87 300 | 80 721 | 105 942 | 95 523 | 71 909 | 49 219 | 80 596 |
| ***Total consumption*** | 133 290 | 127 442 | 114 927 | 142 074 | 142 420 | 163 084 | 244 369 | 135 093 |
| ***Total production*** | 2 750 | 148 140 | 227 115 | 202 079 | 9 101 | 1 033 | 169 | 113 168 |
| ***Consumption - Production*** | 130 540 | -20 698 | -112 188 | -60 005 | 133 319 | 162 051 | 244 200 | 21 925 |

I believe that this paper shows that it is possible to measure the costs in added years of life with a fair degree of accuracy. However, there seems to be a persistent controversy as to whether is it necessary to include costs in added years of life in cost-effectiveness analyses (Meltzer, 2001). For example, the US Panel on Cost-effectiveness failed to reach any consensus on the subject (Gold et al., 1995). They leave it to the discretion of the analyst whether these costs should be included or not. However, from theoretical grounds it seems correct that the costs in added years of life reflect the resource consequences of changes in mortality (Meltzer, 1997; Johannesson, 1994; 1996). Theoretical considerations aside, some may raise the objection that the net contributions that an individual (or group of individuals) makes to others in society should not count when

medical priorities are set. Including the net contribution, which typically is negative for people aged 65 and over, could make treatments for the elderly relatively less attractive compared with treatments offered to people in productive ages. Now, of course, this is already to some extent the case, since changes in productivity are usually included in the indirect costs in economic evaluations that are carried out from a societal perspective. The difference here is primarily that changes in consumption are considered as well.

The position that costs in added years of life should not be counted because their inclusion leads to an unethical distribution of health care resources between generations is a respectable one. Even so I think we should try to measure these costs in order to see what is given up. Otherwise we cannot make any informed judgement as to whether the perceived benefit of a more equitable health care consumption is worth the cost or not. An additional disadvantage of excluding costs in added years of life is that the analysis is then biased to favour treatments that extend life over those that improve the quality of life (Meltzer 1997; 2001).

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# Appendix 1. Income per age group in 1997.

**Table A1.** *Income per age group in 1997 (SEK).*

| Age | Sex | Income | Part of income coming from self-employment | Number of persons with income | Average income | Total number of persons | Total average income | Total average income incl extra labour taxes |
|---|---|---|---|---|---|---|---|---|
| **00-15** | Men | 257 577 965 | 5,62% | 39 147 | 6 580 | 900 305 | 286 | 380 |
| | Women | 207 558 402 | 5,61% | 34 471 | 6 021 | 853 565 | 243 | 323 |
| | Total | 465 136 367 | 5,62% | 73 818 | 6 318 | 1 753 870 | 265 | 352 |
| **16-19** | Men | 2 212 167 744 | 0,70% | 135 453 | 16 332 | 206 330 | 10 722 | 14 258 |
| | Women | 1 782 975 431 | 0,37% | 132 824 | 13 424 | 196 877 | 9 056 | 12 044 |
| | Total | 3 995 143 175 | 0,55% | 268 277 | 14 892 | 403 207 | 9 908 | 13 177 |
| **20-24** | Men | 21 865 923 086 | 0,99% | 230 792 | 94 743 | 280 269 | 78 018 | 103 750 |
| | Women | 15 324 776 625 | 0,61% | 220 531 | 69 490 | 269 193 | 56 929 | 75 709 |
| | Total | 37 190 699 711 | 0,83% | 451 323 | 82 404 | 549 462 | 67 688 | 90 012 |
| **25-29** | Men | 43 556 895 242 | 1,77% | 287 571 | 162 788 | 304 492 | 143 048 | 190 209 |
| | Women | 26 941 708 962 | 1,04% | 242 747 | 110 987 | 293 500 | 91 795 | 122 070 |
| | Total | 70 498 604 204 | 1,49% | 510 318 | 138 148 | 597 992 | 117 892 | 156 768 |
| **30-34** | Men | 59 536 054 251 | 2,82% | 299 415 | 198 841 | 338 412 | 175 928 | 233 897 |
| | Women | 33 956 851 705 | 1,62% | 268 127 | 126 645 | 319 925 | 106 140 | 141 136 |
| | Total | 93 492 905 956 | 2,38% | 567 542 | 164 733 | 658 337 | 142 014 | 188 819 |
| **35-39** | Men | 57 058 004 642 | 3,69% | 261 936 | 217 832 | 299 124 | 190 750 | 253 575 |
| | Women | 34 365 179 181 | 1,99% | 244 102 | 140 782 | 285 361 | 120 427 | 160 126 |
| | Total | 91 423 183 823 | 3,05% | 506 038 | 180 665 | 584 485 | 156 417 | 207 951 |
| **40-44** | Men | 60 967 064 572 | 4,03% | 263 398 | 231 464 | 299 046 | 203 872 | 271 006 |
| | Women | 40 420 764 409 | 2,00% | 253 273 | 159 594 | 288 989 | 139 870 | 185 978 |
| | Total | 101 387 828 981 | 3,21% | 516 671 | 196 233 | 588 035 | 172 418 | 229 219 |
| **45-49** | Men | 66 578 086 743 | 4,13% | 275 936 | 241 281 | 311 369 | 213 824 | 284 231 |
| | Women | 45 993 578 769 | 1,97% | 267 314 | 172 058 | 303 708 | 151 440 | 201 363 |
| | Total | 112 571 665 512 | 3,23% | 543 250 | 207 219 | 615 077 | 183 020 | 243 314 |
| **50-54** | Men | 72 170 981 734 | 4,07% | 292 983 | 246 332 | 332 321 | 217 172 | 288 685 |
| | Women | 48 077 092 294 | 2,01% | 278 101 | 172 876 | 322 190 | 149 220 | 198 410 |
| | Total | 120 248 074 028 | 3,24% | 571 084 | 210 561 | 654 511 | 183 722 | 244 246 |
| **55-59** | Men | 47 485 697 537 | 4,33% | 205 727 | 230 819 | 248 786 | 190 870 | 253 712 |
| | Women | 31 050 502 745 | 2,09% | 194 023 | 160 035 | 244 668 | 126 909 | 168 742 |
| | Total | 78 536 200 282 | 3,43% | 399 750 | 196 463 | 493 454 | 159 156 | 211 582 |
| **60-64** | Men | 22 713 581 930 | 5,62% | 127 195 | 178 573 | 199 351 | 113 938 | 151 425 |
| | Women | 14 843 624 614 | 2,60% | 118 223 | 125 556 | 207 470 | 71 546 | 95 123 |
| | Total | 37 557 208 544 | 4,40% | 245 418 | 153 034 | 406 821 | 92 319 | 122 713 |
| **65-69** | Men | 3 278 566 053 | 15,93% | 52 215 | 82 790 | 184 535 | 17 767 | 21 750 |
| | Women | 1 410 283 196 | 9,64% | 33 769 | 41 763 | 207 350 | 6 801 | 8 328 |
| | Total | 4 688 849 249 | 13,96% | 85 984 | 54 532 | 391 885 | 11 965 | 14 647 |
| **70-74** | Men | 774 016 103 | 29,33% | 27 238 | 28 417 | 172 223 | 4 494 | 5 502 |
| | Women | 270 670 304 | 19,37% | 13 672 | 19 797 | 207 101 | 1 307 | 1 600 |
| | Total | 1 044 686 407 | 26,59% | 40 910 | 25 536 | 379 324 | 2 754 | 3 372 |
| **75-79** | Men | 279 793 243 | 35,89% | 14 534 | 19 251 | 146 367 | 1 912 | 2 340 |
| | Women | 101 710 652 | 21,08% | 6 583 | 15 451 | 197 310 | 515 | 631 |
| | Total | 381 503 895 | 31,60% | 21 117 | 18 066 | 343 677 | 1 110 | 1 359 |
| **80-84** | Men | 80 138 768 | 43,26% | 4 371 | 18 334 | 89 944 | 891 | 1 091 |
| | Women | 28 357 379 | 33,38% | 1 925 | 13 692 | 144 792 | 182 | 223 |
| | Total | 106 496 147 | 40,67% | 6 296 | 16 915 | 234 736 | 454 | 555 |
| **85+** | Men | 19 362 963 | 82,93% | 1 103 | 17 555 | 59 039 | 328 | 401 |
| | Women | 7 272 704 | 28,34% | 539 | 13 493 | 133 713 | 54 | 67 |
| | Total | 26 635 667 | 62,99% | 1 642 | 16 221 | 192 752 | 138 | 169 |
| **20-64** | Total | 742 908 389 041 | 2,89% | 4 311 394 | 172 312 | 5 148 174 | 144 305 | 191 852 |
| **All** | Total | 753 614 819 948 | 3,01% | 4 809 238 | 156 702 | 8 847 625 | 85 177 | 113 168 |

Source: Statistics Sweden.

## Appendix 2. Value-added taxes.

**Table A2.** *Value-added taxes (VAT) in MSEK per sector in 1997.*

| *Sector* | *Consumption* | *Net VAT* |
|---|---|---|
| Corporations | 1 509 782 | 17 925 |
| Households | 893 427 | 96 147 |
| NPISH* | 11 402 | 1 680 |
| Government | 239 714 | 283 |
| Gross fixed capital formation | 269 430 | 8 528 |

* NPISH = Non-profit institutions serving households, such as trade unions, sports associations, etc.

Source: Statistics Sweden.

## Appendix 3. The family expenditure survey.

The so-called consumption units in tables A3 to A5 are due to the fact that children consume less than adults and that, ceteris paribus, couples living together have lower average expenses per person than people who are living on their own. All expenditures are not increasing in proportion to the number of members in the household. The consumption units are meant to take account of this, in order to make comparisons between households with different compositions more relevant. The National Board of Health and Welfare has recommended the consumption units shown in table A3 for calculation of municipal social allowances for households. These values for the consumption units have also been used in the Family Expenditure Survey.

**Table A3.** *Households in the family expenditure survey.*

| *Family composition* | *Number of consumption units* |
|---|---|
| Single | 1,16 |
| Cohabitating | 1,92 |
| Additional adult | 0,96 |
| Child up to 3 years old | 0,56 |
| Child 4-10 years old | 0,66 |
| Child 11-17 years old | 0,76 |

Source: Statistics Sweden.

**Table A4.** *Households in the family expenditure survey.*

| *Age* | 20-34 | 35-49 | 50-64 | 65-74 | 20-74 |
|---|---|---|---|---|---|
| Number of participating households | 258 | 367 | 311 | 165 | 1 101 |
| Estimated size of population | 991 406 | 1 107 671 | 955 946 | 609 455 | 3 664 478 |
| Estimated number of persons | 1 930 334 | 3 288 198 | 2 033 066 | 1 008 997 | 8 260 596 |
| Estimated number of consumption units | 1 791 986 | 2 892 438 | 1 960 892 | 1 013 387 | 7 658 704 |
| Average number of persons | 1,95 | 2,97 | 2,13 | 1,66 | 2,25 |
| Average number of consumption units | 1,81 | 2,61 | 2,05 | 1,66 | 2,09 |
| Average number of children (0-17) | 0,52 | 1,16 | 0,27 | 0,00 | 0,56 |
| Average number of CU:s for children | 0,32 | 0,80 | 0,20 | 0,00 | 0,38 |
| Average number of adults | 1,43 | 1,81 | 1,86 | 1,66 | 1,69 |
| Average number of CU:s for adults | 1,49 | 1,81 | 1,85 | 1,66 | 1,71 |

Source: Statistics Sweden.

**Table A5.** *Expenditures in SEK per consumption unit in 1996.*

| *Age* | 20-34 | 35-49 | 50-64 | 65-74 | 20-74 |
|---|---|---|---|---|---|
| ***Health care*** | 1 683 | 1 578 | 3 061 | 3 323 | 2 213 |
| **whereof** | | | | | |
| **Medicines** | 294 | 352 | 595 | 896 | 473 |
| **Physician and hospital care** | 579 | 320 | 516 | 1 061 | 529 |
| ***Total expenditures*** | 90 108 | 86 802 | 114 364 | 103 206 | 96 803 |

Health care: including vitamines, dental care and eyeglasses.
Medicines: including OTC drugs.
Physician and hospital care: including treatments by chiropractors, massage therapists,etc.

Source: Statistics Sweden.

In the Family Expenditure Survey, the consumption expenditures are measured on a household basis. These figures are presented in table A6.

**Table A6.** *Expenditures in SEK per household in 1996.*

| *Age* | 20-34 | 35-49 | 50-64 | 65-74 | 20-74 |
|---|---|---|---|---|---|
| ***Health care*** | 3 041 | 4 119 | 6 278 | 5 524 | 4 624 |
| **whereof** | | | | | |
| **Medicines** | 531 | 918 | 1 220 | 1 490 | 987 |
| **Physician and hospital care** | 1 046 | 836 | 1 058 | 1 764 | 1 105 |
| ***Total expenditures*** | 162 871 | 226 663 | 234 590 | 171 608 | 202 316 |

Source: Statistics Sweden.

The consumption units presented in table A3 were applied to the data from the Family Expenditure Survey in order to obtain an estimate of consumption expenditure per capita, which is presented in table A7.

**Table A7.** *Expenditures in SEK per adult in 1996.*

| *Age* | 0-19 | 20-34 | 35-49 | 50-64 | 65-74 | 0-74 |
|---|---|---|---|---|---|---|
| ***Health care*** | 1 377 | 1 754 | 1 580 | 3 052 | 3 337 | 2 073 |
| **whereof** | | | | | | |
| **Medicines** | 291 | 306 | 352 | 593 | 900 | 444 |
| **Physician and hospital care** | 325 | 604 | 321 | 514 | 1 066 | 499 |
| ***Total expenditures*** | 60 131 | 93 925 | 86 932 | 114 026 | 103 655 | 88 606 |

Source: Statistics Sweden and my own calculations.

## Appendix 4. National accounts relationships.

The following set of national accounting identities is intended to describe the flow of transactions in the economy (Beckerman, 1976). It is assumed that this particular economy has no trade with other countries. This makes no difference for the argument.

Production account: $Y_h + T_f + T_i + S_f = C_h + C_g + GDCF$

Capital account: $GDCF = S_h + S_g + S_f$

Household account: $C_h + S_h + T_h = Y_h + TP_g$

Government account: $C_g + TP_g + S_g = T_i + T_f + T_h$

An indirect tax will increase the GDP at market prices in spite of the fact that the production volume in society does not increase. This is illustrated by the following example.

Assume:

$Y_h = 550$ (wages and distributed profits)

$T_f = 100$ (directs taxes paid by firms)

$S_f = 100$ (depreciation and undistributed profits, equals savings by firms)

$T_i = 0$ (net indirect taxes, i.e. indirect taxes net of subsidies)

GDP at market prices = GDP at factor prices = 750

$C_h = 450$ (private consumption)

$C_g = 100$ (public consumption)

$GDCF = 200$ (gross domestic capital formation)

$S_h = 50$ (savings by households)

$S_g = 50$ (savings by government)

$T_h = 100$ (direct taxes on households)

$TP_g = 50$ (transfer payments from government)

Now assume that an indirect tax of 20% is levied on private consumption. For simplicity, assume also that the tax incidence is entirely on the consumers, and that of the tax receipts half are used to finance government consumption and the other half used for transfer payments that go back to the consumers (but probably with a different distribution among them). If all of the increased transfer payments from the government goes to consumption, we get the following expression for the indirect tax: $T_i = 0{,}2 \cdot C_h^1 = 0{,}2 \cdot (C_h + T_i/2)$. Since the consumption previously was $C_h = 450$, the indirect tax will be $T_i = 100$. The private consumption will now be $C_h^1 = C_h + T_i/2 = 450 + 50 = 500$. The public consumption will be $C_g^1 = 100 + 50 = 150$, and the transfer payments from government will be $TP_g^1 = 50 + 50 = 100$. This corresponds to a GDP at Market Prices $= C_h^1 + C_g^1 + GDCF = Y_h + T_f + S_f + T_i = 850$, while the GDP at factor prices is still 750.

As a result of the indirect tax, the GDP at market prices as well as the total consumption at market prices have increased by 100. However, the GDP at factor prices as well as the total consumption at factor prices have not increased. Neither has the production volume, if we assume that the government uses the indirect tax receipts to buy existing production. The only thing that has changed is the relation between private and public consumption. Yet the GNP at market prices has been boosted. This is not to say that such a measure would be meaningless. The transfer payments and the publicly provided consumption could, for example, be used for achieving a more equitable distribution of consumption among the consumers.

# The possibility of predicting health care costs in the future from predicted changes in age structure and age-specific mortality: The case of Sweden

By Mattias Ekman

**Abstract**

In this paper, the possibility of predicting future health care costs from predicted changes in age structure and age-specific mortality is explored, based on data for the Swedish population. A linear relationship between age-specific mortality and age-specific health care costs is established for 1997. By combining this relationship with predictions of the future age structure and the future age-specific mortality rates, the Swedish health care costs in 2010 and 2030 are predicted. In order to test the validity of the method, the same methodology is applied retrospectively to data from 1985 in order to predict the health care costs in 1997. The results show that the method gives an underestimation of the actual costs. This should come as no surprise, since international research has shown that the age structure plays a relatively insignificant role for the level of health care expenditures. The most important factor for explaining differences in health care expenditures over time, and across countries, is the level of GDP per capita.

Key words: Ageing, mortality, age structure, health care expenditures.

# 1. Introduction

## 1.1. Background

Rising health care costs, particularly for the elderly, is a major concern in many countries (Fuchs, 1998; Batljan & Lagergren, 2000). As the number of elderly people is expected to grow, the health care costs are expected to grow as well. Traditionally, forecasts have often taken current age-specific health care costs as given, and then applied these costs to the demographically predicted future age structure in order to arrive at an estimate of future health care costs. However, such predictions disregard that fact that the high costs for the elderly are a function of higher mortality for the elderly rather than age per se. Since the ageing of the population is by necessity tied to lower age-specific mortality, predictions based on the age structure alone would overestimate the future health care costs. It could thus be of interest to explore the relationship between age-specific mortality and age-specific health care costs in order to investigate whether future health care costs can be better predicted by taking the effect of changing mortality patterns into account.

## 1.2. A historical perspective on health and mortality

Mortality has decreased steadily over the course of the 20$^{th}$ century, while health care costs have risen. Today, people live longer than ever before. In year 1900, the life expectancy at birth was 53 years for men and 55 years for women in Sweden. In year 2000, the life expectancy at birth was 77 years for men and 82 years for women (Statistical Yearbook of Sweden 2000). It would be tempting to attribute the gains in longevity to medical advances, such as the introduction of antibiotics and better surgical procedures. In the beginning of the 20thy century, infectious diseases such as tuberculosis and pneumonia were the leading causes of death. However, as shown by McKeown et al. (1975), the decline in mortality from infectious disease began long before any effective medicines or therapies were available. According to McKeown et al. (1975), the main reason for the decreased mortality from infectious diseases was improved nutrition, particularly in the case of airborne infections, while immunization and therapy made only a small contribution. For example, when drugs against tuberculosis were introduced in the 1940s, the infant mortality in the disease in the US had already fallen from about 300 per 100 000 in 1900, to about 20 per 100 000 in 1945

(Cutler & Meara, 2001). Medicines thus played a relatively small role in the fight against tuberculosis.

Fogel (1994) has argued along the lines of McKeown et al. (1975) by stressing the importance of improved nutritional standards for the fall in mortality due to infectious and parasitic diseases. Preston (1996), however, is skeptic about this explanation for several reasons. The U.S., for example, was already a well-fed country by 1900. Preston instead presents evidence indicating that it was better hygiene and public health practices that were the main factors behind the decreased mortality. The germ theory of disease was a major medical breakthrough that had a profound impact on hygiene in health care and in the handling of food and water. One indication is that it was among professionals such as teachers and physicians that child mortality declined most rapidly in the early 20$^{th}$ century, while child mortality had been about average in these groups at the turn of the century.

As a result of the decline in mortality due to infectious diseases, people by mid-century increasingly survived long enough to develop cardiovascular diseases and cancer, which replaced infectious diseases as the main causes of death. Since the 1960s, the gradual decrease in mortality has continued, mainly thanks to a decrease in cardiovascular mortality (Preston, 1996; Cutler & Meara, 2001). The views on the reasons for this decline are once again slightly diverging. While Cutler & Meara (2001) primarily stress the role of medical care in the reduction of cardiovascular disease mortality, Preston (1996) is a little more skeptic. While it is true that many high-tech treatments such as bypass surgery and angioplasty are now available, as well as medicines for dissolving blood clots, and for lowering blood pressure and cholesterol levels, lifestyle choices also seem to play a significant role. In fact, people who are well educated have had the largest reductions in mortality. There is a clear relationship between years of schooling and mortality among the elderly. That is an indication of the importance a healthy life-style in preventing heart disease. Those who are better educated tend to live healthier lives in terms of physical exercise, a well balanced diet without excessive fat intake or alcohol consumption, and smoking habits. However, as Cutler & Meara (2001) note, also the behavioral part of the story has its root in knowledge about diseases and their causes.

To conclude, it is hard to say what the relationship really is between health care costs and health effects in terms of a longer life. There seems to be an increasing medicalization of the advances in longevity, but preventive measures (diet, physical exercise, smoking habits etc) that largely fall outside of the health care budget still are of great importance as an explanation for continuing reductions in mortality.

### 1.3. Health care costs and the age factor

Gerdtham and Jönsson (1990) performed an earlier study of the impact of the changing age structure for the future health care costs in Sweden. They used a traditional demographic approach for making a prediction of future health care costs, i.e. they assumed that future health care costs are only contingent upon the age structure, with age specific costs taken as constant over time. (The supply of health care was also assumed to be perfectly elastic with respect changes in demand.) They note that such predictions tend to be overestimates in one respect and underestimates in another. The predictions are overestimates in the sense that health care costs are a function of how many years people have left to live rather than a function of calendar age (see also Fuchs, 1984, for a discussion). If the age-specific mortality rates are falling, this means that the age specific costs will also go down, all else equal, since the costs will be incurred at a higher average age. However, all else is not equal. Demographic changes alone cannot account for the increased costs for health care. In fact, the medical care costs for the elderly has increased more than their portion of the population (Gerdtham & Jönsson, 1990; Fuchs 1984; 1998). This effect is explained primarily by the introduction of new medical treatments, which have contributed to raising the costs of intervention. If the technological development is neglected, the future costs of intervention will perhaps be underestimated.

Gerdtham and Jönsson (1990) show that demographic patterns do not explain the increasing health care costs over time in Sweden. The cost increase has to be explained in other terms. According to an econometric analysis performed by Gerdtham et al. (1992), the most important determinants of health expenditure variation between countries are the level of GDP per capita, institutional factors such as the mixture of public and private funding, and payment principles in outpatient care. The ratio between population

65 years and over and population 15-64 years plays a less significant role. Apart from the choice of institutional arrangements, the single most important factor for the future health care expenditure seems to be the economic growth in terms of GDP per capita, rather than changes in demographic patterns. Countries have the health care expenditures that they can afford, rather than the health care expenditures that they need (Getzen, 2001).

With insurance, the income elasticities of health care expenditures are typically near zero on the individual level, while on the national level the elasticities are typically greater than 1.0 (Getzen, 2000). This implies that health care is an individual necessity (expenditures are not responsive to changes is income), but a national luxury, since the health care expenditures increase relatively more than per capita income.

Studies of Medicare[1] records in the U.S. have shown that health care costs tend to be concentrated to the patients' last year of life. In a given year, about 30% of all Medicare payments are spent on those who died during that year, even though those who die only comprise 6% of the total Medicare population. Looking at the individual level, about 50% of the health care costs during the last year of life are incurred during the last two months (Lubitz & Prihoda, 1984; Lubitz & Riley, 1993). An interesting fact is that in Medicare records, younger decedents have higher costs than older ones. The average Medicare payments for decedents aged 65-69 years were $15 436, and for those aged 90 or over the payments were $8 888. A methodological problem here is that the older patients have higher nursing home costs, which are not included in the Medicare records.

The hypothesis that it is remaining lifetime rather than calendar age that determines the level of health care costs has been further investigated by Zweifel et al. (1999). Their study was based on longitudinal data of per capita health care expenditure during the two lasts years of life. The rising health care costs with age seem to be explained by the strong relationship between age and mortality. Since the health care consumption for each age group seems to be correlated to the age specific mortality, the mortality patterns could perhaps be used for forecasting future health care costs. If the mortality

[1] Medicare is the US federal insurance program for the elderly and other selected groups.

rates will continue to decrease, then the health care cost per age group will also decrease, all else equal.

## 2. Method

I used data on age-specific health care consumption in Sweden in 1997 assembled elsewhere (Ekman, 2002) in order to find out what the relationship between age-specific health care costs and age-specific mortality is in Sweden. The health care costs also include costs for elderly care, e.g. costs for nursing homes and home help. The figures on age-specific mortality rates were obtained from Statistics Sweden. When a relationship between age-specific health care costs and age-specific mortality has been established, this relationship can be used for making predictions of future health care costs, given that we have access to a prediction of future mortality rates. Predictions of future mortality rates for different age groups are available from Statistics Sweden, where demographic projections of Sweden's future population structure are made regularly (Statistical Yearbook of Sweden, 1999, 2000).

The next step was to check what the results would have been if we had been able to apply the same methodology to old data on health care consumption by age. Here I used a study from 1990, which includes figures on health care consumption from 1976 and 1985 (Gerdtham & Jönsson, 1990). If the method works well for old data, i.e. if we can predict the present health care costs by combining the relationship between age-specific health care costs and age-specific mortality in the past with figures on age-specific mortality from today, it would be a good indication that the method is reliable.

## 3. Results

### 3.1. Relationship between health care costs and mortality

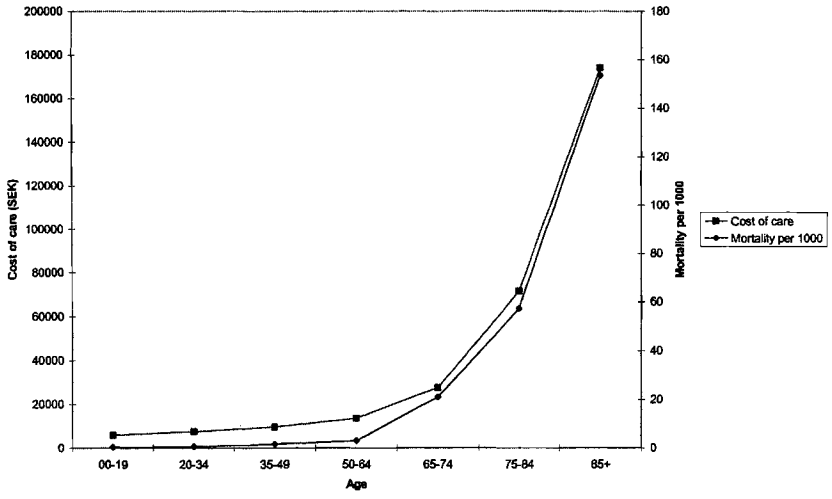
As the data in table 1 suggest, and the curves in figure 1 illustrate, there is a strong correlation between the health and elderly care costs and the mortality rates in Sweden in 1997.

**Table 1.** *Correlation between age-specific health and elderly care costs, and age-specific mortality.*

| *Age* | 00-19 | 20-34 | 35-49 | 50-64 | 65-74 | 75-84 | 85+ |
|---|---|---|---|---|---|---|---|
| **Cost of care (SEK)** | 5 914 | 7 529 | 9 652 | 13 623 | 27 581 | 71 422 | 174 111 |
| Health care | 5 914 | 7 529 | 9 652 | 13 623 | 20 395 | 26 732 | 27 601 |
| Elderly care | 0 | 0 | 0 | 0 | 7 186 | 44 690 | 146 510 |
| **Mortality rate per 1000** | 0,356 | 0,578 | 1,627 | 6,012 | 20,982 | 57,268 | 153,670 |

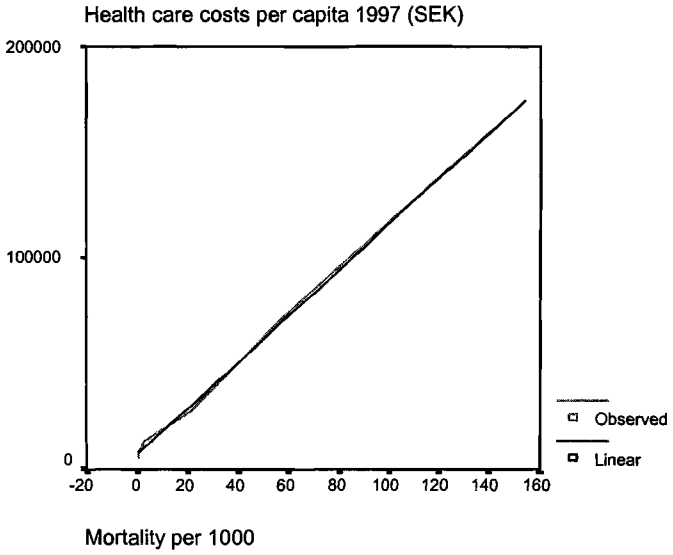
Source: Ekman M (2002) & Statistical Yearbook of Sweden, 1999.

**Figure 1.** *The age-specific cost of care (SEK) and the age specific mortality (per 1000) plotted in the same figure.*




If the two curves in figure 1 are instead plotted against each other, the close relationship becomes even more apparent, as can be seen in figure 2. Linear curve fitting with the age specific mortality as the independent variable gives an adjusted $R^2$-value of 0.999.

**Figure 2.** *The age specific cost of care and the age specific mortality plotted against each other.*




### 3.2. Using the relationship for prediction of future health care costs

Assuming that the relationship displayed above will hold also in the future, we can use it in order to make a forecast of the demographic influence on future health care costs. The present relationship between health care costs and mortality is combined with the predicted future age specific mortality according to Statistics Sweden. If the predicted age specific mortality figures for 2010 are inserted into the linear relationship obtained from the 1997 figures, then the predicted values displayed in table 2 are obtained for 2010.

**Table 2.** *Predicted health and elderly care costs for 2010.*

| *Age* | *Mortality rate per 1000* | *Predicted cost (SEK)* | *Predicted population* | *Predicted total cost (MSEK)* |
|---|---|---|---|---|
| **0-19** | 0,29 | 7 036 | 2 035 273 | 14 319 |
| **20-34** | 0,48 | 7 243 | 1 669 359 | 12 092 |
| **35-49** | 1,33 | 8 172 | 1 831 996 | 14 971 |
| **50-64** | 4,86 | 12 030 | 1 742 017 | 20 956 |
| **65-74** | 16,97 | 25 263 | 936 315 | 23 654 |
| **75-84** | 48,29 | 59 488 | 544 679 | 32 402 |
| **85+** | 139,86 | 159 552 | 256 266 | 40 888 |
| **All** | | | 9 015 905 | 159 282 |

The estimate of MSEK 159 282 for 2010 is in fact about the same as the total costs in 1997, which amounted to MSEK 160 930. The costs that we predict for 2010, considering only the population structure and not the expected changes in mortality, amount to MSEK 175 364, i.e. about 9% higher than the 1997 figure.

If the same kind of calculation is performed for 2030, we get the estimates in table 3.

**Table 3.** *Predicted health and elderly care costs for 2030.*

| *Age* | *Mortality rate per 1000* | *Predicted cost (SEK)* | *Predicted population* | *Predicted total cost (MSEK)* |
|---|---|---|---|---|
| **0-19** | 0,23 | 6 970 | 2 064 818 | 14 392 |
| **20-34** | 0,38 | 7 134 | 1 549 020 | 11 051 |
| **35-49** | 1,05 | 7 866 | 1 779 036 | 13 994 |
| **50-64** | 3,76 | 10 827 | 1 669 934 | 18 081 |
| **65-74** | 13,13 | 21 067 | 1 062 270 | 22 378 |
| **75-84** | 39,29 | 49 653 | 833 542 | 41 388 |
| **85+** | 125,06 | 143 379 | 358 612 | 51 418 |
| **All** | | | 9 317 232 | 172 702 |

The estimate of MSEK 172 702 can once again be compared with the total costs in 1997, and are only about 7% higher than these. The costs that we predict for 2030, considering only the population structure and not the expected changes in mortality, amount to MSEK 215 065, which is about 34% higher than the 1997 figure. In this case, the overestimate caused by not taking the change in mortality into account is even greater.

As noted by Batljan and Lagergren (2000), the number of elderly *per se* will not be the primary problem for the development of the future heath care costs, since the growing number of elderly is to a great extent an effect of a better health status. The major challenge is rather that people tend to retire earlier today than a couple of decades ago, in spite of a better health status.

### 3.3. Comparison with U.S. figures

It is likely that patterns similar to those in figure 1 and 2 would be observed for other countries as well. For the U.S., Victor Fuchs (1998) has compiled health care expenditures for people age 65 and over. When age-specific health expenditures are plotted together with the age-specific mortality as in figure 3, it is apparent that there is a fairly

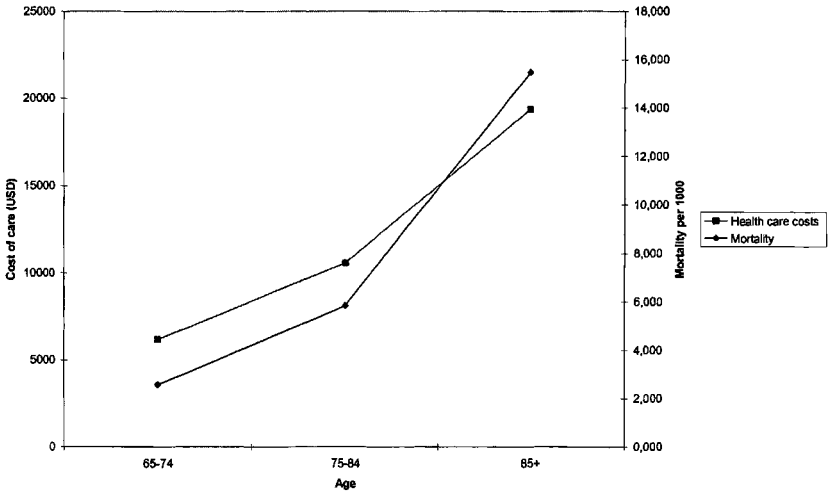
close relationship between these variables also in the U.S., at least for people over 65 years of age.

**Table 4.** *Age-specific health care costs and mortality in the U.S. in 1995.*

| Age | Health care costs per capita (USD) | Mortality per 1 000 |
|---|---|---|
| **65-74** | 6 183 | 25,64 |
| **75-84** | 10 582 | 58,52 |
| **85+** | 19 358 | 154,69 |

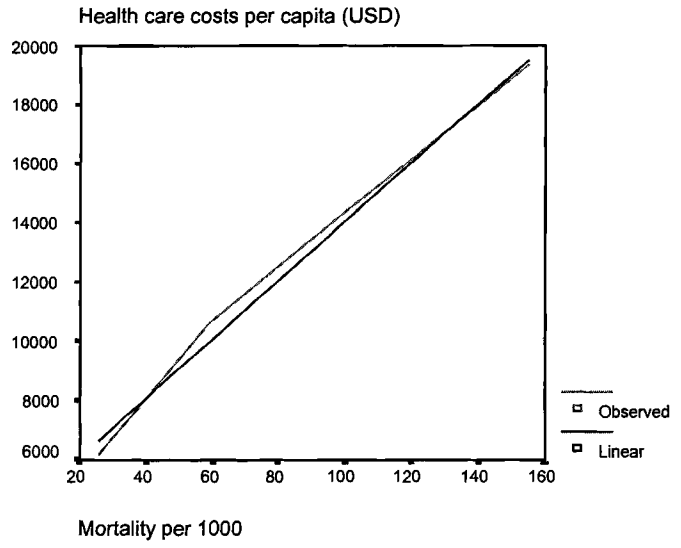
Sources: Statistical Abstract of the United States 1996 & 1998, Fuchs (1998), and my own calculations.

**Figure 3.** *Health care expenditures per person and age-specific mortality in the U.S. in 1995.*




As for the Swedish data, the linearity in the relationship between age-specific health care costs and age-specific mortality is strong. The adjusted $R^2$-value for the regression line in figure 4 is 0.993.

**Figure 4.** *Linear curve fitting between age specific health care expenditure and age-specific mortality in the U.S..*




### 3.4. Evolution of health care costs over time

It could be of interest to investigate how the age-specific health care costs have evolved over time in Sweden, not the least since this could cast some further light on the relationship between health care costs and mortality. Comparisons of costs for health care and elderly care over time in Sweden are difficult to perform, particularly since a major health care reform took effect in Sweden in 1992. The purpose of this reform was to give the municipalities an overall responsibility for elderly care. As a consequence, a large part of the costs for elderly care shifted from the counties to the municipalities. Earlier, counties and municipalities were responsible for different types of elderly care. The main problem we face if we want to compare the cost development over time is that we need to track the cost development for elderly care services that were part of the health care budget of the counties before 1992. We then have to estimate what the costs for the same kinds of services were in the municipalities in 1997. An accurate estimate of these costs would probably require a major research effort. Based on certain assumptions, however, it is possible to make an assessment of the effects of the health care reform of 1992.

In 1997, the costs for care and social services to elderly and handicapped people were SEK 77.4 billion, whereof SEK 59.6 billion concerned elderly care. This means that 77.0% of the total costs concerned elderly care. We can also look at the figures on elderly care costs in 1992. By looking at how the costs changed for the municipalities from 1991 to 1992, we can get an estimate of how large the part of the costs that came from the counties was. My estimate is that the costs transferred from county councils to municipalities represented 51.1% of the costs in 1992 (Socialstyrelsen följer upp och utvärderar 2000:4). This figure is based on the assumption that 77.0% of the total costs in 1992 represented elderly care costs, i.e. that the relation between total costs and elderly care costs remained unchanged between these dates. The next step is to apply the percentage of 51.1% from 1992 to the elderly care costs in 1997. The costs that were transferred from county councils to municipalities are thus estimated to SEK 59.6 · 0.511 = 30.5 billion. These elderly care costs should then be added to the health care costs for 1997, in order to make the total costs comparable to the figures from 1976 and 1985.

A further problem is that I only included health care consumption that was allocated to patients in the investigation of age-specific health care costs that was performed in performed in Region Skåne. These figures exclude some cost items that are part of the total health care costs, such as government subventions to pharmacies, and government reimbursements to private health care providers. In order to make a comparison with the health care costs in 1976 and 1985, these costs also have to be added. All in all, this gives a cost profile that is somewhat different from the one that would be obtained if we used the costs for 1997 that I specified earlier.

Table 5 shows the health and elderly care costs for 1997, as well as for two earlier years, 1976 and 1985. The age groups for the 1997 figures have been adapted to conform to the age groups used for presenting the 1976 and 1985 figures. As we can see in table 5, the per capita cost has grown from 1985 to 1997 for all age groups, except for those aged 75 and over. If the cost estimation for 1997 is true, then the costs of those aged 75 and over have decreased in real terms since 1985. It seems that the total resources spent on elderly care have increased less in real terms than the increase in the number of elderly. While the number of people 75 and over have grown with 24%, the

growth in elderly care expenditures has been only 14%. Apparently, the increase in costs has not kept pace with the growth in the number of people aged 75 and over. Hence, a lower per capita cost in these age groups.

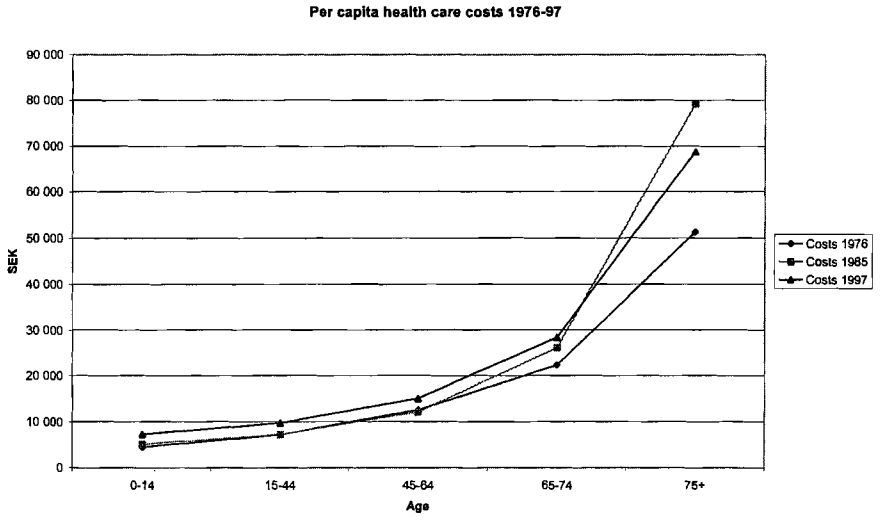
**Table 5.** *Swedish health and elderly care costs in different years (1997 prices). Age-specific per capita costs and age-specific portion of the total costs.*

| | 1976 | | 1985 | | 1997 | |
|---|---|---|---|---|---|---|
| *Age* | *Costs (SEK)* | *Percentage* | *Costs (SEK)* | *Percentage* | *Costs (SEK)* | *Percentage* |
| **0-14** | 4 468 | 7,7% | 5 101 | 6,1% | 7 272 | 7,8% |
| **15-44** | 7 184 | 24,2% | 7 202 | 19,9% | 9 738 | 22,1% |
| **45-64** | 12 646 | 25,0% | 12 167 | 17,6% | 15 168 | 21,4% |
| **65-74** | 22 404 | 18,1% | 26 138 | 17,3% | 28 447 | 14,3% |
| **75+** | 51 336 | 25,0% | 79 186 | 39,1% | 68 612 | 34,4% |

Source: Gerdtham & Jönsson (1990), and my own calculations.

If the age-specific costs for all three years are plotted in the same diagram, the trends can be clearly seen.

**Figure 5.** *Health care costs for 1976, 1985, and 1997 plotted in the same diagram.*




If we look at the development of the mortality in table 6, we can see that the mortality has decreased in all age groups since 1976. In relative terms, the mortality of the oldest has decreased the least.

**Table 6.** *The mortality has decreased for all age groups.*

| | Mortality per 1000 | | |
|---|---|---|---|
| *Age* | **1976** | **1985** | **1997** |
| **00-14** | 0,78 | 0,60 | 0,37 |
| **15-44** | 1,11 | 0,97 | 0,77 |
| **45-64** | 7,55 | 6,69 | 4,97 |
| **65-74** | 27,83 | 24,68 | 20,98 |
| **75+** | 92,67 | 84,44 | 81,36 |

Source: Statistical Yearbook of Sweden, 1979, 1989, and 1999.

In figures 6, 7, and 8 the relationships between mortality and health care costs for 1976, 1985 and 1997 are displayed. The same relationship has already been shown for the 1997 data in figure 1, but, in order to facilitate comparisons, the data are adapted to the same age groups and cost items as those for the 1976 and 1985 data.

**Figure 6.** *Age-specific cost of care and the age specific mortality in 1976.*

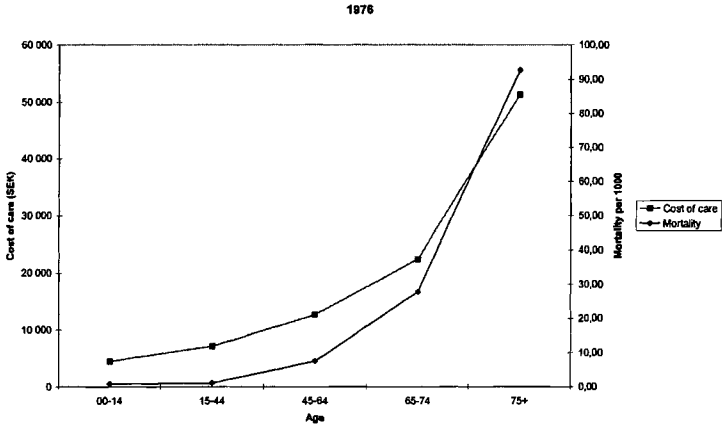


**Figure 7.** *Age-specific cost of care and the age specific mortality in 1985.*

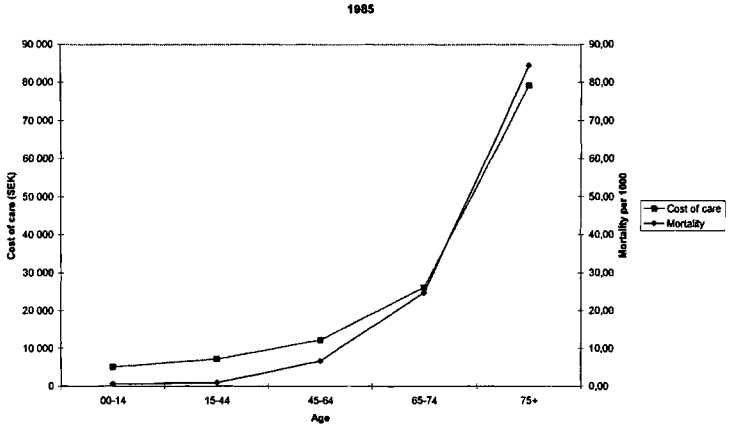
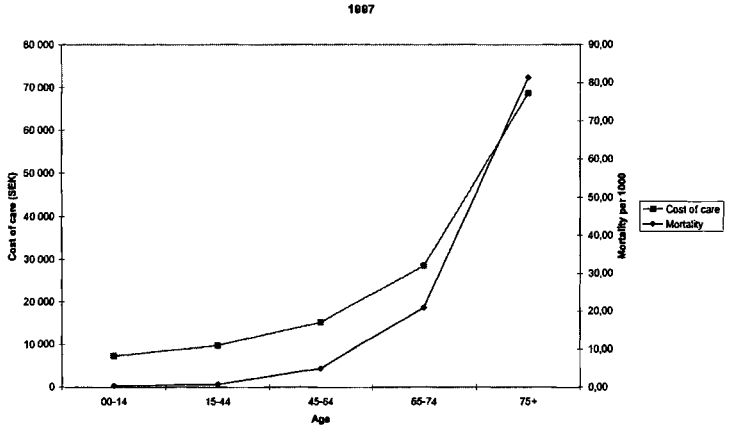
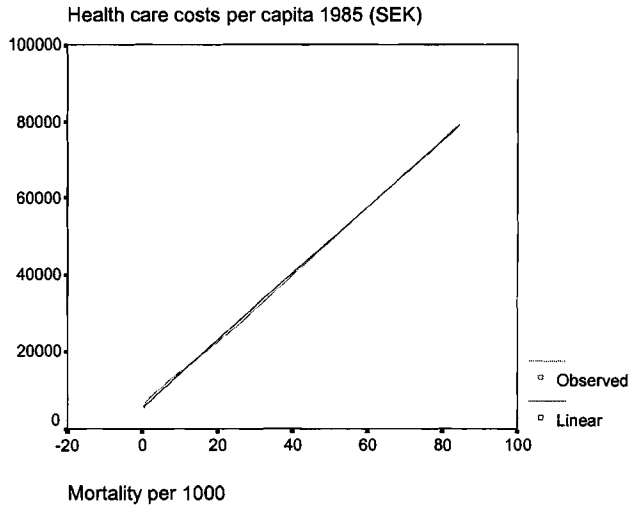



**Figure 8.** *Age-specific cost of care and the age specific mortality in 1997.*




Finally, the two curves in figure 7 are plotted against each other. As for the 1997 data, there is a nearly linear relationship between health and elderly care costs and mortality, as can be seen in figure 9. Linear curve fitting with the age specific mortality as the independent variable gives an adjusted $R^2$-value of 0.999.

**Figure 9.** *The relationship between age-specific cost of care and the age-specific mortality in 1985.*




### 3.5. Testing the forecasting method on old data

The relationship between age-specific health care costs and age-specific mortality in 1985 can be used in order the reliability of the forecasting method I applied to the 1997 data. If the linear relationship between health and elderly care costs and mortality obtained from the 1985 data are applied to the actual mortality in 1997, we get the predicted per capita costs in table 7. As can be seen, these are lower than the actual 1997 costs. The predicted total costs are consequently lower than the actual total costs. For comparison, I also used the 1985 costs directly, i.e. I applied the 1985 per capita costs to the age structure in 1997. Though a better estimate than the mortality based prediction, the total costs are still lower than the actual total costs in 1997. However, it is interesting to note that the predictions based on mortality of extrapolation of 1985 age-specific cost levels are actually overestimates for those aged 75 and over.

**Table 7.** *Health and elderly care costs in 1997 predicted from 1985 data. (Per capita costs in SEK and total costs in MSEK.)*

| Age | Mortality rate per 1000 | Predicted per capita costs | Actual per capita costs | Population | TC* predicted from mortality | TC* predicted from 1985 costs | Actual total costs |
|---|---|---|---|---|---|---|---|
| 00-14 | 0,37 | 5 853 | 7 272 | 1 654 452 | 9 684 | 8 439 | 12 032 |
| 15-44 | 0,77 | 6 199 | 9 738 | 3 480 936 | 21 577 | 25 070 | 33 897 |
| 45-64 | 4,97 | 9 860 | 15 168 | 2 169 863 | 21 395 | 26 402 | 32 913 |
| 65-74 | 20,98 | 23 787 | 28 447 | 771 209 | 18 345 | 20 158 | 21 938 |
| 75+ | 81,36 | 76 319 | 68 612 | 771 165 | 58 855 | 61 065 | 52 911 |
| All | | | | 8 847 625 | 129 856 | 141 134 | 153 690 |

TC = Total costs.

What is made clear from this exercise is that while there is a strong relationship between age-specific mortality and age-specific health and elderly care costs in any given year, it is doubtful whether this relationship can be used for forecasting purposes. Obviously factors other than the development of the age structure are driving the health care costs upwards, presumably technological and institutional factors.

## 4. Discussion

### 4.1. The failure of prediction

A couple of rather firm conclusions can be drawn from my survey of the literature, and my own investigation.

1) The total health care costs are largely independent of the age structure. This hypothesis is supported by international research, see e.g. Gerdtham et al. (1992).
2) Given certain total health care costs, the age-specific costs are strongly correlated to age-specific mortality.

The second conclusion is supported by my own analysis and by the data in Zweifel et al. (1999). The relationship holds strongly for Sweden, for Medicare records in the U.S., and for the Swiss health insurance data used by Zweifel et al. (1999). I would be surprised if the relationship did not hold for other comparable OECD countries as well.

Unfortunately, the first conclusion means that the second one cannot be used in order to predict the future health care costs. If we want to predict future health care costs, it would probably be a better idea to try to predict the growth in per capita income, and

then use the income elasticity for national health expenditures that is discussed by Getzen (2000). For example, a value of 1.33 could be used for the national income elasticity for health care expenditures, as estimated by Gerdtham et al. (1992) from a cross section of 19 OECD countries. We could then apply a prediction of the age-specific mortality rates in order to make a forecast of how large the age-specific health care costs would be. From 1985 to 1997, the real GDP per capita in Sweden grew by 17.1%, i.e. by 1.32% annually (Statistical Yearbook of Sweden 1999). An elasticity of 1.33% means that the health care expenditure should have grown by 1.76% per year in real terms. Since the health care expenditures in 1985 were MSEK 126 554 in 1997 prices (based on figures from Gerdtham & Jönsson, 1990), the retrospective prediction for the health care expenditures in 1997 is MSEK $(1+0.0176)^{12} \cdot 126\,554 = 156\,027$. The actual figure for 1997 is MSEK 153 690, which is close to this estimate. If we would like to use this method for prospective predictions, we will of course first have to find a reliable estimate of future growth in GDP, a task that is definitely beyond the scope of this paper.

### 4.2. Questions for further research

Accurate comparisons of health care costs over time in Sweden are difficult, primarily because of the major health care reform, Ädelreformen, which took effect in Sweden in 1992. The responsibility for long-term care of the elderly was transferred from the counties to the municipalities. According to my calculations, the health care costs have actually decreased since 1985 for those aged 75 and over. The problem is that my calculation of the health care costs in 1997 that are comparable to the health care costs in 1976 and 1985 builds on two assumptions that may not be fulfilled: (1) The percentage of the total costs that goes to impaired people was the same in 1992 as in 1997; (2) The percentage of the total elderly care costs that belongs to costs items that were the responsibility of the counties before 1992 has remained the same until 1997. Therefore, it could certainly be of value to track the cost development more accurately than I have done here.

In the U.S., the situation seems to be different from the one in Sweden. According to Medicare records, the health care costs have increased the most for the oldest. A plausible explanation of this is that introduction of new medical technology drives the

costs. In the U.S., it has been observed that almost the whole increase in health care costs for the elderly is caused by high-cost cases with very expensive treatments, often involving surgery, e.g. bypass surgery or other operations performed to treat ischemic heart disease (Cutler & Meara, 1997). Cutler & Meara found that the growth in health care spending was most rapid among children less than one years old, probably because of improvements in the care of prematurely born infants, and among those 65 years of age or older. Among the elderly, high costs are primarily tied to treatments for cardio-vascular disease and cancer. In fact, it is in the top ten percent of the spending distribution that the largest increases in cost have appeared. The growth in spending is thus primarily driven by the high cost cases.

An important issue is how to compare health care costs over time and across countries. For example, are health care costs from Medicare records in the U.S. comparable to Swedish health care costs?

Interesting questions for future research are

(1) to find a more accurate estimate of how the health care costs in Sweden has evolved over the last 30 years, and
(2) to compare the cost development in Sweden with that of the U.S. and some other OECD countries in order to find out to what extent technology, institutional factors, and economic growth explain the development of health care costs over time.

It is possible that such an investigation would only duplicate the results of, e.g., Gerdtham et al. (1992), but it can nevertheless be valuable to make a follow-up on earlier research in order to see if something has changed.

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ORIGINAL RESEARCH ARTICLE

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# Cost Effectiveness of Bisoprolol in the Treatment of Chronic Congestive Heart Failure in Sweden

## Analysis Using Data from the Cardiac Insufficiency Bisoprolol Study II Trial

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## Abstract

**Objective:** To investigate the cost effectiveness of adding the β-blocker bisoprolol to standard treatment in patients with congestive heart failure (CHF).
**Design and setting:** A cost-effectiveness study was based on the Cardiac Insufficiency Bisoprolol Study II (CIBIS-II), a randomised clinical trial investigating the efficacy of adding bisoprolol to standard therapy of CHF. The cost-effectiveness analysis was carried out from a societal perspective.
**Methods:** Health effects were measured in terms of years of life gained. On the cost side, treatment costs for pharmaceuticals and hospitalisations were included. Data on healthcare resource consumption from CIBIS-II were used and were combined with average Swedish retail prices for medicines, and average costs for hospitalisations based on hospital admissions, in the base case. The costs of added years of life, i.e. consumption net of production during life-years gained were also included.
**Results:** If costs of added years of life were not included, then bisoprolol therapy increased life expectancy at an incremental cost of Swedish kronor (SEK) 13 094 (1999 values) per year of life gained. If costs of added years of life were included, then the incremental cost-effectiveness ratio of bisoprolol therapy was SEK168 858 per year of life gained.
**Conclusions:** For patients with CHF with the characteristics of those in CIBIS-II, the cost effectiveness of bisoprolol therapy compares favourably with that of other cardiovascular therapies.

The prevalence of congestive heart failure (CHF) has increased in recent years. As mortality attributable to coronary heart disease and hypertension has decreased, more patients have survived with a myocardial injury, which makes them likely to develop CHF later on.[1] Another important factor behind the increased prevalence of CHF is the aging population. Estimates[1] based on the Framingham Study indicate that the prevalence is about 1% in those aged 50 to 59 years and 10% in those aged 80 to 89 years. The incidence increases from about 0.2% in persons aged 45 to 54 years, to 4% in men aged 85 to 94 years.[1] In Sweden, the prevalence for the whole population has been estimated to be about 2 to 3%, which means that there are about 200 000 patients with heart failure.[2] CHF is

not only common, but also a serious condition with a poor prognosis. In the Framingham study, for example, the 6-year mortality was 82% for men and 67% for women.[1]

The high prevalence of CHF is also reflected in the economic burden the disease inflicts on society. Studies have shown that the direct costs of CHF represent about 1 to 2% of the total healthcare expenditures.[3-5] According to a Swedish cost-of-illness study, the annual treatment costs for heart failure in Sweden are about Swedish kronor (SEK) 2000 to 2600 million (1996 values).[3] The major part of the treatment costs (65 to 75%) consists of institutional care costs in hospitals and nursing homes, whereas the costs for pharmaceuticals account for only 11%. The indirect costs were not estimated in the Swedish study, but they are probably less important than the total treatment costs, since about 95% of all hospital discharges attributable to heart failure concern people over the age of 65 years.[3]

Standard therapy for CHF has traditionally involved diuretics to relieve congestive symptoms. The diuretics have often been combined with digoxin and nitrates. Because of the well established use of diuretics in the treatment of CHF, few systematic clinical trials testing the effectiveness of these drugs have been reported in the literature.[6] In contrast, the introduction of ACE inhibitors has been supported by a number of extensive studies. Some of the major studies are Studies of Left Ventricular Dysfunction (SOLVD),[7,8] Cooperative New Scandinavian Enalapril Survival Study (CONSENSUS),[9] Acute Infarction Ramipril Efficacy (AIRE)[10] and Survival and Ventricular Enlargement (SAVE).[11] Economic evaluations have shown that the addition of ACE inhibitors to traditional therapy with diuretics and digoxin is cost effective, primarily since the costs for hospital care are decreased.[4,12-15] In fact, there is also some evidence indicating that ACE inhibitors are underprescribed.[16,17]

Traditionally, β-blockers have not been considered standard therapy for heart failure. However, some Swedish groups have over 20 years of experience of including these pharmaceuticals in the treatment of CHF.[18] Recently, a number of large clinical trials have been conducted to determine the mortality effects of β-blocker treatment.[19,20] Some of the major studies in this area are the US Carvedilol Study,[21] Cardiac Insufficiency Bisoprolol Study (CIBIS) I,[22] CIBIS-II[23] and Metoprolol Controlled-Release Randomised Intervention Trial in Heart Failure (MERIT-HF).[24] Not many economic evaluations of β-blocker therapy for heart failure have as yet been published. In table I, a few representative cost-effectiveness studies of ACE inhibitors[12,13,15,25] and β-blockers[5,26-28] are presented.

In addition to decreasing mortality, β-blocker therapy delays the progression of heart failure and therefore reduces the number of hospital admissions. This in turn leads to cost savings.[27,28] However, cost savings resulting from reduced morbidity and mortality do not necessarily offset the treatment costs. As clinical evidence is now showing that β-blocker therapy is of prognostic benefit,[19-24] it is time to assess whether or not it is also cost effective.

The purpose of this study was to perform a cost-effectiveness analysis for Sweden based on survival and healthcare resource consumption data from the clinical study described in CIBIS-II Investigators and Committees,[23] combined with costs relevant for Swedish conditions. CIBIS-II, a multicentre, randomised, placebo-controlled trial, showed that bisoprolol added to optimal standard therapy (including an ACE inhibitor), lowered all-cause mortality in patients with decreased ejection fraction and symptoms of heart failure. To investigate whether the addition of bisoprolol to standard therapy is an efficient use of scarce healthcare resources, the costs must be related to the benefits of the treatment. This study differs from previous economic evaluations of β-blockers in several respects. Most notably, the costs of added years of life are considered. Other differences concern how the dosage titration of the study medication was performed and how the survival after the end of the trial was modelled.

**Table I.** A selection of cost-effectiveness studies of heart failure therapy. These data are partly based on table I in Rich & Nease;[29] some additional studies are listed in Cleland[30]

| Study | Data source | Therapeutic agent(s) | Outcomes[a] | Methods and assumptions |
|---|---|---|---|---|
| Paul et al.[12] | V-HeFT I, V-HeFT II, SOLVD | Enalapril (ACE inhibitor), hydralazine hydrochloride-isosorbide dinitrate | Hydralazine-isosorbide compared with standard therapy: $US5600/y of life saved; enalapril compared with hydralazine-isosorbide: $US9700/y of life saved | Decision-analytic model, therapy continued for 10y, benefits linear over time; 5% discount rate |
| van Hout et al.[13] | SOLVD and others | ACE inhibitors | Survival improves by about 4% over the first 10y, while costs decrease by 17% over the same period | Modelling approach; 2 scenarios, standard therapy and standard therapy plus ACE inhibitor |
| Erhardt et al.[15] | AIRE | Ramipril (ACE inhibitor) | Compared with standard therapy: SEK14 148 to SEK33 033/y of life saved | Cost effectiveness estimated over 3 periods: 1, 2, and 3.8y; 5% discount rate |
| Tsevat et al.[25] | SAVE | Captopril (ACE inhibitor) | Cost per QALY ranged from $US60 800 to $US3700 for patients aged 50 to 80y if benefit ceased after 4y | Sensitivity analysis showed that ICER is always favourable for patients aged 60 to 80y |
| Delea et al.[26] | US Carvedilol Heart Failure Trials, SOLVD | Carvedilol (β-blocker) | Compared with standard therapy (including enalapril): $US12 799.to $US36 677/y of life saved depending on the assumptions | Decision-analytic model; 2 scenarios with different assumptions regarding the duration of the benefits; 5% discount rate |
| Schädlich et al.[27] | CIBIS-I | Bisoprolol (β-blocker) | Compared with standard therapy (including ACE inhibitor): difference in mortality not statistically significant, but therapy improved functional status; cost savings of DM157 272 per 1000 patient-years | Cost-minimisation analysis; sensitivity analysis showed that the beneficial results are stable for varying assumptions |
| Levy et al.[28] | CIBIS-I | Bisoprolol (β-blocker) | Compared with standard therapy (including ACE inhibitor): cost savings of FF4330 per patient | Direct costs considered, i.e. medication and hospitalisation costs |
| Malek[5] | CIBIS-II | Bisoprolol (β-blocker) | Compared with standard therapy (including ACE inhibitor): £680/y of life saved | Tentative economic evaluation, considering direct costs |

a Exchange rates in 1999: $US1 = SEK8.27; DM1 = SEK4.50; FF1 = SEK1.34; £1 = SEK13.37 (average exchange rates; source: Bank of Sweden).

**AIRE** = Acute Infarction Ramipril Efficacy; **CIBIS** = Cardiac Insufficiency Bisoprolol Study; **DM** = deutchmarks; **FF** = French francs; **ICER** = incremental cost-effectiveness ratio; **QALY** = quality adjusted life-year; **SAVE** = Survival and Ventricular Enlargement; **SOLVD** = Studies of Left Ventricular Dysfunction; **V-HeFT** = Vasodilator Heart Failure Trial; **£** = pounds sterling.

## Methods

### Target Population for the Intervention

The cost-effectiveness study focused on an identified patient with symptomatic chronic CHF corresponding to class III or IV of the New York Heart Association (NYHA) classification, with an ejection fraction lower than or equal to 35%. For a detailed presentation of the patients, see CIBIS-II Investigators and Committees.[23]

### Type of Analysis

The present study is a cost-effectiveness analysis, which has been conducted, as far as possible, from a societal perspective. On the cost side, all costs concerning the resource consumption measured in the clinical study were included, i.e. costs for medication and hospitalisations. Costs for up-titration of bisoprolol were estimated from expert opinion. Costs of added years of life estimated for the general Swedish population were also included in the study. Time costs such as patient-time costs

and informal caregiving by relatives, and disease-related costs for transportation and other nonmedical services, were not included in the analysis since no such information was available from the clinical trial. Productivity losses attributable to sick leave were also not included. On the outcome side of the analysis, the health effects were measured in terms of life-years gained.

The measure used for evaluating the cost effectiveness of the intervention was the incremental cost-effectiveness ratio (ICER). The ICER is calculated as the ratio between the difference in cost and the difference in effect between the 2 treatments. ICER = $\Delta C/\Delta E$, where $\Delta C$ is the difference in average cost between the treatment group and the placebo group, and $\Delta E$ is the difference between the 2 treatments in terms of average life time from the point of randomisation. The ICER thus represents the incremental cost per year of life gained by adding bisoprolol to standard therapy.

Previous economic evaluations in this area have not included costs of added years of life in the analysis, with the exception of future medical costs for related illnesses. Costs of added years of life consist of both future healthcare consumption and future nonhealth–related consumption, since, from a societal viewpoint, there is no reason to make a distinction between the use of healthcare resources and other resources. Future production also has to be taken into consideration, since what matters is not consumption and production *per se*, but rather consumption net of production.

On the basis of welfare theory arguments, diverging views have been presented on whether or not to include costs of added years of life in cost-effectiveness analyses. Garber and Phelps[31] show that, under certain conditions, it does not matter whether future costs that are not directly related to the treatment are included or not, as long as the practice is consistent across studies. Meltzer,[32] arguing from a less restrictive welfare theoretical framework, comes to the conclusion that all future costs, whether medical or nonmedical, should be included in cost-effectiveness analyses if the latter are to be consistent with a model of lifetime utility maximisation. If future costs are not included, the economic evaluation will be biased in the sense that the total resource consequences for society resulting from the change in morbidity and mortality will not be accounted for.[32,33] Since the issue of future costs has not been resolved, the US Panel on Cost-Effectiveness in Health and Medicine recommended that the decision whether to include unrelated future costs or not should be left to the discretion of the analyst.[34,35] Since the inclusion of future costs is an issue for debate, our base-case results will be presented with costs of added life-years both included and excluded.

### Estimation of Costs

The costs are divided into inpatient costs, outpatient costs and costs of added years of life. The outpatient costs consist of costs for bisoprolol and other pharmaceuticals together with costs associated with the up-titration of the bisoprolol dosage. The quantity of resources consumed (besides the consultation visits) was extracted from the clinical study, and pharmaceutical prices and hospitalisation costs were collected from local and national sources in Sweden. Costs are expressed in SEK and in 1999 values. If needed, prices have been converted to 1999 prices by using the consumer price index for Sweden.

#### *Outpatient Costs*

Medication costs include bisoprolol and other drugs identified (table II). Not all medicines taken by the patients were included in this list, which includes only medicines taken by more than 5% of the patients in the study. In the database, some 70 other medicines taken by the patients were also listed. However, since there was no significant difference between the treatment group and the placebo group in terms of pharmaceutical consumption other than bisoprolol, the analysis was not carried any further.

The mean number of days that a patient was taking bisoprolol or some other medication was available in the clinical study. The price per day for bisoprolol was based on the average daily dosage in CIBIS-II,[23] which was 6.5mg. It was assumed

**Table II.** Identified medication costs. Costs are in Swedish kronor (SEK) at 1999 prices

| Treatment | Price (SEK/day) | Mean number of days | | Mean drug cost (SEK) | | Difference (bisoprolol minus placebo) [SEK] |
|---|---|---|---|---|---|---|
| | | bisoprolol | placebo | bisoprolol | placebo | |
| Bisoprolol/placebo | 3.10/0 | 458 | 442 | 1420 | 0 | 1420 |
| Other pharmaceuticals [Anatomical-Therapeutic-Chemical (ATC) codes] | | | | | | |
| Antacids, antiflatulents, anti-peptic ulcer [A2A, A2B] | 13.01 | 34 | 40 | 438 | 523 | –85 |
| Antidiabetic therapy [A10] | 5.57 | 47 | 45 | 259 | 251 | 9 |
| Mineral supplements [A12] | 2.47 | 87 | 75 | 214 | 185 | 29 |
| Antithrombotic agents [B1] | 0.97 | 155 | 157 | 150 | 152 | –2 |
| Cholesterol and triglyceride reducers [C10A] | 9.60 | 75 | 63 | 721 | 602 | 120 |
| Cardiac glycosides [C1A] | 0.35 | 257 | 254 | 90 | 89 | 1 |
| Antiarrhythmics, class I and III [C1B] | 7.28 | 69 | 94 | 505 | 682 | –177 |
| Vasodilators used in cardiac diseases [C1F] | 2.69 | 287 | 269 | 772 | 723 | 48 |
| Selective calcium antagonists [C8A] | 5.58 | 13 | 11 | 73 | 62 | 10 |
| ACE inhibitors [C9A] | 4.22 | 474 | 464 | 2000 | 1956 | 44 |
| Low ceiling diuretics, thiazides [C3A3] | 0.79 | 67 | 66 | 53 | 52 | 1 |
| Low ceiling diuretics (excluding thiazides) [C3A2] | 0.65 | 28 | 27 | 18 | 18 | 0 |
| High ceiling diuretics [C3A2] | 0.65 | 401 | 384 | 260 | 250 | 11 |
| Potassium-sparing agents [C3A1] | 1.52 | 78 | 78 | 119 | 118 | 1 |
| Diuretics and potassium-sparing agents [C3A5] | 0.54 | 51 | 45 | 28 | 24 | 4 |
| Peripheral vasodilators [C4A] | 8.96 | 21 | 14 | 185 | 122 | 63 |
| Antibacterials for systemic use [J1] | 7.42 | 5 | 8 | 35 | 56 | –21 |
| Anti-inflammatory/antirheumatic [M1A] | 2.79 | 13 | 9 | 37 | 26 | 10 |
| Antigout preparations [M4A] | 2.08 | 47 | 38 | 98 | 78 | 20 |
| Analgesics [N2B] | 2.86 | 205 | 210 | 585 | 601 | –17 |
| Psycholeptics [N5] | 1.63 | 29 | 37 | 47 | 61 | –14 |
| Antiasthmatics [R3] | 5.31 | 14 | 15 | 74 | 80 | –7 |
| Cough and cold preparations [R5] | 2.55 | 7 | 7 | 18 | 18 | 0 |
| Total other pharmaceuticals | | | | 6777 | 6730 | 47 |

that 70% of the patients took a dose of 5mg (SEK 2.9/day) and that 30% took a dose of 10mg (SEK 3.7/day), which implies an average cost per day of SEK3.10. The price per day for different doses of bisoprolol was extracted from the March 2000 price list of Apoteket AB.[1]

The price per day for other drugs was calculated based on information from LIF (The Swedish Association of the Pharmaceutical Industry)[2] and Apoteket AB. In each of the therapeutic classes, the 5 most frequently consumed drugs were extracted. The total sale in purchase price for each drug was divided by the total defined daily dosage (DDD). The purchase price/DDD was transformed into the sales price/DDD by multiplying by a factor of 1.2, which was provided by Apoteket AB. The price per day in a certain therapeutic class was calculated as a weighted average of the sales prices for the 5

1 This price list is available upon request from the Association of Swedish Pharmacies (Apoteket AB, SE-131 88 Stockholm).

2 This information is available on request from The Swedish Association of the Pharmaceutical Industry, LIF, Box 17608, SE-118 92 Stockholm.

**Table III.** Reasons for admission, diagnosis-related groups (DRG) codes and cost per DRG. Costs are in Swedish kronor (SEK) at 1999 prices[a]

| Reason for admission | DRG code | SEK/DRG | SEK/admission | Mean number of admissions | | Mean admission cost (SEK) | | Difference (bisoprolol minus placebo) [SEK] |
|---|---|---|---|---|---|---|---|---|
| | | | | bisoprolol | placebo | bisoprolol | placebo | |
| Heart failure worsening | 127 | 23 770 | 23 770 | 0.159 | 0.298 | 3780 | 7077 | −3297 |
| Ventricular tachycardia/fibrillation | 138, 139 | 16 652, 9606 | 13 129 | 0.005 | 0.019 | 69 | 249 | −179 |
| Arrhythmia | 138, 139 | 16 652, 9606 | 13 129 | 0.020 | 0.033 | 257 | 438 | −180 |
| Bradycardia | 138, 139 | 16 652, 9606 | 13 129 | 0.011 | 0.002 | 139 | 20 | 119 |
| Hypotension | 141, 142 | 14 094, 9199 | 11 647 | 0.003 | 0.008 | 35 | 97 | −62 |
| Stroke | 16, 17 | 28 160, 21 733 | 24 947 | 0.023 | 0.013 | 583 | 321 | 261 |
| Myocardial infarction | 122, 123 | 26 419, 24 415 | 25 417 | 0.012 | 0.008 | 306 | 212 | 95 |
| Angina | 140 | 13 617 | 13 617 | 0.035 | 0.041 | 472 | 557 | −85 |
| Cardiogenic shock | 127 | 23 770 | 23 770 | 0.005 | 0.005 | 125 | 126 | −1 |
| Cardiac transplant surgery | 103 | 1 194 781 | 1 194 781 | 0.005 | 0.004 | 5402 | 4526 | 876 |
| Revascularisation | 112, 106, 107 | 56 486, 121 276, 102 942 | 84 298 | 0.009 | 0.010 | 762 | 830 | −68 |
| Other cardiac surgery | 108 | 93 848 | 93 848 | 0.001 | 0.001 | 71 | 71 | 0 |
| Other cardiovascular | 145 | 19 847 | 19 847 | 0.063 | 0.061 | 1256 | 1218 | 38 |
| Noncardiovascular | (weight = 1) | 21 266 | 21 266 | 0.150 | 0.195 | 3189 | 4157 | −967 |
| **Total** | | | | **0.500** | **0.698** | **16 447** | **19 898** | **−3451** |

a All prices were converted to 1999 prices by using the Consumer Price Index for Sweden.

best-selling drugs in that class, the weight being the number of DDDs for a given drug divided by the total number of DDDs for the 5 drugs in that class.

In order to find the highest tolerated dosage, the bisoprolol concentration was increased successively (i.e. up-titrated) from a low dosage.[23] The up-titration of bisoprolol means that costs arise for outpatient and/or general practitioner (GP) consultations. In the CIBIS-II trial the up-titration amounted to a maximum of 6 visits (1.25, 2.5, 3.75, 5, 7.5, and 10 mg). Physicians in the CIBIS panel assumed that a patient with CHF is always seen on a regular basis, and that not every patient is up-titrated to 10mg. They concluded that 4 GP visits is an appropriate assumption for the average patient. In general, a nurse at a cardiology department handles the up-titration. In some cases a physician may be involved. After the last visit, when the patient has been up-titrated to the highest tolerated dosage, a further control visit may be added. For some of the patients more visits may be necessary, and for some fewer (because they are not up-titrated to the maximum level of 10mg). As a base-case scenario, we assumed that the mean number of nurse and physician visits amount to 3 and 1, respectively. The cost per physician visit at the cardiology department is SEK2240, and the cost per nurse visit at the cardiology department is SEK1185.[3]

#### *Inpatient Costs*

The inpatient care cost was calculated in 2 ways, either based on cost per hospital admission as measured by diagnosis-related groups (DRGs), or based on cost per day in different types of hospital departments.

The cost-per-admission calculation was based on the DRGs shown in table III. The mean number of admissions in each category was available from the clinical study. Based on the description of the

3 Price list available upon request from Linköping University Hospital, SE-581 85 Stockholm.

admissions from the clinical study, we assigned each type of admission to the corresponding DRG code. In some cases, more than one DRG were applicable to a particular reason for hospitalisation. Then the cost per admission was calculated as the average of the DRGs. The DRG prices were based on NordDRG,[36] where the price per DRG is calculated as the average cost per patient.

The cost per day in different hospital departments is shown in table IV. The cost per day in a cardiology department was based on an average of cost-per-day figures extracted from hospital price lists in Uppsala, Sahlgrenska Göteborg and Linköping. The cost per day in intensive care was based on the average cost per day for the university hospitals in Malmö and Linköping. The cost in a general ward was based on the average cost per day in internal medicine. The cost for other wards were defined as the average cost per day for all inpatient-care departments [costs according to the Swedish Federation of County Councils (Landstingsförbundet), 1996].[4]

#### *Costs of Added Years of Life*

In order to take account of consumption and production attributable to increased life expectancy after the end of the study, costs of added years of life were also included in the cost-effectiveness analysis. The costs of added years of life consist of the difference between annual production and consumption in different age groups.[32,33] In table V, production and consumption figures for different age groups in Sweden in 1999 are displayed.

Since patients with CHF in NYHA class III/IV are quite ill, we made the conservative assumption that patients do minimal work. Patients in NYHA class III have moderately severe heart failure with dyspnoea and tiredness at modestly intense physical exercise, such as walking uphill or putting on one's clothes, and patients in NYHA class IV have severe heart failure with dyspnoea and tiredness even at rest. The symptoms worsen at the slightest physical effort. Class IV patients are often more or less confined to bed. For simplicity, we assumed in our base-case analysis that all patients under the age of 65 years have the same production and consumption pattern as those between 65 and 74 years.

4 Information available upon request from the Swedish Federation of County Councils, SE-118 82 Stockholm.

**Table IV.** Unit costs at different departments. Costs are in Swedish kronor (SEK) at 1999 prices[a]

| Ward | SEK/day |
|---|---|
| Cardiology | 3573 |
| Intensive care unit | 4780 |
| General | 2999 |
| Other | 4556 |

a All prices were converted to 1999 prices by using the Consumer Price Index for Sweden.

### Estimation of Health Effects

The health effects were measured in terms of life-years gained, based on the clinical study. To predict the survival after the end of the clinical study, modelling of the remaining lifetime was required. As the base case, we assumed that patients surviving throughout the clinical trial have an expected additional lifetime of 5 years after the end of the follow-up period. During the follow-up time the mortality was of course taken as that given in the clinical trial. For simplicity, we assumed that the number of survivors decreased linearly (fig. 1). This means that after the follow-up period, a constant proportion of the original surviving population dies each year. For example, to accomplish an average additional lifetime of 5 years for the population that had survived to the end of follow-up, 10 possible life-years were modelled. It was assumed that during each year 10% of the population would die, resulting in an expected survival of 5 years. The probability of surviving each year was then calculated as the average value of the linear function in figure 1 during that particular year. For the first year, the chance of survival is thus (1 + 0.90)/2 = 0.95, for the second (0.90 + 0.80)/2 = 0.85, etc.

In practice, this assumption will underestimate the mortality somewhat in the beginning of the modelling period, and probably overestimate the mortality towards the end. As the CONSENSUS

**Table V.** Production and consumption in different age groups in Sweden in 1999. Data from: Statistics Sweden, The Swedish National Board of Health and Welfare, The Swedish Association of County Councils, and our own unpublished data and calculations. Costs are in Swedish kronor (SEK) at 1999 prices

| Activity | 20-34 years | 35-49 years | 50-64 years | 65-74 years | 75-84 years | ≥85 years |
|---|---|---|---|---|---|---|
| Production | 158 997 | 243 761 | 216 890 | 9 768 | 1 109 | 181 |
| Consumption | 151 230 | 138 455 | 172 121 | 173 420 | 188 803 | 267 745 |
| healthcare | 6 842 | 9 250 | 12 669 | 19 647 | 26 190 | 27 170 |
| social services | 2 168 | 2 168 | 2 175 | 9 883 | 49 370 | 156 641 |
| other public consumption | 28 386 | 21 542 | 19 091 | 19 070 | 19 070 | 19 070 |
| private consumption | 113 834 | 105 494 | 138 186 | 124 820 | 94 172 | 64 863 |
| Production minus consumption | 7 767 | 105 306 | 44 768 | −163 652 | −187 694 | −267 563 |

study[37] has shown, there can still be some survivors left after 10 years, even for populations where all patients belong to NYHA class IV at the beginning of the study. The reason why a base case of 5 additional life-years was chosen is that this corresponds reasonably well with empirical data from SOLVD (for NYHA class III patients) and CONSENSUS (for NYHA class IV patients).[7,37,38] We have estimated the expected remaining lifetime of patients with the characteristics of those in CIBIS-II to be about 5 years in the placebo group. Adding an average of 5 additional life-years comes reasonably close to this (table VI).

### Discounting

In the base case, both the health effects and the costs of added years of life were discounted at a real rate of 3%.[39] Costs occurring within the context of the clinical study have not been discounted.

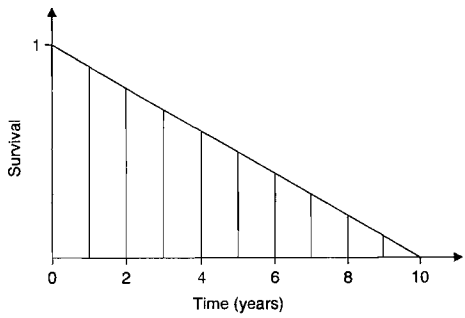


**Fig. 1.** Survival after the end of follow-up was assumed to decrease linearly.

The reason for this is 2-fold. Firstly, these costs have been incurred during a relatively short time span, and secondly we do not have information in our database regarding the exact timing of the costs within the study. If a patient has been hospitalised, for example, we do not know whether this occurred during the beginning, the middle or the end of the follow-up period. However, because of the short time span of the study, this is a problem of minor importance. In the CIBIS-II study, the mean follow-up time was 1.3 years, and the maximum follow-up time was 2.3 years.[23]

### Quality of Life

Quality of life weights that could be used directly were not available in the study. However, the NYHA class of each patient at the beginning of the study was available. In a recent paper by Kirsch and McGuire,[40] health state valuations for the 4 NYHA classes were derived by the time trade-off method. The quality weights from their 2-year time trade-off health state valuations were assigned to the patients in CIBIS-II according to age and NYHA class.

The change in NYHA class during the course of the study was not available on an individual basis. We only had access to data on the average change in NYHA class at different points in time. For this reason we do not include quality-adjusted life-years in our base-case analysis. Instead we limit ourselves to a brief account of the likely effect of quality adjustment in our discussion.

## Results

### Base-Case Results

In table VI, the base-case results of the incremental cost-effectiveness analysis of bisoprolol are presented. Bisoprolol added to standard heart failure therapy was compared with placebo added to the same standard therapy. Previous studies in this area have not included costs of added years of life. In order to facilitate comparisons with previous economic evaluations, our results are presented both with and without these costs included. The hospitalisation costs are presented with hospital admissions as the base case for the cost calculation. It is evident from table VI that if costs of added years of life are included in the analysis, these clearly dominate over the other costs. The number of life-years within the study is shown, as well as the expected number of life-years per patient after the end of follow-up. The ICERs were calculated by dividing the incremental costs by the incremental number of life-years. The reason why the cost-effectiveness ratio becomes considerably larger when the costs of added years of life are considered is that the age and health status of the patients mean that on average their net economic contribution (production minus consumption) is negative.

**Table VI.** Base-case results. Costs are in Swedish kronor (SEK) at 1999 prices

| Item | Bisoprolol | Placebo | Difference (bisoprolol minus placebo) |
|---|---|---|---|
| **Costs (SEK per patient)** | | | |
| Hospitalisation | 16 447 | 19 898 | –3 451 |
| Bisoprolol | 1 420 | 0 | 1 420 |
| Other medication | 6 777 | 6 730 | 47 |
| Dosage titration | 5 795 | 0 | 5 795 |
| Added life-years | 849 122 | 803 778 | 45 343 |
| Total | 879 560 | 830 406 | 49 155 |
| **Effects (life-years per patient)** | | | |
| Within study | 1.332 | 1.292 | 0.041 |
| Expected additional lifetime | 4.016 | 3.766 | 0.250 |
| Total | 5.348 | 5.057 | 0.291 |
| **Incremental cost-effectiveness ratio (Δcost/Δeffect) [SEK per life-year gained]** | | | |
| Including costs of added life-years | | | 168 858 |
| Excluding costs of added life-years | | | 13 094 |

**Table VII.** Cost per year of life gained based on per diem hospitalisation costs. All other items are as in table VI. Costs are in Swedish kronor (SEK) at 1999 prices

| Item | Bisoprolol | Placebo | Difference (bisoprolol minus placebo) |
|---|---|---|---|
| **Costs (SEK per patient)** | | | |
| Hospitalisation | 28 277 | 34 564 | –6 287 |
| **Incremental cost-effectiveness ratio (Δcost/Δeffect) [SEK per life-year gained]** | | | |
| Including costs of added life-years | | | 159 117 |
| Excluding costs of added life-years | | | 3 353 |

As can be seen in table VI, the expected additional lifetime after the end of follow-up is less than 5 years. This is attributable to 2 effects. Firstly, not all patients were alive at the end of follow-up. Since those who did not survive were also included, the average for all patients will always be lower than 5 years. Secondly, future life-years have been discounted, which further reduces the number of (discounted) gained life-years.

### Hospitalisation Costs Based on Hospital Days

The cost-effectiveness analysis was repeated with hospital days and per diem costs as a basis for the calculation. The cost-effectiveness ratios, which are shown in table VII, do not differ greatly from the figures in table VI. The number of life-years gained and the costs other than those for hospitalisations are the same as in table VI.

### Sensitivity Analysis

We performed sensitivity analyses of the cost and effect parameters that seemed to be most critical for the final results. The sensitivity of the base-case results was checked with regard to variations in the titration costs, the costs of added life-years, the average additional lifetime after the end of

follow-up, the discount rate and the difference in survival between the bisoprolol group and the placebo group. We have concentrated our exposition of the sensitivity analysis mainly on the results with costs of added life-years included.

The titration costs were varied, since it is uncertain how many medical consultations are actually necessary for this process. There are also some other uncertainties regarding the titration process, for example whether a doctor or a nurse will primarily handle it, or whether it will primarily occur in outpatient care or during a visit to a GP. In the base-case analysis it was assumed that 4 visits per patient would be necessary for the titration process (3 nurse visits and 1 physician visit). If 6 visits were assumed (4 nurse visits and 2 physician visits) the titration costs would increase from SEK5795 to SEK9220 per patient in the treatment group. The total incremental costs per patient (including costs of added years of life) would then amount to SEK52 580 based on costs per admission. This implies a cost per life year gained of SEK180 623 (52 580/0.291).

Patients with CHF could be expected to visit the doctor on a regular basis even in the absence of bisoprolol treatment. For many patients, it is thus not certain that treatment with bisoprolol would lead to any additional costs for physician and nurse visits. Assuming that no extra medical visits are needed, the total incremental cost per patient (including costs of added years of life) would amount to SEK43 360 based on costs per admission. This would imply a cost per life year gained of SEK148 950 (43 360/0.291). With the assumption of no extra costs for up-titration, treatment with bisoprolol would lead to cost savings of a few thousand SEK if the costs of added years of life were not taken into account.

Both the length of life after the end of follow-up and the size of the costs of added years of life were varied. The survival after the end of the study was subject to sensitivity analysis, since this part of the analysis is by necessity based on plausible modelling assumptions rather than facts from the study. The number of additional life-years was varied between 3 and 7, with 5 as the base case. The costs of added years of life were varied in order to take account of the fact that our assumption in this respect is perhaps rather conservative. As regards the costs of added years of life, these are based on an assumption of almost no production in any age group. Patients with CHF are obviously less healthy than is the average person of similar age. For example, in 1997 hospitalisation costs for the average person in Region Skåne in Sweden ranged from about SEK1700 for people aged 15 to 44 years to about SEK14 700 for those aged 85 years or over (Region Skåne 1998).

A patient in the CIBIS-II study had an average age of 61 years, and an average yearly hospitalisation cost of about SEK12 650 (based on hospital admissions) for the bisoprolol group. For the placebo group, the corresponding cost was SEK15 300. Not surprisingly, this shows that patients with CHF have higher hospitalisation costs than the average person. The costs are of about the same order of magnitude as for the average person aged 85 years or over. It is also reasonable to assume that patients of productive age with CHF work considerably less than the average person. NYHA class IV patients are not likely to work at all, for example. However, it is possible that at least some of the younger patients in class III are working. Therefore, as an alternative scenario, we assumed that all patients have the same net production as the average Swedish citizen in the same age group (table V). In table VIII, this assumption is called 'average costs of added years of life', as opposed to the base-case costs of added years of life.

As can be seen in table VIII, the cost effectiveness is quite sensitive to the assumptions regarding the costs of added years of life. The number of additional life-years also has a clear effect. However, the assumption of 3 additional life-years is unrealistically low, and 7 additional years is perhaps too high. A notable effect in table VIII is that the incremental cost effectiveness decreases with longer expected lifetime. The reason for this is that there are 2 competing effects, namely gained life-years and increasing costs associated with those years.

The gain in life-years with a longer expected survival time more than offsets the increased costs of added years of life, which in turn leads to decreasing cost-effectiveness ratios.

In light of the fact that the choice of discount rate is an issue for debate in health economics, at least with regard to the discounting of health effects, the impact of varying discount rates on the cost effectiveness was also explored. In the base case, both costs of added years of life and life-years were discounted at a real rate of 3%. The results in table IX show that the cost effectiveness is not particularly sensitive to sensible variations in the discount rate. For example, it would be hard to argue for discounting costs of added years of life at a rate of 0% and life-years at a rate of 5%, as in the upper right corner.

For simplicity, the survival probabilities were chosen to decrease linearly with time. However, figures on the yearly mortality within the trial are available from the CIBIS-II study. Therefore, it could be interesting to see what the effect on the results would be if the survival probabilities were extrapolated from the trial results. We studied 3 different scenarios. In the first scenario we assumed that the survival benefits from the CIBIS-II study persist, i.e. the difference in survival between the bisoprolol and placebo group extends into the future (18 years at most). Here, the yearly mortality rates were taken directly from the clinical trial, with a mortality rate of 8.8% in the bisoprolol group and 13.2% in the placebo group.[23] In a second scenario we assumed persisting survival benefits, but with survival probabilities age-adjusted by using life tables.[41] In a third scenario we assumed that the survival benefits converged over 4 years between the 2 groups, i.e. 4 years after the end of follow-up the mortality rate was assumed to be at the level of the bisoprolol group in the placebo group. Compared with the base case, these scenarios had a rather small effect on the ICER, at least when costs of added years of life were included. The ICER was in the range of SEK548 to SEK3 901 when costs of added life-years were not included, and in the range of SEK160 548 to SEK163 451 when costs of added life-years were included. If the survival benefits are extrapolated, the incremental difference in survival between the bisoprolol and placebo groups will of course increase, but so too will the difference in costs of added years of life.

Finally, we considered the sensitivity of varying the difference in mortality between the bisoprolol group and the placebo group in the CIBIS-II study. In the bisoprolol group, 88.2% of the patients survived during the follow-up time, whereas 82.7% survived in the placebo group. The point estimate for the difference in survival was 0.055. The 95% confidence interval for the difference in survival was 0.028 to 0.082. This confidence interval was chosen as a basis for the sensitivity analysis. The method used for this purpose was simulation. In order to attain the lower end of the confidence interval, the mortality in the bisoprolol group was artificially increased by randomly changing each survivor in the database to a nonsurvivor with a 3% chance in each round of simulation. The problem is that if the mortality is increased, then follow-up time as well as medication and hospitalisation costs, which are variables depending on the mor-

**Table VIII.** Effect on incremental cost-effectiveness ratio (ICER) of varying costs of added years of life (AYL) and the number of additional life-years

| Additional life-years | ICER (SEK per life-year gained)[a] | |
|---|---|---|
| | average cost of AYL | base-case cost of AYL |
| 3 | 19 563 | 174 236 |
| 5 | 15 758 | 168 858 |
| 7 | 13 926 | 166 268 |

a Per patient in the target population. Costs are in 1999 Swedish kronor (SEK). Both costs and life-years were discounted at 3%.

**Table IX.** Effect of variations in the discount rate on the incremental cost-effectiveness ratio (ICER). Costs are in Swedish kronor (SEK) at 1999 prices

| Percentage discount for costs | ICER (SEK per life-year gained) when life-years discounted at | | |
|---|---|---|---|
| | 0% | 3% | 5% |
| 0% | 172 042 | 187 678 | 198 148 |
| 3% | 154 789 | 168 858 | 178 277 |
| 5% | 144 925 | 158 097 | 166 916 |

tality, will have to be changed as well. Nonsurvivors have an average follow-up time that is 228 days shorter than for survivors. If a survivor was switched to a nonsurvivor as a result of the simulation, his or her follow-up time was therefore decreased by 228 days. The purpose of this was to reflect the likely effect on the follow-up time of a higher mortality in the bisoprolol group. For the same reason, the costs for hospitalisations and pharmaceuticals were also changed with their mean differences between survivors and nonsurvivors. The average hospitalisation costs for those who survived were on average about SEK15 000 lower than for those who did not. Since the follow-up time tends to be longer for survivors (for obvious reasons), they also tend to consume more pharmaceuticals. The costs for pharmaceuticals other than bisoprolol were on average about SEK3500 higher for survivors in the bisoprolol group, and the costs for bisoprolol were SEK900 higher.

In order to attain the upper end of the confidence interval, the mortality was instead increased in the placebo group in the same way as above. The follow-up time and costs were also adjusted in a similar fashion. The cost-effectiveness ratios obtained from varying the difference in survival ranged from SEK163 930 (simulated upper end mortality difference of 0.081) to SEK180 830 (simulated lower end mortality difference of 0.028) per life year gained if the cost of added life-years was accounted for. The corresponding ratios if costs of added life-years are not included were SEK3790 (upper end) and SEK29 720 (lower end).

To conclude, the maximum cost-effectiveness ratio in the one-way sensitivity analysis was SEK198 148. In general, the results seem to be fairly stable for variations of the parameters we regard as critical. The most critical parameter seems to be the costs of added years of life, for which we made the conservative assumption that even the younger patients are doing minimal work or none at all. If some of the patients are actually working, this will only lower the cost-effectiveness ratio.

## Discussion

Both the French and the German economic evaluations of CIBIS-I indicated that bisoprolol treatment leads to cost savings.[27,28] Why then do our results give a different outcome? The primary reason behind the difference seems to be that our titration costs are higher. If we do not take account of costs of added years of life and assume that there are no extra costs for up-titration, our calculations also lead to cost savings. When hospital admissions are considered, the cost savings would amount to SEK1983 per patient. Under similar premises, the results of our analysis are in line with the results of the French and the German studies. The French study, which took costs for bisoprolol and costs for hospital admissions into consideration, as well as titration costs of French francs (FF) 663 (SEK920 in 1999 Swedish prices), indicated that treatment with bisoprolol leads to cost savings of FF 4331 (SEK6010) per patient. The German study resulted in cost savings of Deutchmark (DM) 157 272 per 1000 patient-years, corresponding to DM 299 (SEK1430) per patient. However, both the French and the German studies assumed lower titration costs than those used in our study. If costs of added years of life are not considered, the costs for up-titration seem to be rather critical for the size of the cost-effectiveness ratio of bisoprolol. The relatively high cost of the up-titration of the bisoprolol dosage in a clinical setting therefore merits further attention. A tentative cost-effectiveness analysis of bisoprolol (based on data from CIBIS-II) was performed by Malek.[5] It resulted in a cost per life-year gained of pounds sterling £680 (SEK9090), a figure that is in line with the results of our study when the costs of up-titration are included, but the costs of added years of life are excluded.

Earlier, we presented our results based on both hospital admissions and hospital days. We chose hospital admissions as our base case. But which of hospital admissions or hospital days really provides the best basis for a cost-effectiveness analysis in a Swedish setting? As a check, we calculated the hospitalisation costs based only on the Swedish subpopulation in CIBIS-II. In fact, both per admis-

sion and per diem hospitalisation costs per patient in the Swedish subsample were close to the per admission hospitalisation costs per patient in the total sample. In general, it is open to question how well a multinational study with data from clinical centres in 18 different countries can represent the conditions in a single country like Sweden. For comparison, in table X we therefore show what the cost-effectiveness ratios would be if based only on the Swedish subpopulation in CIBIS-II (88 patients out of 2647).

It is perhaps not wise to try to draw any firm conclusions from a small subsample of the whole study. The hospitalisation cost differences between bisoprolol and placebo are in fact not statistically significant at the 5% level in the Swedish subsample. In any case, the results in table X seem to be in reasonable agreement with the results of table VI and table VII.

Although the part of the economic evaluation that was based entirely on data from the clinical trial was rather straightforward, the modelling for the follow-up period was strongly dependent on the assumptions regarding future survival and costs of added years of life. In fact, when costs of added years of life were included in the analysis, these costs clearly became dominant over the costs occurring during the course of the clinical trial. As regards the mortality after the trial, we made the conservative assumption that it would be the same in both the treatment and the placebo group after the end of follow-up. It is quite possible, however, that the benefits from the treatment during the clinical trial would persist some time after the trial has been concluded, perhaps for several years afterwards. In the CONSENSUS study,[37] for example, the positive effects of the ACE inhibitor enalapril on survival in the treatment group was sustained for at least 3.5 years after the end of follow-up.[37] A more realistic assumption would perhaps be that the mortality rate in the placebo group catches up with that in the treatment group after a shorter or longer time span. However, as indicated by our sensitivity analysis, such an assumption does not seem to affect the cost-effectiveness results significantly, at least not when costs of added years of life are included.

**Table X.** Incremental cost-effectiveness ratio (ICER) based only on the Swedish subsample. Costs are in Swedish kronor (SEK) at 1999 prices

| Cost effectiveness | ICER (SEK per life-year gained) based on | |
|---|---|---|
| | hospital days | hospital admissions |
| Including costs of added life-years | 150 612 | 148 553 |
| Excluding costs of added life-years | 4 597 | 2 538 |

Even if our study is in some respects more complete than most of the earlier economic evaluations of β-blocker therapies, there are still some limitations. One limitation is that indirect costs are not considered. No data on the patients' labour force participation were available from the study. This deficiency makes our evaluation more conservative, since treatment with bisoprolol decreases morbidity, and is therefore likely to reduce the sick leave of those patients who are actually working.

Another limitation is that data on the patients' quality of life were not directly available in the study. With the help of the NYHA class available for each patient, and quality weights from a paper by Kirsch and McGuire,[40] it is at least possible to say something about the likely effects on quality of life. If we assume that the quality of life for each patient, as given by the NYHA classification and the corresponding quality weights, is unchanged throughout the study and afterwards, then the average quality weight per patient would be about 0.50. This means that cost-effectiveness ratios based on cost per quality-adjusted life-year (QALY) would be about twice as large as the cost-effectiveness ratios in table VI. However, since quality of life improves during the course of the study, especially in the bisoprolol group, this leads to an overestimation of the cost per QALY. Only the average improvement in quality of life was available to us, but if these average improvements are randomly assigned to the patients, and a number of simulations made, the quality-of-life effects on the cost-effectiveness ratios can be roughly estimated. For example, at 12 months into the follow-up period,

42% of the patients in the bisoprolol group had improved by 1 or more NYHA classes, compared with 35% in the group that only received standard treatment.

We do not know how the quality of life developed after the study, but a plausible scenario would be that the difference in quality of life between the bisoprolol group and the placebo group during the follow-up period equalises rather quickly after the end of the trial. For simplicity, we settled for a scenario where the quality of life equalises directly after the end of the trial. If costs of added years of life were not included, an ICER of about SEK5200 to 21 200 per QALY was obtained, and if costs of added years of life were included, an ICER of about SEK246 000 to 274 000 per QALY was obtained.

A factor that is both a strength and a limitation is the fact that our economic evaluation was based on a clinical trial. It is a strength in the sense that randomised, controlled trials minimise observer bias and confounding from known and unknown variables.[42] It is a limitation in the sense that the conditions during clinical trials are optimised for showing efficacy and safety rather than effectiveness. Therefore, the conditions during a clinical trial tend to differ from a more realistic clinical setting in several important respects.[42-44]

Patients in clinical trials are usually younger than in clinical practice. As has been mentioned before, about 95% of all hospital discharges attributable to CHF in Sweden concern people over the age of 65 years.[2] In CIBIS-II, the average age was 61 years.[23]In CIBIS-II, 81% of the patients were men, and 19% were women.[23] This is not representative of actual clinical conditions. Men are clearly over-represented among younger patients with heart failure, but among the more elderly patients, female patients are almost as common as male patients.[45] The patients in clinical trials often have only a single disease. In clinical practice, most patients have several diseases. The patients in clinical trials are closely monitored, and have a better compliance than patients in general.The costs are often higher in a clinical trial than in regular clinical practice (protocol-driven costs).[43]

Thus, the treatment results from clinical trials are often better than those achieved in clinical practice, where the conditions are less idealised. These factors raise concerns for the validity of the present study for more realistic clinical settings, where patients are often older and sicker, and compliance is not as good. Some of these problems could perhaps have been remedied by way of modelling, but in the absence of reliable data we decided to concentrate on an economic evaluation that was as close as possible to the data available from the clinical trial.

In spite of the deficiencies mentioned above, clinical trial data still seem to provide the best basis for an economic evaluation of a new pharmaceutical, or a new indication for an old one, in the absence of more naturalistic trials. Even if results from a clinical trial are available, a certain amount of modelling is nevertheless required. Since the follow-up time is limited, it is necessary to combine the survival data from the clinical trial with modelling to obtain reasonable results. For example, an evaluation that did not take the survival after the end of the trial into account would clearly lead to unrealistic results.

There does not seem to be any consensus about the value per life year gained (or value per QALY gained).[46,47] Rules of thumb have been presented. According to Goldman et al.,[48] a treatment is often regarded as highly cost effective if the cost per QALY is lower than US dollar ($US) 20 000 (1992 US prices), or about SEK190 000 in 1999 Swedish prices. They further state that a cost-effectiveness ratio in the range of $US 20 000 to $US40 000 per QALY (SEK190 000 to 380 000) is consistent with currently funded programmes such as haemodialysis and hypertension treatment. On the other hand, cost-effectiveness ratios over $US60 000 (SEK570 000) are regarded as high, and ratios over $US100 000 (SEK950 000) are regarded as unattractive compared with other funded treatments. However, it should be noted that all of these values are based on a definition of costs including indirect costs but excluding costs of added years of life. If costs of added years of life were considered, the

thresholds reported by Goldman et al.[48] would perhaps be higher, since many cost-effectiveness ratios for generally accepted treatments might be higher if such costs were included. (See, however, Meltzer[32] or Johannesson et al.[33] for discussions.)

Rules of thumb such as those above are generally based on comparisons between different medical treatments. Suggested thresholds for cost-effectiveness ratios can also be established by willingness-to-pay (WTP) methods. For example, Johannesson and Meltzer[49] have estimated the WTP for saving statistical lives in cost-benefit analyses of road investments in Sweden to be about $US90 000 per QALY, or SEK750 000 in 1999 Swedish prices. However, different methods of estimating the WTP for a QALY yield widely varying results, from a median of $US24 777 per QALY for estimates based on human capital methods to a median of $US 428 286 for estimates based on wage premiums for job risks,[47] or about SEK210 000 to SEK3 600 000 per QALY in 1999 Swedish prices. This wide interval makes it difficult to put any clear-cut value on gained life-years and QALYs.

Given that other economic evaluations of heart failure therapy do not consider costs of added years of life, our results are in this respect not comparable with other published studies in this area. If costs of added years of life are not considered, however, the cost effectiveness of bisoprolol compares favourably with that of other heart failure treatments. The cost-effectiveness ratios obtained without considering costs of added years of life were lower than for any of the treatments displayed in table I, with the exception of the earlier evaluations of bisoprolol, and much lower than any of the thresholds mentioned above. Also, if costs of added years of life, and our tentative quality adjustment of life-years gained, are taken into consideration, the cost effectiveness must still be regarded as rather favourable according to most methods of estimating the WTP for life-years gained.

## Conclusions

We found that treatment of CHF with bisoprolol without regard to costs of added life-years is cost effective compared with generally accepted treatments. If costs of added life-years are included, the cost-effectiveness ratio is still favourable compared with most estimates of the WTP for life-years gained. Our sensitivity analysis implies that this conclusion is stable for reasonable variations of key variables and assumptions, such as survival after the end of the clinical study.

For patients with the characteristics of those in the clinical trial CIBIS-II, in which the patients were older and much sicker than the average person, the incorporation of costs of added years of life increases the cost-effectiveness ratio substantially. Since more patients survive in the bisoprolol group than in the group that only received standard therapy, and the production net of consumption is negative, the incremental costs of added years of life between the 2 treatments compared in the trial are quite important. However, it should be noted that the costs of added life-years mostly consist of general costs of living, and that their inclusion in this case does not change the conclusion as to whether the treatment is cost effective or not.

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# Assessing uncertainty in cost-effectiveness analysis by combining resampling of clinical trial data with stochastic modelling: The economic evaluation of bisoprolol for heart failure revisited

By Mattias Ekman

**Abstract**

The purpose of this paper is to evaluate the cost-effectiveness of the beta blocker bisoprolol in heart failure by combining resampling of the clinical trial data with stochastic modelling of the expected remaining lifetime for patients alive at the end of the clinical trial. This is a reassessment of an economic evaluation of the beta blocker bisoprolol that has previously been published. The main difference between this study and the previous one lies in the estimation of uncertainty. In the earlier study, the health effects were estimated by combining the survival times from the clinical trial, which the economic evaluation was based on, with a deterministic additional survival time for the patients who were alive at the end of clinical trial. The results were then evaluated by performing a sensitivity analysis. In this study, the deterministic modelling of the survival after the end of the clinical trial is replaced by stochastic modelling, and the uncertainty of the experimental data is assessed by a repeated resampling (bootstrap) procedure. The average value of the net (monetary) benefit is SEK 101 400 at a value of SEK 450 000 per year of life gained. A one-sided confidence interval on the 5% level shows that the net (monetary) benefit is significantly larger than zero.

Key words: Cost-effectiveness analysis, net benefit, stochastic simulation, sensitivity analysis, beta blocker, bisoprolol, heart failure.

# 1. Introduction

The present paper is a reassessment of an economic evaluation of the beta blocker bisoprolol in heart failure that has previously been published (Ekman et al., 2001). In the original evaluation, clinical trial data on resource consumption and survival were combined with a modelling assumption about the survival after the end of the clinical trial. However, the modelling of the survival after the end of the clinical trial was deterministic, and neither did we explore the uncertainty of the experimental data available to us in the economic analysis. The analysis of uncertainty in the earlier study was limited to a sensitivity analysis of parameters such as the discount rate and the expected length of life after the end of follow-up. The problem is that sensitivity analysis is associated with some limitations that often make the results unreliable. O'Brien et al. (1994) list three major limitations: 1) The choice of which variables to include in the sensitivity analysis as well as the ranges to consider are at the discretion of the analyst. 2) It can be difficult to assess what variation of the results is acceptable. 3) Since variables are often varied one at a time, the interactions between variables carry the risk of being neglected.

The purpose of this paper is to make up for the deficiencies of the earlier publication with respect to the treatment of uncertainty by providing a stochastic rather than deterministic analysis. What I have done, essentially, is to combine resampling of experimental data from the clinical trial with stochastic simulation of the length of life after the end of follow-up. The costs of added years of life were also included, as in the previous study.

This paper is reasonably self-contained, but readers wishing to pursue background information are encouraged to consult the earlier publication. Details about the clinical trial on which the economic evaluation is based, and about the cost estimations, are not repeated here. I will begin by summarising the earlier study. I will then go on to discuss the method of the present study. Thereafter the results follow. I will conclude by discussing the advantages and disadvantages of the approach used in this paper.

## 2. The previous study

In the study reported in Ekman et al. (2001), the cost-effectiveness of adding the β-blocker bisoprolol to standard treatment for patients with congestive heart failure in Sweden was evaluated. The cost-effectiveness analysis was based on data from the Cardiac Insufficiency Bisoprolol Study II (CIBIS-II), a clinical randomised trial investigating the efficacy of adding bisoprolol to standard therapy of congestive heart failure (see CIBIS-II Investigators and Committees, 1999).

The cost-effectiveness analysis was as far as possible carried out from a societal perspective, but productivity losses and time costs for the patients were not taken into account. The health effects were measured in terms of gained years of life. The costs included pharmaceuticals and hospitalisations. We used data on health care resource consumption from CIBIS-II and combined them with average Swedish retail prices for medicines, and average costs for hospitalisations based on either hospital admissions or hospital days.

The evaluation was carried out both with costs of added years of life, i.e. consumption net of production during gained life years, included and excluded. If costs of added years of life were excluded, then bisoprolol therapy increased life expectancy at an incremental cost of SEK 3 353 or 13 094 per year of life gained, depending on whether the hospitalisation costs were based on hospital days or hospital admissions. If costs of added years of life were included, then the incremental cost-effectiveness of bisoprolol therapy was SEK 159 117 or 168 858, depending on whether the hospitalisation costs were based on hospital days or hospital admissions. The conclusion was that for heart failure patients with characteristics like those in CIBIS-II, the cost-effectiveness of bisoprolol therapy compares favorably with that of other cardiovascular therapies.

## 3. Method

### 3.1. Choice of method

Studies of cost-effectiveness in health and medical care have traditionally relied on the incremental cost-effectiveness ratio for comparing two alternative treatments. The cost-effectiveness ratio is defined as $R = \Delta C/\Delta E$, where $\Delta E = \overline{E}_1 - \overline{E}_0$ denotes the difference in effect, and $\Delta C = \overline{C}_1 - \overline{C}_0$ denotes the difference in cost, between two treatments 1 and 0.

In studies exploring the uncertainty of the cost-effectiveness results, e.g. in terms of a confidence interval around a point estimate, it is doubtful whether the use of cost-effectiveness ratios is a good approach. The statistical problems with cost-effectiveness ratios are well known. If two stochastic variables both follow a standard normal distribution, then the ratio of these stochastic variables will follow a Cauchy distribution, which has neither a finite mean nor a finite variance (Van Hout et al., 1994). If the averages are not standard normal, the distribution is generally unknown (Briggs and Fenn, 1998). However, if there is a substantial risk of the difference in effect, $\Delta E$, between two treatments being close to zero, then the distribution is likely to have properties similar to those of the Cauchy distribution. As a consequence, the mean and variance may perhaps not even be defined. These difficulties make it problematic to compute a confidence interval for cost-effectiveness ratio by traditional statistical means. Although several statistical methods have been proposed in the literature, the most suitable method seems to be Fieller's method. See, e.g., Briggs and Fenn, 1998, for a description. In addition to the statistical difficulties, cost-effectiveness ratios have an ambiguous interpretation, since the interpretation varies depending on the sign of the cost and effect differences (Stinnett and Mullahy, 1998).

A solution to both the statistical problem with cost-effectiveness ratios and the problem of ambiguity in their interpretation is to use the net benefit formulation of cost-effectiveness (Tambour et al., 1998; Stinnett and Mullahy, 1998). The net benefit of a treatment compared to an alternative is defined as $NB(p) = p \cdot \Delta E - \Delta C$. As for the cost-effectiveness ratio, $\Delta C$ and $\Delta E$ represent incremental differences in costs and effects between the two treatments. The net benefit is a function of $p$, where $p$ denotes

the willingness to pay (or the willingness to accept, if $\Delta E$ is negative) per gained year of life. The statistical advantages of the method of net benefits are discussed, e.g., in Löthgren and Zethraeus (2000), Stinnett and Mullahy (1998), and Zethraeus et al. (2001).

If the net benefit method seems superior to cost-effectiveness ratios for representing uncertainty, the choice of statistical methodology is less clear. I have here chosen a simulation modelling approach based on resampling of the clinical trial data combined with stochastic modelling of the remaining lifetime for the survivors after the end of the clinical trial. The methodology is inspired by the bootstrap method, the main difference being that I also incorporate stochastic modelling of the expected remaining lifetime after the clinical trial, rather than only resampling from an experimental sample. Otherwise it would be hard to obtain results that are meaningful from an economic point of view.

A problem is that it is difficult to incorporate modelling, or evidence from several sources, in a statistically valid way within a framework of classical statistical inference. The present economic evaluation is therefore to be regarded primarily as a modelling study, even though much of the evidence is taken from a clinical trial. In a Bayesian approach, which could have been used as an alternative methodology, evidence from several sources can be combined in a statistically valid (but not uncontroversial) way. The main disadvantages are that a prior distribution as well as distributional assumptions are needed, since non-parametric techniques are difficult to incorporate into a Bayesian framework (Lee, 1997).

### 3.2. The bootstrap

The bootstrap method is a resampling technique that is useful for estimating various statistics, for example the variance, without using traditional parametric formulas. The basic idea of bootstrapping is to use the available data sample for resampling with replacement. The experimental data are used as an empirical distribution, where each observation $x_1, x_2, \ldots, x_n$ has a probability of $1/n$. Parameters of interest, such as the mean, and their standard deviation can then be estimated by repeated sampling with replacement from this empirical distribution. For each resample, a bootstrap estimate of the parameter is calculated.

The great advantage of the method is its conceptual simplicity. For example, if we want to create a 95% confidence interval for the mean, then if we have 100 observations, we simulate a resample of size 100 with replacement. We then calculate the mean for this resample. The process is then repeated, say, 1000 times. If we have made 1000 resamples, then a 95% confidence interval consists of the range of the 950 middle resamples. This is called the bootstrapping percentile method (see Efron and Tibshirani, 1993, for details).

A disadvantage with the method is that its theoretical foundations are somewhat unclear. Despite an intensive methodological development, this problem seems to remain, except for relatively simple cases where it can be shown that the bootstrap method gives results that are asymptotically equivalent to exact methods (Efron and Tibshirani, 1993). A lot of computations are also required, but thanks to the development of more and more powerful computers, this is much less of a problem than it used to be.

In practice, the method of finding a confidence interval for the mean of a sample of size $n$ by using the bootstrap percentile method has the following steps:

1. Create a random resample of size $n$, with replacement.
2. Calculate the resample mean.
3. Repeat step 1 and 2 a large number of times in order to get a large number of resample means.
4. When a suitable number of resample means have been collected, e.g. 1000, create a 95% confidence interval by taking the $25^{th}$ largest value as an upper bound and the $975^{th}$ largest value as a lower bound.

Bootstrapping by the percentile method has been used in several earlier economic evaluations as a method for assessing uncertainty, see e.g. Chaudary and Stearns (1996), Briggs et al. (1997), Obenchain et al. (1997), Hunink et al. (1998), and Jönsson et al. (1999).

### 3.3. The model

In the overall structure of the analysis, the differences from the economic evaluation that has been reported in Ekman et al. (2001) are not very large. The major differences all concern the treatment of uncertainty. A major deficiency of the previous economic evaluation was that the additional lifetime was deterministic, i.e. the same expected additional lifetime was added to every patient who was alive at the end of follow up. This makes it very difficult to correctly assess the overall uncertainty of the cost-effectiveness analysis. In order to overcome this problem and make the analysis more realistic, the additional lifetime after the end of the clinical trial has here been made stochastic, with an individual lifetime for each patient generated from a probability distribution. Hopefully, the uncertainty that could be expected for the actual survival is reflected in a realistic way by this approach.

Another difference from the earlier study is that discounting of costs and health effects is here continuous. This is hardly a disadvantage, since both added years of life and costs of added years of life are better represented by continuous discounting. Continuous discounting of the lifetime means that if someone lives for $T$ years, the discounted lifetime is equal to integral of the function $e^{-rt}$ from 0 to $T$, i.e. $(1 - e^{-rT})/r$. Since the chosen base-case discount rate is small, 3%, continuous discounting differs little from annual compounding.

### 3.4. Estimation and modelling of health effects

*Estimating additional life-years*

The health effects are measured in terms of gained years of life, as in the previous economic evaluation of bisoprolol. Just as in the previous economic evaluation, the gained years of life consist of two components, the lifetime within the clinical trial, which is known, and the expected lifetime after the end of the clinical trial. The expected lifetime after the end of the clinical trial has to be based on assumptions, which are in turn grounded on empirical data.

The reason for adding an expected remaining lifetime for those who survive throughout the clinical trial is that the follow-up times for survivors do not contain any information that can be used directly in a cost-effectiveness analysis. The survival data given in the

clinical trial are censored, i.e. all patients who withdraw from the study prematurely, or who are alive at the end of follow-up, have an unknown survival time. For health economic purposes this is not sufficient, and some prediction has to be made as to how long the survival is likely to be after the end of follow-up in order to estimate the health effects in terms of gained life years. This means that the total uncertainty will consist of two components: the uncertainty given by the data from the clinical trial, and the stochastic element in the modelling of what happens after the end of follow-up. By necessity, predicting the expected survival requires modelling of future events, so we are here dealing with modelling uncertainty rather than uncertainty in an empirical data set, although the predictions are usually based on empirical data.

From the survival data in the clinical trial we can obtain an estimate of the hazard rate, i.e. the mortality risk per unit of time, during the clinical trial. A possible way of modelling the expected remaining lifetime is to extrapolate the hazard rate found in the clinical trial under the assumption that the patients will have about the same hazard rate after the end of the study. This is possible if the follow-up time is long enough (see e.g. Johannesson et al., 1997). Another way is to look at epidemiological data or data from other clinical trials with similar patient groups. The problem with using other data sources is that it can be difficult to assess whether patient groups in different studies are comparable or not. In this particular case the survival in the clinical trial CIBIS II (1999) is a little better than would be expected from the patient composition, compared with clinical trials of ACE inhibitors, such as CONSENSUS (1987) and SOLVD (1991).

If data from a clinical trial are used, the survival data can be analysed either parametrically or non-parametrically. A popular non-parametric method is the Kaplan-Meier method (Lee, 1992). The advantage of this method is that it does not require that any specific functional form for the survival distribution be chosen. A disadvantage is that with censored data, the Kaplan-Meier estimate of the survival curve does not stretch beyond the end of follow-up. For modelling purposes, parametric distributions are therefore required.

Popular parametric distributions for survival analysis are the exponential, Weibull, gamma, lognormal, and Gompertz distributions. The exponential distribution is the

simplest, since it has only one parameter, namely the hazard rate, which is assumed to be constant. As already mentioned, the hazard rate signifies the mortality risk during a given time period. For the CIBIS-II data, for example, the yearly hazard rate $\lambda$ was estimated to be 0.133 for the placebo group (95% C.I.: $0.115 < \lambda_0 < 0.151$), and 0.0878 for the treatment group (95% C.I.: $0.0735 < \lambda_1 < 0.1020$). The corresponding survival functions are $S_0(t) = \exp(-\lambda_0 t)$ for the placebo group, and $S_1(t) = \exp(-\lambda_1 t)$ for the treatment group. See Appendix 1 for details of the calculations. The variability of these estimates can be used as a basis for stochastic modelling of the uncertainty of the survival after the clinical trial.

It is of course far from certain that the exponential distribution provides the best representation of the survival curves in CIBIS-II. For this reason, a life table approach was used for determining which of several survival distributions that is most suitable for the present data set. If a life table approach is used for estimating an empirical survival curve, this curve can then be fitted to various distributions with the help of linear regression (see Lee, 1992, pp. 224-227). The results show that although it is the simplest, the exponential distribution appears to be the best choice for representing the survival function in this case. See Appendix 2 for details.

*Base-case assumption*

As the base case, I assumed that the yearly mortality after the end of the trial would be normally distributed with a mean hazard ratio of 0.15, and a standard deviation of 0.010. This is slightly higher than for the placebo group, but since the population is ageing this may not be unreasonable. The value also lies within the upper end of the confidence interval for the hazard rate in the placebo group, and it is an estimate that is close to hazard rates from other clinical studies with similar patient populations. For each round of bootstrapping of the experimental data, a new hazard ratio is simulated. Each patient is then assigned an additional survival time according to the distribution $S(t) = \exp(-\lambda t)$, with mean $\lambda = 0.15$. For reasons of realism, the maximum age has been limited to 110 years.

In the base-case analysis I assumed that the survival in the treatment group and in the placebo group would equalise immediately after the end of the clinical trial. This cautious assumption corresponds to the base case in the earlier publication.

*Model*

In the computer-based model, implemented in a spreadsheet program, the additional lifetime is given by the formula

$$T = \min\left\{110 - Age, -\frac{1}{\lambda}\ln\left[U(0,1)\right]\right\}. \qquad (1)$$

The minimum condition has been imposed because no patient in the model should be allowed to live beyond the age of 110. Since the likelihood of longer lifetime is very low, and the gained years of life are discounted, this condition makes little difference for the final results, as already mentioned above.

The function $-1/\lambda \cdot \ln[U(0,1)]$ has been introduced since the exponential distribution is generated from a uniform one (see Law & Kelton, 1991, p.486). The factor $1/\lambda$ is the standard deviation of the exponential distribution, where the parameter $\lambda$ is in turn assumed to follow a normal distribution with standard deviation $\sigma_\lambda$. A new value of $\lambda$ is not drawn for each patient individually, but generated for each new round of simulation.

The number of additional lifeyears is then discounted continuously according to the formula

$$T_{disc} = \frac{1}{r}\left[1 - e^{-rT}\right]e^{-rt}, \qquad (2)$$

where $T$ follows equation (1) above, and $r$ is the discount rate. The discount factor $e^{-rt}$ has been introduced because the lifetime of all patients are discounted back to a common point of reference, irrespective of their individual follow-up times. Thus $t$ will be dependent on the follow-up time of the individual patient.

### 3.5. Costs

The costs within the clinical trial, i.e. the individual patients' costs for medication, dosage titration, and hospital admissions, are the same as in the previous economic evaluation of bisoprolol (see Ekman et al. (2001) for details). The only difference is that the hospitalisation costs have here only been based on admissions, but not on *per diem* costs. The costs of added years of life are here somewhat lower, because the net indirect taxes on private consumption have been subtracted.

The costs of added years of life follow, essentially, the formula

$$C_{disc} = \frac{C(Age)}{r}\left[1 - e^{-rT}\right]e^{-rt}, \qquad (3)$$

where $C(Age)$ represent the costs of added years of life, which are age dependent. In practice, I have evaluated the total costs of added years of life for a patient as a sum of at most three stages, 0-74, 75-84, and 85+, depending on how long each patient is expected to live. For example, if a patient is 70 at the end of follow-up and is expected to live an additional 10 years, then between 70-74 the yearly costs of added years of life will be SEK 141 890, and between 75-80 the costs of added years of life will be SEK 171 388. The two time periods are evaluated separately, but discounted back to a common point of reference and summed together. If the patient had lived past the age of 85, the costs of added years of life would then have increased to SEK 256 290.

The total costs for each patient are thus given by two components: 1) medical costs from the clinical trial, and estimated non-medical costs of added years of life during the course of the clinical trial, and 2) estimated costs of added years of life (medical and non-medical) after the end of the clinical trial. The medical costs during the course of the clinical trial have been calculated by combining the resource consumption from the clinical trial with Swedish unit cost data (see Ekman et al., 2001, for details). Since the unit costs are deterministic, the uncertainty of the medical costs is essentially given by the sampling uncertainty of the resource consumption.

The uncertainty of the costs of added years of life was assumed to follow a normal distribution, with mean varying according to age as discussed above, and a standard

deviation of SEK 8 000 (irrespective of age). This standard deviation is perhaps a little too high, but since I have only estimated the uncertainty of the costs of added years of life approximately, I decided to err on the higher side rather than the lower. The standard deviation is not drawn for each patient individually. Like the hazard rate, a new draw is made for each round of bootstrapping.

### 3.6. Threshold value of the willingness to pay per life year gained

For the net benefit method, the threshold value $p$ for the willingness to pay per life year gained was set to SEK450 000. This value is based on the estimated willingness to pay for saving lives on the Swedish roads, which was estimated to SEK444 000 for 1997. Of course, it is far from evident that the willingness to pay (WTP) for saving lives on the roads should be relevant also for saving lifeyears for heart failure patients. In any case, in the absence of more specific surveys for the WTP in Sweden for such interventions, it seems reasonable to use a value from another area. See Johannesson & Meltzer (1998), Johannesson (2001), and Hirth et al. (2000) for discussions of WTP for (quality-adjusted) life years.

### 3.7. Simulation

The simulation procedure has the following steps:

1. For each round of simulation, a new value is drawn of the hazard rate for the exponential survival function that represents the expected survival after the end of the clinical trial. A new value is also drawn of the cost of an added year of life. Both of these parameters are drawn from normal distributions.

2. For each round of simulation, a couple of resamples of the same size as the original samples are drawn with replacement from the treatment group (1327 observations) and the control (or placebo) group (1320 observations).

3. For each resampled observation, a stochastic expected remaining lifetime is added to the survival time within the clinical trial by drawing from the exponential distribution mentioned in step 1, given that the patient is alive at the end of follow-up.

4. For each resampled observation, the cost of added years of life during the expected remaining lifetime is added to the costs within the clinical trial by multiplying the expected remaining lifetime with the constant yearly cost of an added year of life mentioned in step 1 (given that the patient is alive at the end of follow-up). Non-medical costs of added years of life that are incurred during the follow-up time are also added by multiplying the follow-up time with a constant cost per added life year (somewhat lower than that above since most medical care expenses have been deducted).

5. For each round of simulation, average costs and average health effects are computed for the treatment group and the control group. The net benefit is then computed as $NB_n^*(p) = p \cdot \left(\overline{E}_1^* - \overline{E}_0^*\right) - \left(\overline{C}_1^* - \overline{C}_0^*\right)$. The star signifies a value based on resampling/simulation.

6. Steps 1-5 are then repeated a large number of times, say $N$, in order to obtain simulation replicates of the net benefit: $NB_1^*, NB_2^*, ..., NB_N^*$. The bootstrap estimate of $NB$ and its variance are calculated by the following formulas:

$$NB = \frac{1}{N}\sum_{n=1}^{N} NB_n^*, \text{ and } V(NB) = \frac{1}{N-1}\sum_{n=1}^{N}\left(NB_n^* - NB\right)^2. \qquad (4)$$

Using these estimates of mean and variance, a confidence interval can be constructed. A percentile confidence interval can also be constructed directly from the simulation replicates of the net benefit.

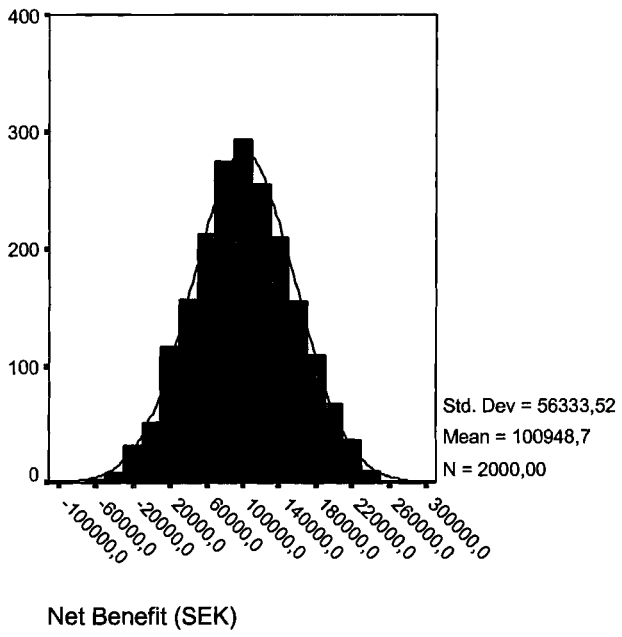
The number of resampling/simulation rounds $N$ was set to 2000. This number is chosen because bootstrapping studies in medical cost-effectiveness analysis have usually been performed with a similar number of rounds (Chaudhary & Stearns, 1996; Briggs et al., 1997).

# 4. Results

## 4.1. The net benefit

The net benefit resamples follow a normal distribution very closely, as can be seen in figure 1. This is to be expected, since by the central limit theorem both the average cost and the average health effects follow a normal distribution regardless of the underlying distribution of individual costs and health effects (Wackerly et al., 1996). Because the net benefit is a linear function of two normally distributed variables, it will also follow a normal distribution. The 95% confidence interval for the net benefit is SEK [-8 999, 210 839] if the percentile method is used, i.e. if we take the $50^{th}$ and the $1950^{th}$ values as lower and higher boundaries. If we instead use the average value and the standard deviation estimated from the simulation results, we get a 95% confidence interval that is equal to SEK $100\,949 \pm 1.96 \cdot 56\,334 = [-9\,466, 211\,364]$, which is more or less equivalent to the percentile interval. It should be noted, however, that these confidence intervals are defined only for a particular value for the threshold $p$ (here SEK 450 000).

**Figure 1.** *Histogram of 2000 resamples of the net health benefit.*



### 4.2. Stability of the results

To check the stability of the results, I performed up to 12 000 simulations. For the net benefit method with $p$ = 450 000, this resulted in the following 95% percentile confidence interval: [-9 044, 213 478]. The average was SEK 100 741. The standard deviation was 56 656. This is quite close to the results for 2 000 runs.

### 4.3. One-sided confidence interval

The results seems to indicate that on the 5% level the net benefit of treatment with bisoprolol is not significantly larger than zero. However, from a decision-making viewpoint, the upper limit of the confidence interval is not interesting. The proper confidence interval for assessing whether the net benefit is significantly larger than zero or not is one-sided. At the 5% level, and based on 12 000 simulations, the one-sided percentile confidence interval is $\overline{NB} > \text{SEK } 8\,424$. This means that the net benefit is significantly larger than zero at the 5% level.

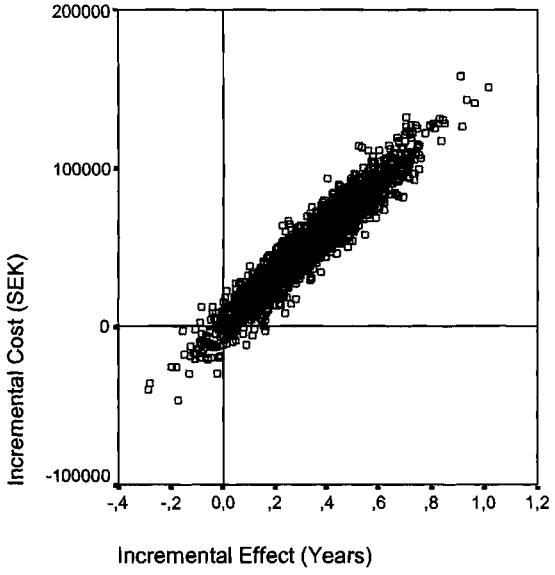
### 4.4. With costs of added years of life excluded

For the net benefit with costs of added years of life excluded, the two-sided 95% percentile confidence interval based on 12 000 simulations is SEK [-14 057, 317 464], with an average of SEK 149 350. However, a one-sided 5%-level confidence interval, analogous to the one above, shows that the net benefit is significantly larger than zero. Based on 12 000 simulations, the one-sided 5% confidence interval for the net benefit is $\overline{NB} > \text{SEK } 10\,936$.

### 4.5. The cost-effectiveness ratio

The results illustrate that it is questionable whether it is at all meaningful to present a confidence interval for the cost-effectiveness ratio. In figure 2, the 2 000 bootstrap/simulation resamples for the base-case are shown on the cost-effectiveness plane. There are points located in all four quadrants. This makes it difficult to calculate an easily interpretable confidence interval. Figure 3 also illustrates the strong relationship between $\Delta E$ and $\Delta C$ that is introduced by taking costs of added years of life into account. The correlation coefficient is 0.96.

**Figure 2.** *The incremental cost plotted against the incremental health effect.*




Negative ratios are of two types. In the lower right quadrant, the new treatment dominates over the old one, since it is both less costly ($\Delta C < 0$) and more effective ($\Delta E > 0$). In figure 2 there are 25 such points. For the 16 points in the upper left quadrant, the old treatment dominates instead, since it is less costly ($\Delta C > 0$) and more effective ($\Delta E < 0$). In a confidence interval the points where the old treatment dominates should placed at the bottom end, and the points where the new treatment dominates should be placed at the top end. However, also the positive cost-effectiveness ratios have two different interpretations. For the upper right quadrant ($\Delta C$, $\Delta E > 0$), the treatment is cost-effective if $\Delta C/\Delta E < p$, and for the lower left ($\Delta C$, $\Delta E < 0$) if $\Delta C/\Delta E > p$. In figure 2, there are 51 points in the lower left quadrant. Because of this, even a confidence interval taking account of dominance (represented by negative cost-effectiveness ratios) is hard to interpret in a consistent way for decision making.

A further problem is that when $\Delta E$ is close to zero, very large positive or negative values of the cost-effectiveness ratio can be obtained. In the example above, the largest positive cost-effectiveness ratio was equal to about MSEK 22.1, and the largest negative cost-effectiveness ratio was equal to about MSEK –3.6. The existence of outliers make

it difficult to illustrate the distribution of cost-effectiveness ratios in a histogram. The range of C/E ratios is so wide that most C/E ratios obtained in the simulation procedure would be assembled in only one bar of the histogram. Since the cost-effectiveness ratio is a ratio of two normally distributed variables, the ratio itself could be expected to follow something similar to a Cauchy distribution, where the mean and variance are not defined, since the risk of obtaining extreme outliers is substantial. It is this kind of erratic behaviour that we can observe in this case. The only possibility here would be to use a percentile confidence interval, but as discussed above, it is doubtful whether it would be possible to interpret such an interval in a consistent way.

An ingenious way around these problems is the method of angular transformations presented by Cook & Heyse (2000), whereby the cost-effectiveness ratios are transformed to angles before calculating a confidence interval. The confidence interval is then transformed back to the usual scale for interpretation. However, since the net benefit method seems to work well, I did not apply the method of angular transformations to my data.

**4.6. Cost-effectiveness acceptability curves**

A non-parametric cost-effectiveness acceptability curve can be estimated by calculating the proportion of bootstrap replications lying on the acceptable side of the threshold willingness to pay per gained year of life. Since the decision rules on the cost-effectiveness plane are applied, there is no difference between a calculation based on cost-effectiveness ratios, or a calculation based on the net benefit method (Briggs and Fenn, 1998, Löthgren and Zethraeus, 2000).

For the net benefit method, the cost effectiveness acceptability curve can be calculated from the expression

$$CE_{acc}(p) = \frac{1}{N}\sum_{n=1}^{N} I\{NB_n^*(p) > 0\} = 1 - F(0), \qquad (5)$$

where $N$ is the number of bootstrap replications, $I$ is the indicator function (equal to 1 when the expression within the bracket is fulfilled, and equal to 0 when it is not),

$NB_n^*(p)$ is bootstrap replicate $n$, and $F(x)$ is the sampling distribution of the net benefit estimator.

In figure 3, we see the cost-effectiveness acceptability curve when the costs of added years of life are included. In figure 4, we see the cost-effectiveness acceptability curve when costs of added years of life are excluded. As can be seen, neither of the curves attains the value of one. This is because there are some simulation realisations where the old treatment is dominating. (The figures are based on 12 000 simulation rounds).

**Figure 3.** *Cost-effectiveness acceptability curve with costs of added years of life included.*

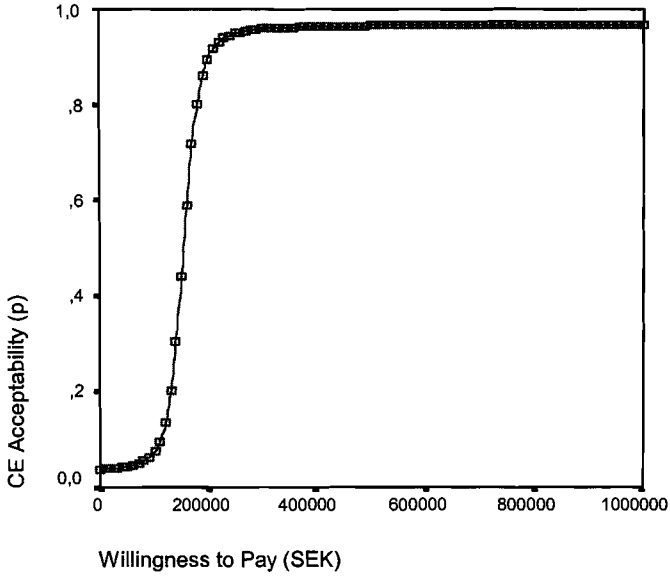
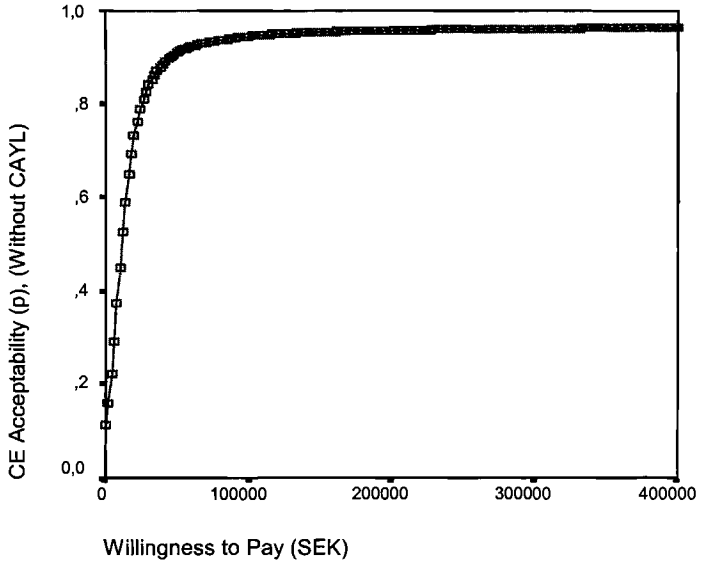


**Figure 4.** *Cost-effectiveness acceptability curve (costs of added years of life excluded).*




The inflexion points where the cost-effectiveness acceptability is equal to 0.50 in figures 3 and 4 are close to the median estimates of the cost-effectiveness ratio, about SEK 154 000 per year of life gained with costs of added years of life, and about SEK 11 000 without. This is to be expected, given the definition of the cost-effectiveness acceptability curve.

The connection between the bootstrap acceptability estimate and the confidence interval is that the minimum confidence level that gives a confidence that just covers zero is equal to 1 – $F(0)$, which exactly corresponds to the bootstrap estimate $CE_{acc}(p)$ (Löthgren and Zethraeus, 2000). The curves represent the proportion of simulation realizations of the net benefit that are larger than zero for various values for the threshold value. Unless a Bayesian framework is used, the curves should not be directly interpreted as the probability that the treatment is cost-effective.

## 5. Sensitivity analysis

A sensitivity analysis was conducted in order to find out how sensitive the confidence intervals are to different parameter values. The most significant parameter was the hazard rate $\lambda$, which was used for the stochastic survival function. The reason for this is clear. For an exponential probability distribution, the standard deviation is the same as the mean, i.e. $1/\lambda$. Furthermore, the survival after the end of the trial is longer and has a greater variability than the follow-up time during the trial. Most of the total variability is thus derived from the modelled additional lifetime after the trial (about 90% in fact). This means that when $\lambda$ is varied, the standard deviation of the discounted total lifetime of the patients (i.e. the standard deviation health effect in the cost-effectiveness analysis) will be roughly proportional to $\lambda$. If $\lambda = 0.15$, for example, then the patients who survive will on average get an undiscounted additional lifetime after the end of the trial that is equal to $1/\lambda = 6.67$. When this expected survival time is added to the follow-up time during the trial and discounted, we end up with a mean total lifetime of 6.3 years in the bisoprolol group and about 5.9 in the placebo group. In both groups, the standard deviation is about 4.7. As can be seen in table 1, the results were considerably less sensitive to variations in the standard deviation of the hazard rate, and variations of the standard deviation of the costs of added years of life. For the latter two parameters, it is even difficult to discern any clear patterns, even if it seems that the net benefit increases slightly when the standard deviation of the cost of added years of life decreases.

**Table 1.** *Sensitivity analysis of some model parameters. The percentile confidence intervals (C.I.) are at the 95% level, and are based on 2000 simulations.*

| $\lambda$ | $\sigma_\lambda$ | $\sigma_{cayl}$ | Average NB | C.I. NB |
|---|---|---|---|---|
| Base case | | | | |
| 0.15 | 0.010 | 8000 | 100 949 | -8 999 – 210 839 |
| Variation of $\lambda$ | | | | |
| 0.19 | 0.010 | 8000 | 83 662 | -8 398 – 178 127 |
| 0.11 | 0.010 | 8000 | 126 724 | -5 670 – 264 123 |
| 0.05 | 0.010 | 8000 | 210 580 | 10 507 – 418 566 |
| Variation of $\sigma_\lambda$ | | | | |
| 0.15 | 0.015 | 8000 | 100 586 | -11 493 – 208 148 |
| 0.15 | 0.005 | 8000 | 103 143 | -8 567 – 213 936 |
| 0.15 | 0 | 8000 | 98 794 | -17 970 – 206 635 |
| Variation of $\sigma_{cayl}$ | | | | |
| 0.15 | 0.010 | 12000 | 98 954 | -14 059 – 208 019 |
| 0.15 | 0.010 | 4000 | 103 896 | -10 781 – 212 654 |
| 0.15 | 0.010 | 0 | 104 462 | -3 828 – 216 340 |

Because of the difficulties in interpreting confidence intervals for cost-effectiveness ratios, I have decided not to include them in the sensitivity analysis. This is no loss, since cost-effectiveness analyses based on cost-effectiveness ratios or the net benefit method are equivalent if interpreted properly. However, the results of the net benefit method are easier to handle and to display.

## 6. Discussion

Modelling is a controversial, but necessary, part of economic evaluations in health care. In this context the following question is important: How much of the total uncertainty comes from the experimental data in the clinical trial and how much comes from the modelling of the costs and effects after the end of the clinical trial? It seems that most of the uncertainty in this case actually comes from the modelling. In particular, the choice

of expected length of life not only to a large extent determines the size of the cost-effectiveness ratio and the net benefit, but it also heavily influences the uncertainty in terms of both health effects and cost of added years of life. Since the costs of added years of life come to dominate over other costs, and the costs of added years of life are directly tied to the length of life, there will be a strong correlation between total costs and total health effects.

On one hand, about 90% of both the mean and the variance of the final results come from the modelling part of the analysis. On the other hand, the modelling part is also partly based on figures from the clinical trial. The modelled difference in effect consists of two factors, the difference in the proportion of survivors in the clinical trial and the survival function for those who were alive at the end of follow-up. These two factors have different effects on the mean and the variance. While the mean is affected in equal measure by both, the variance is primarily determined by the variance of the survival after the end of the clinical trial. Thus the choice of stochastic model for the survival after the end of the clinical trial will to a large extent determine how wide the confidence intervals are. A realistic representation of the uncertainty therefore requires a realistic model for the remaining lifetime. That in turn means that any stochastic model of what happens after the end of the clinical trial will have to be firmly grounded in empirical data on survival in similar patient groups.

In light of the calculation in appendix 3, it is doubtful whether the simulation modelling approach taken here is necessary. Essentially the same results could be achieved by direct calculations based on the clinical trial data and some simplified modelling assumptions. However, this was only possible because the model is a relatively simple one. For example, the survival function was exponential. For more complex models, it is perhaps not possible to replicate the simulation results so closely by formula-based calculations. Some assumptions used in the calculations, such as those regarding the covariances and the normality of $\Delta E$ and $\Delta C$, may also be harder to justify, if there are no simulation results that confirm their validity.

A striking feature of the present stochastic study is that the insights about the uncertainty are quite different from the essentially non-stochastic evaluation of bisoprolol that was reported in Ekman et al. (2001). In the previous study, the point estimate was very

stable for different assumptions tested in the sensitivity analysis. In a sense, that gave a false impression that the results had a high degree of certainty. However, a sensitivity analysis does not take account of the sampling uncertainty, only of parameter uncertainty. The analysis here shows that the confidence intervals are quite wide, and that the results are not that certain from a hypothesis-testing point of view. I think this underlines the importance of stochastic studies as opposed to deterministic ones. However, even if a cost-effectiveness analysis is based on stochastic modelling, there is still a role for sensitivity analysis. The parameters used in the stochastic model should be subject to sensitivity analysis in the same way that parameters in a deterministic model are.

Calculation of a cost-effectiveness acceptability curve is a good way of representing the uncertainty. For every choice of threshold willingness to pay, we can see how large the minimum confidence level that gives a confidence interval that just covers zero is. The cost-effectiveness acceptability curve has the additional advantage of being defined in a way that it will be identical either if it is based on cost-effectiveness ratios or if it is based the net benefit method.

The present study also illustrates the problems with cost-effectiveness ratios for an analysis of uncertainty. The net benefit method is easier to handle and to interpret. For the cost-effectiveness ratio it is even difficult to give a sensible interpretation of a cost-effectiveness interval. Apart from the problems of interpretation, the average cost-effectiveness ratio is distorted by extreme observations, so the average is not reliable as a point estimate. The median or a trimmed mean would have to be used instead. The net benefit method is much more robust, since it is an approximately normal variable. Its interpretation is also unambiguous, since a positive net benefit always means that the treatment is cost-effective for a given threshold value. (These matters are further discussed in Stinnett and Mullahy (1998)). One may object that for the net benefit, a threshold value for the societal willingness to pay per unit of health effect is needed, but such a value is in the end needed for decision making based on cost-effectiveness ratios as well.

Finally, does the present analysis indicate whether treatment of heart failure with bisoprolol is cost-effective or not? The previous study seemed to show rather firmly that

it is indeed cost-effective, but here we saw that the simulation resamples of the net benefit had a non-negligible probability of being negative. A one-sided confidence interval at the 5% level shows that the treatment seems to be cost-effective in light of the stochastic study as well, but the range of uncertainty is much wider. It should not come as a surprise that the results are even quite close to being non-significant. After all, clinical trials are designed to detect the smallest possible clinically relevant difference in effect between two treatments, not to detect whether a treatment is cost-effective compared to the alternative treatment.

# Appendix 1

**Survival analysis**

The exponential survival function can be written as

$$S(t) = e^{-\lambda t}, \quad t \geq 0, \ \lambda > 0,$$

where $\lambda$ is the hazard rate.

The maximum likelihood estimator of $\lambda$ is

$$\hat{\lambda} = \frac{r}{\sum_{i=1}^{r} t_i + \sum_{i=1}^{n-r} t_i^+},$$

where $r$ is the number of uncensored observations, $t_i$ the uncensored lifetimes, and $t_i^+$ the censored follow-up times.

The variance is given by the formula

$$Var(\hat{\lambda}) = \frac{\hat{\lambda}^2}{\sum_{i=1}^{n} \left(1 - e^{-\hat{\lambda} T_i}\right)}$$

An approximate confidence interval for $\lambda$ is then given by

$$\hat{\lambda} - z_{\alpha/2}\sqrt{Var(\hat{\lambda})} < \lambda < \hat{\lambda} + z_{\alpha/2}\sqrt{Var(\hat{\lambda})}$$

where $T_i$ is the follow-up time of individual i during the clinical trial.

For the data from CIBIS II, the following estimates were obtained

$$\hat{\lambda}_0 = 365.25 \cdot \frac{228}{65230 + 560529} = 0.1331$$

$$\hat{\lambda}_1 = 365.25 \cdot \frac{156}{44938 + 604344} = 0.0878$$

Finally, the variances were 0.0093 and 0.0073 for the placebo and bisoprolol groups respectively.

For further details and explanations of the formulas, see Lee (1992, chapter 8).

## Appendix 2

**Choice of survival function**

The following four distributions were investigated:

1. Exponential: $h(t) = \lambda,\ \lambda > 0.$

2. Linear exponential: $h(t) = \lambda + \gamma t,\ h(t) > 0.$

3. Weibull: $h(t) = \lambda^{\gamma} \gamma t^{\gamma-1},\ \lambda, \gamma > 0.$

4. Gompertz: $h(t) = \exp(\lambda + \gamma t),\ h(t) > 0.$

All of the hazard functions shown above can be written in linear form, y = a + bx, either as they stand or if one or more terms are logarithmated.

1. $y = h(t),\ a = \lambda,\ b = 0.$

2. $y = h(t),\ a = \lambda,\ b = \gamma,\ x = t.$

3. $y = \log h(t),\ a = \log(\lambda^{\gamma}\gamma),\ b = \gamma - 1,\ x = \log t.$

4. $y = \log h(t),\ a = \lambda,\ b = \gamma,\ x = t.$

The hazard function was estimated by the life-table method, with a 10-day interval as width. The linear expressions above could then be fitted by linear regression (see Lee 1992, or Gehan and Siddiqui, 1973, for details).

The models were subsequently compared by considering the logarithms of their likelihoods. The simple exponential model was best in this respect, both for the placebo group and for the bisoprolol group, and the difference was significant at the 5% level. I also compared the survival curves derived from the four models with the empirical survival curve by the least squares method. Once again, the exponential model was the best one for the placebo group. For the bisoprolol group, both the linear exponential and the Gompertz model was slightly better. However, the overall conclusion is that the exponential model is not only the simplest, but also the best model for representing the present data set.

## Appendix 3

**Statistical calculations**

Would it be possible to calculate the confidence interval for the net benefit directly, without recourse to bootstrapping and simulation? It is difficult to obtain an exact solution, but an approximate confidence interval based on certain simplifying assumptions can in fact be calculated.

The statistical analysis will proceed in several steps. First, I will calculate the mean and variance of the discounted expected additional lifetime after the end of the clinical trial. Since this distribution is of course valid only for survivors, I will combine it with the survival given from the clinical trial in order to obtain a distribution that is valid for the entire study population. The distribution for the costs of added years of life is then calculated directly from the distribution of additional lifetime.

When the modelled additional lifetime and cost distributions have been calculated, these will be combined with the means and variances of costs and lifetimes within the clinical trial. Finally, the mean and variance of the net benefit measure of the social gains from the treatment will be calculated in order to construct a confidence interval for the net benefit.

**The expected additional lifetime**

Let us begin with a statistical analysis of the modelling of what happens after the clinical trial. The discounted expected lifetime after the end of the clinical trial is given by the formula

$$g(T)=\frac{1}{r}\left(1-e^{-rT}\right),$$

where $T$ follows an exponential distribution with $E(T) = 1/\lambda$ and $V(T) = 1/\lambda^2$. For simplicity, I disregard that the costs for all patients are discounted back to a common point of reference, since this effect is in general very small. I also disregard the fact that the hazard rate $\lambda$ is itself a stochastic variable in the actual computer model. However,

as the analysis has shown, varying $\lambda$ within a small range does not affect the results to any large extent. Finally, I disregard the fact that I have limited the maximum age of any patient to 110, but this is not likely to have a great impact on the final results either.

If $g(T)$ is a function of the stochastic variable $T$, then the expected value $E[g(T)]$ will be given by

$$E[g(T)] = \int_{-\infty}^{\infty} g(t) f(t)\, dt,$$

where $f(t)$ is the exponential distribution (Rice 1994, p.116).

Since $f(t) = \lambda e^{-\lambda t}, \lambda > 0, t \geq 0,$ we get

$$E[g(T)] = \int_0^{\infty} \frac{1}{r}\left(1 - e^{-rt}\right)\lambda e^{-\lambda t} dt = \frac{\lambda}{r}\int_0^{\infty}\left(e^{-\lambda t} - e^{-(r+\lambda)t}\right)dt = \frac{\lambda}{r}\left(\frac{1}{\lambda} - \frac{1}{r+\lambda}\right) = \frac{1}{r+\lambda}.$$

This result can be interpreted intuitively. $E[g(T)]$ represents the expected value of the discounted lifetime after the end of the clinical trial. This expected value will of course decrease as $r$ (the discount rate) and $\lambda$ (the hazard rate) increases. An increased hazard rate means shorter average survival. With $r = 0.03$ and $\lambda = 0.15$, as in the base-case analysis, we get $E[g(t)] = 5.56$.

The variance of $g(T)$ can be calculated by observing that $V[Y] = E[Y^2] - (E[Y])^2$ (Rice 1994, p.124). For $E[(g(T))^2)$ we get,

$$E\left[(g(t))^2\right] = \int_0^{\infty} (g(t))^2 f(t)\, dt = \int_0^{\infty} \frac{1}{r^2}\left(1 - e^{-rt}\right)^2 \lambda e^{-\lambda t} dt = \frac{\lambda}{r^2}\int_0^{\infty}\left(e^{-\lambda t} - 2e^{-(r+\lambda)t} + e^{-(2r+\lambda)t}\right)dt =$$

$$= \frac{\lambda}{r^2}\left(\frac{1}{\lambda} - \frac{2}{r+\lambda} + \frac{1}{2r+\lambda}\right) = \frac{2}{(r+\lambda)(2r+\lambda)}.$$

The variance of $g(T)$ is then given by

$$V[g(T)] = E\left[(g(T))^2\right] - (E[g(T)])^2 = \frac{2}{(r+\lambda)(2r+\lambda)} - \frac{1}{(r+\lambda)^2} = \frac{\lambda}{(r+\lambda)^2(2r+\lambda)}.$$

With $r = 0.03$ and $\lambda = 0.15$, we get $V[g(t)] = 22.05$. This result does not lend itself to an intuitive interpretation in the same way as the expected value, but, in any case, we should expect the variance of the discounted additional lifetime to be lower than the undiscounted additional lifetime.

The expected value and variance calculated above are only valid for those who have survived the clinical trial. What is needed is the mean and variance for the whole population, including non-survivors. For the bisoprolol group, the survival can be modelled as a bimodal discrete distribution. The probability that a patient survives through the clinical trial is 0.882 in the bisoprolol group. Survival in the bisoprolol group is represented by the stochastic variable $X_1$.

$$P_{X_1}(1) = p_1 = 1 - 0.118 = 0.882, \quad P_{X_1}(0) = 1 - p_1 = 0.118,$$
$$E[X_1] = p_1, \quad V[X_1] = p_1(1 - p_1) = 0.104.$$

For the placebo group, the corresponding probability distribution is

$$P_{X_0}(1) = p_0 = 1 - 0.173 = 0.827, \quad P_{X_0}(0) = 1 - p_0 = 0.173,$$
$$E[X_0] = p_0, \quad V[X_0] = p_0(1 - p_0) = 0.143.$$

The expected survival after the end of the clinical trial can now be formed as a product of the probability distribution for the discounted additional lifetime (given that the patient has survived) and the probability of survival. Since $g(T)$ is independent of $X_1$ and $X_0$, the expected value of the products is equal to the products of the expectation values (see, e.g., Mood, Graybill, and Boes (1974), p.180).

For the bisoprolol group we get

$$E[X_1 \cdot g(T)] = E[X_1]E[g(T)] = 0.882 \cdot 5.556 = 4.900,$$

and for the placebo group we get

$$E[X_0 \cdot g(T)] = E[X_0]E[g(T)] = 0.827 \cdot 5.556 = 4.594.$$

For the variances we obtain the following expressions for the bisoprolol and placebo groups respectively:

$$V[X_1 \cdot g(T)] = V[X_1](E[g(T)])^2 + V[g(T)](E[X_1])^2 + V[X_1]V[g(T)] =$$
$$= 0.104 \cdot 5.556^2 + 22.046 \cdot 0.882^2 + 0.104 \cdot 22.046 = 22.657,$$

$$V[X_0 \cdot g(T)] = V[X_0](E[g(T)])^2 + V[g(T)](E[X_0])^2 + V[X_0]V[g(T)] =$$
$$= 0.143 \cdot 5.556^2 + 22.046 \cdot 0.827^2 + 0.143 \cdot 22.046 = 22.648.$$

**Costs of added years of life**

Now the analysis of the expected additional lifetime after the end of the clinical trial is complete. The expectations and variances for the costs are obtained by multiplying the expectation values by the average costs of added years of life and the variances by multiplying with the square of these costs. This is due to the fact that the costs have been calculated as

$$h(T,C) = \frac{C}{r}\left(1 - e^{-rT}\right).$$

In the actual model, $C$ is not a constant but a function of age. For simplicity, I here use age-independent costs of added years of life. The value of $C$ has been set to SEK155 000, which I believe is an amount that is fairly representative of the average costs of added years of life.

For the bisoprolol and placebo groups respectively we get

$$E[X_1 \cdot h(T,C)] = 735\,000, \quad V[X_1 \cdot h(T,C)] = 5.098 \cdot 10^{11},$$

$$E[X_0 \cdot h(T,C)] = 689100, \quad V[X_0 \cdot h(T,C)] = 5096 \cdot 10^{11}.$$

**Costs and effects within the clinical trial**

Our attention will now be turned to the average values and variances for health effects and costs within the clinical trial. The average follow-up times within the clinical trial were $\overline{E}_{1trial} = 1.3368$ for the bisoprolol group and $\overline{E}_{0trial} = 1.296$ for the placebo group. The corresponding variances were $V(E_{1trial}) = 0.224$ and $V(E_{0trial}) = 0.243$. The average costs, including costs of added years of life, were $\overline{C}_{1trial} = 203\ 180$ and $\overline{C}_{1trial} = 194\ 335$ for the bisoprolol and placebo groups respectively. The corresponding variances for the costs were $V(C_{1trial}) = 1.134 \cdot 10^{10}$ and $V(C_{0trial}) = 1.124 \cdot 10^{10}$.

**Total costs and health effects**

The task is now to sum together the average health effects and costs within the clinical trial with the expected additional lifetimes and costs. However, we have to take account of the covariances between health effects and costs within and after the trial. The problem is that it is not clear how the covariances should be calculated. I have reasoned as follows: The additional lifetime $g(T)$ is independent of what happens within the trial, but the survival is not. As a proxy for the true covariances, I have therefore chosen to estimate the covariances between the survival and the costs and effects within the clinical trial.

A correlation analysis gives the following results:

| Correlation between | Pearson's | Spearman's |
|---|---|---|
| survival and health effects: | | |
| Bisoprolol | 0.421 | 0.353 |
| Placebo | 0.473 | 0.423 |
| survival and costs: | | |
| Bisoprolol | 0.202 | 0.286 |
| Placebo | 0.294 | 0.338 |

The Pearson correlation coefficient requires that the data be normally distributed. Since the costs and effects within the clinical trial are certainly not normally distributed in this case, I have chosen to work with the Spearman correlation coefficients, which are non-parametric.

We are now in a position to calculate what we are really after, namely the expected values and variances for $\Delta E$ and $\Delta C$.

Expectancy values are additive, so

$$E[\Delta E] = \overline{E}_{1trial} + E[X_1 \cdot g(T)] - \left(\overline{E}_{0trial} + E[X_0 \cdot g(T)]\right) =$$
$$= 1.337 + 4.900 - (1.296 + 4.594) = 0.347,$$

and

$$E[\Delta C] = \overline{C}_{1trial} + E[X_1 \cdot h(T,C)] - \left(\overline{C}_{0trial} + E[X_0 \cdot h(T,C)]\right) =$$
$$= 203\,180 + 735\,000 - (194\,335 + 689\,100) = 54\,678.$$

For stochastic variables in general we have that

$$V[Y \pm Z] = V[Y] + V[Z] \pm 2r_{YZ}\sqrt{V[Y]V[Z]},$$

where $r_{YZ}$ is the correlation coefficient between $Y$ and $Z$.

Since we are dealing with an average, another useful relation from statistics is

$$V[\Delta E] = \frac{V[E_1]}{n_1} + \frac{V[E_0]}{n_0},$$

where $n_1$ and $n_0$ are the sample sizes of the bisoprolol and placebo groups. These samples are independent, so there is no covariance term here.

Combining these two relations for the variance, we arrive at the following value for the variance and standard deviation of the difference in effects:

$$V[\Delta E] = \frac{V[E_{1trial}] + V[X_1 \cdot g(T)] + 2r_{S1}\sqrt{V[E_{1trial}]V[X_1 \cdot g(T)]}}{n_1} +$$

$$+ \frac{V[E_{0trial}] + V[X_0 \cdot g(T)] + 2r_{S0}\sqrt{V[E_{0trial}]V[X_0 \cdot g(T)]}}{n_0} =$$

$$= \frac{0.224 + 22.657 + 2 \cdot 0.353 \cdot \sqrt{0.224 \cdot 22.657}}{1327} + \frac{0.243 + 22.648 + 2 \cdot 0.423 \cdot \sqrt{0.243 \cdot 22.648}}{1320} =$$

$$= 0.037,$$

$$s_{\Delta E} = \sqrt{V[\Delta E]} = 0.1931.$$

The standard deviation for the costs can be calculated in an analogous way:

$$s_{\Delta C} = 27\,752.$$

By the central limit theorem, we should expect the distributions of $\Delta E$ and $\Delta C$ to be approximately normal. From the simulation analysis we can see that this indeed seems to be the case. The histograms of $\Delta C$ (figure 5) and of $\Delta E$ (figure 6) display the shape of the normal distribution.

**Figure 5.** *The distribution for $\Delta C$ is approximately normal.*

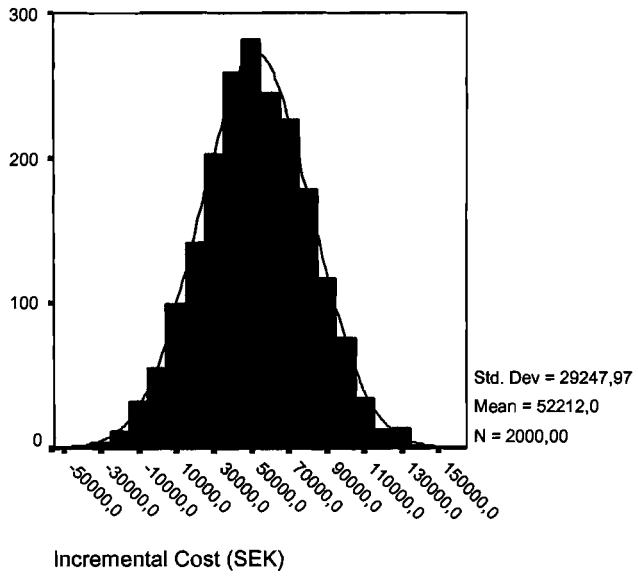
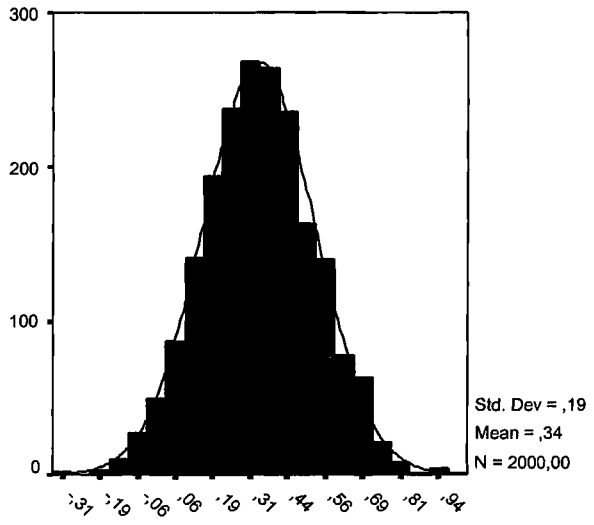


**Figure 6.** *The distribution for ΔE is also approximately normal.*




**Confidence interval for the net benefit**

In order to calculate a confidence interval for the net benefit we also need the correlation between the cost and effect differences. This poses a problem, since Cov($\Delta E$, $\Delta C$) is not readily available. However, with constant costs of added years of life, the correlation between the added years of life and costs of added years of life after the clinical trial is equal to 1, because the costs are directly related to the additional lifetime. Within the clinical trial, the costs and the effects have a Spearman correlation coefficient of 0.94, so the positive relationship is strong here as well. The correlation coefficient for the total costs and effects should therefore be somewhere between 0.94 and 1. In the simulation analysis, the actual value for the correlation coefficient was 0.96 in the base case. This is the value I have chosen as input here as well.

The point estimate of the net benefit is

$$NB = p \cdot \Delta E - \Delta C = 450\,000 \cdot 0.347 - 54\,678 = 101\,357.$$

Here, $p$ is the price we are willing to pay for additional lifeyears, in the base-case set to SEK450 000.

The standard deviation of the net benefit is

$$\sigma_{NB} = \sqrt{p^2 \cdot \sigma_{\Delta E}^2 + \sigma_{\Delta C}^2 - 2pr_{\Delta E \Delta C}\sigma_{\Delta E}\sigma_{\Delta C}} =$$

$$= \sqrt{450\,000^2 \cdot 0.1931^2 + 27\,752^2 - 2 \cdot 450\,000 \cdot 0.96 \cdot 0.1931 \cdot 27\,752} = 60\,749.$$

At the 5% level, the confidence interval is thus

$$NB \pm z_{\alpha/2} \cdot \sigma_{NB} = 101\,357 \pm 1.96 \cdot 60\,749 = [-17\,711; 220\,425].$$

This is somewhat wider than the results from the computer simulation, but it is not to be expected that the results should be identical, since the above calculation has been based on some simplifying assumptions.

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# Survival analysis techniques for estimating the costs attributable to head and neck cancer in Sweden

By Mattias Ekman

**Abstract**

This study concerns statistical methods for estimating the health care cost attributable to a disease for a defined patient. Such estimates may be of value for health economic evaluations. Ways of handling incomplete (or censored) cost and survival data are discussed, with application to data on survival and in-patient resource utilization in head and neck cancer. The database was obtained from the national Swedish cancer registry and includes all patients diagnosed with head and neck cancer in Sweden from 1986 to 1996. The main method of estimating the average in-patient costs attributable to head and neck cancer is the Kaplan-Meier sample-average estimator, which takes account of censored survival and cost data. A parametric analogue to the Kaplan-Meier sample-average estimator is also presented. Towards the end, alternative methods are discussed, e.g. the possibility of refining the analysis by taking account of explanatory variables in a regression model. As for the results, the analysis presented in the study suggests that the average in-patient cost attributable to head and neck cancer in Sweden is about SEK 260 000 per patient from diagnosis to death (2001 prices).

Keywords: Survival analysis techniques, Censoring, Treatment costs, Head and Neck Cancer

# 1. Introduction

## 1.1. Background and purpose

Accurate estimation of treatment costs is an important part of economic evaluations in healthcare. However, often data on survival and treatment costs are incomplete. This is a problem both for clinical studies, which have a limited period of follow-up, and for national patient registries, which are limited to the present. The limited time horizon poses a problem both for estimating survival and for estimating costs. Since many (hopefully most!) patients are usually alive at the end of follow-up, the only thing we know about them is that their survival time is at least as long, and their accrued costs at least as large as those recorded in the data.

For handling incomplete (or censored) survival data, there exist several well-established statistical techniques. Among them are non-parametric methods like the Kaplan-Meier method and the Cox proportional hazards method, where the survival data are not assumed to follow any specific statistical distribution, as well as parametric techniques where the survival data are assumed to follow specific functional forms. These methods are described in standard texts on survival analysis (see, e.g., Lee, 1992; Kleinbaum 1996; Cox & Oakes, 1984; and Kalbfleisch & Prentice, 1980). If, and in that case how, these standard methods of survival analysis can also be applied to cost estimation in the presence of censored cost records is an issue that has been much discussed in recent years (Fenn et al., 1995, 1996; Etzioni et al., 1996, 1999; Lin et al., 1997; Lin, 2000; Hallstrom & Sullivan, 1998; Bang & Tsiatsis, 2000; Carides et al., 2000).

The purpose of this study is to estimate the average treatment costs for head and neck cancer in Sweden. The method chosen for this purpose is the Kaplan-Meier sample-average (KMSA) estimator, which is a method that has been proposed specifically for handling censored cost data. The KMSA estimator builds on the non-parametric Kaplan-Meier method of estimating the survival curve. As an alternative method, a parametric analogue of the KMSA estimator is also presented. Finally, advantages, disadvantages, and possible refinements of the methodology are discussed.

### 1.2. The disease

Head and neck cancer is a relatively common form of cancer, accounting for about 5% of all cancers in the US (Stupp et al. 2000). In Sweden, this figure is slightly lower, 2-3% (Hammerlid & Taft, 2001; Cancer Incidence in Sweden 1999 (2001)). It can occur as lesions of the skin, face, enlarged lymph nodes in the neck, nasal passages, and the mouth, throat and voice box. Tumours of the eyes and the brain are not included. Since the cancer affects vital organs it can often be difficult to treat it effectively. The probability of recurrence is substantial, and the prognosis is poor, the five-year survival is only about 50%. In the US, the overall mortality is 12 000 per year or about 6 per 100 000. The number of new cases is over 40 000 per year or 20 per 100 000 in the US (Stupp et al., 2000). In Sweden, the incidence is 9 per 100 000 (Berrino & Gatta, 1998).

The treatment involves surgery, radiation therapy and/or chemotherapy. The treatment option for particular cases varies depending on tumor size, location, and stage of progression. For small head and neck cancers, surgery and radiation are equally effective, though combination therapy is frequently necessary. Standard therapy for advanced head and neck cancer is surgery followed by planned postoperative radiation therapy, often in combination with chemotherapy.

Apart from genetic predispositions, tobacco and alcohol are known to be risk factors (Stupp et al., 2000; Lewin et al., 1998). A heavy drinker increases his risk two- to sixfold, while a smoker increases his risk 5- to 25-fold depending on the amount of smoking, and sex and racial differences. In a sense, age is also a risk factor (Lacy et al., 2000). A majority of the patients are over 65 years of age. Men seem to be at a higher risk of getting head and neck cancer than women, perhaps because of a higher exposure to certain risk factors such as tobacco and alcohol. About two thirds of cases concern males.

### 1.3. Previous studies

There are few previous studies of the costs attributable to head and neck cancer, and none of the type reported here (Selke et al., 2001). The are several reasons for this. Some of the factors that complicate economic and outcome evaluations in this area are discussed by Pfister et al. (1997). Head and neck tumors are less common than tumors

of the breasts, prostate, colon, and lung, and constitute a heterogeneous group of malignancies. Thus it may be difficult to acquire a sufficiently homogenous study population. This means, in turn, that the relative effectiveness of many interventions is based on lower quality evidence compared with randomized controlled trials. Another major problem is that head and neck cancer is associated with risk factors (tobacco and alcohol) that are common for many diseases. This means that there may often be other primary tumors or comorbidities that can affect treatment, prognosis and resource consumption independent of the index cancer (Piccirillo, 2000).

Previous studies on economic aspects of head and neck cancer include Funk et al. (1998), who performed a cost-identification analysis based on 73 patients with oral cavity cancer, and Tan et al. (1999), who investigated the role of screening chest tomography in patients with advanced head and neck cancer based on 20 patients. Selke et al. (2001), and Pfister et al. (1997) list some other studies.

There are many studies that evaluate the treatment costs attributable various diseases, but to my knowledge there are no major studies specifically concerning head and neck cancer. Of studies that estimate the costs attributable to specific diseases, the articles by Etzioni et al. (1996, 1999), and Lin et al. (1997) have been especially influential on my own work. They apply survival analysis techniques for estimating the average cost attributable to ovarian cancer, with extensive methodological discussions.

## 2. Methods

In the methods section, I will first briefly describe survival analysis in general, with emphasis on life-tables and the Kaplan-Meier technique. I will then go on to discuss how the survival probabilities from a Kaplan-Meier estimate of the survival curve can be combined with costs in order to give an estimate of the average treatment cost per patient from time of diagnosis to death.

### 2.1. Survival analysis techniques

A major problem in estimating long-term disease specific costs is that almost all data sources contain censored observations. Censoring means that a subject in a study or a

database have not experienced the event of interest, e.g. all-cause mortality, at the end of follow-up. All we know about the patients who are alive at the end of follow-up is that their lifetime is at least as long as the lifetime at the censoring point. There may also be censoring during the course of a study because patients are withdrawn prematurely for reasons unconnected with the study objectives (Lee, 1992, p.2).

Censoring is a common phenomenon not only in clinical trials, but also in retrospective data sources such as the Medicare records in the US. In order to cope with the difficulties of censoring, special statistical techniques for survival analysis have been developed. Two of the most widely used methods are the Kaplan-Meier (1958) product-limit estimator, and Cox's (1972) proportional hazards model.

A central concept in survival analysis is the hazard rate. The hazard function $h(t)$ of survival time $T$ gives the conditional failure rate. The hazard rate is defined as the probability that the individual will fail within the short interval $\Delta t$, given that he has survived to time $t$ (Lee, 1992, p.11).

$$h(t) = \lim_{\Delta t \to 0} \frac{P(\text{an individual of age } t \text{ fails in the time interval } (t,\ t\ +\ \Delta t))}{\Delta t} = \\ = \lim_{\Delta t \to 0} \frac{P(t \le T \le t + \Delta t | T \ge t)}{\Delta t}. \qquad (1)$$

When there are no censored observations the hazard function can be estimated as the proportion of patients dying in an interval per unit time, given that they have survived to the beginning of the interval.

$$\hat{h}(t) = \frac{\text{number of patients dying in the interval beginning at } t}{(\text{number of patients surviving at } t)(\text{interval width})}. \qquad (2)$$

The hazard rate is not a probability. It is rather a probability per unit time. The closely related survival function is a probability, however, and is simply defined as

$$S(t) = P(\text{an individual survives longer than } t) = P(T > t). \qquad (3)$$

For a continuous probability distribution, the relationship between the hazard rate and the survival function is given by

$$S(t) = \exp\left[ -\int_0^t h(u)du \right]. \qquad (4)$$

To take a specific example, if the hazard rate is constant and equal to λ, then the survival function is exponential: $S(t) = e^{-\lambda t}$.

If there are no clear indications that the hazard rate and the survival function follow any particular functional form, they can be estimated non-parametrically by using a life-table technique. The follow-up time is divided into small time interval such as weeks, months or years. For each interval, the survival probability is obtained by dividing the number of people at risk with the number of people experiencing an event during the interval. The number of people at risk is defined as the number of people who have lived at least to the beginning of the interval. Estimates from individual intervals are then combined to estimate cumulative survival probabilities.

A popular alternative to the life-table approach is the closely related product-limit or Kaplan-Meier estimator. The difference from the traditional life-table approach to survival analysis is that no time intervals at which the number of people at risk are calculated have to be specified in advance. Instead, the probability of an event such as death is calculated at each time that the event is observed. In fact, the Kaplan-Meier method is a life-table method where the time intervals are defined by the event of interest. The advantage of the Kaplan-Meier method compared with the life-table approach is that it uses all information available in the sample. Some information is lost by arbitrarily dividing the follow-up time into pre-specified intervals, instead of letting the events themselves define the intervals. An advantage of both the Kaplan-Meier method and the life-table method is that they are non-parametric, which means that no particular functional form has to be chosen for the distribution of events. The main disadvantage of non-parametric methods is that they are statistically less efficient, i.e.

the variance is wider, if the survival function actually follows a particular parametric distribution.

The Kaplan-Meier estimator of the probability of survival to time $t$ is

$$S(t)=\prod_{k=1}^{t}[1-h(k)], \tag{5}$$

where $k$ indicates the times at which the events occur, and $h(k)$ is the hazard rate at each point in time $k$. The survival function is then calculated as the product of the survival proportions $1 - h(k)$ for all events up to the time t.

As for the life-table method, the basic idea is that for each period, the number of deaths $n_k$ should be divided by the number at risk. Let the index $j$ represent all periods preceding period $k$. If the number of deaths in period $j$ (where $j<k$) is $n_j$, the number of censored observations is $c_j$, and the total number of observations is $N$, then the Kaplan-Meier estimator can be written as

$$S(t)=\prod_{k=1}^{t}\left\{1-\frac{n_k}{N-\sum_{j=0}^{k-1}(n_j+c_j)}\right\}. \tag{6}$$

A general drawback with the life-table approach (including the Kaplan-Meier approach), is that is presupposes that the chances of survival for a particular condition do not change over time. If treatment options change over time, there is little point in grouping all patients together in the same life table. Another critical assumption is that censoring is independent of survival, i.e., individuals are not censored because they are at an especially high or low mortality risk. Neither of these assumptions is certain to hold in practice. A further problems is that we cannot take account of explanatory variables such as age, sex, and stage of disease.

**2.2. Estimating long-term disease specific costs**

Once a Kaplan-Meier estimate of the survival probabilities at different points in time has been obtained, these survival probabilities can be combined with the average cost for those who are alive in each period of time defined by the Kaplan-Meier analysis. See Etzioni et al. (1996, 1999) or Hallstrom & Sullivan (1998) for background details. The method is called the Kaplan-Meier sample-average (KMSA) estimator, and gives an estimate of the average cost attributable to the disease from the time of diagnosis to the time of death. The KMSA estimator of the average cost is defined as

$$AC = \sum_{i=0}^{I} \hat{S}_i \bar{c}_i \,, \tag{7}$$

where $\hat{S}_i$ is the Kaplan-Meier estimate of the probability of surviving up to time interval $i$, and $\bar{c}_i$ is the average cost that the individuals who experienced time interval $i$ incurred during that time interval. The KMSA estimator is unbiased if the independence assumption between censoring and survival is satisfied. The time value of money can be taken into account by discounting either the individual cost for each patient or the average cost within time interval $i$.

The intuitive interpretation of the estimator is that we calculate the expected average cost by multiplying the probability of being alive until each interval of time $i$ with the average cost for those who are alive in that interval, and then sum for all intervals. Average cost = Σ Probability of being alive at time $i$ * Average cost at time $i$.

As already mentioned, it is not necessary to use the Kaplan-Meier method in order to calculate the survival probabilities. The probabilities $\hat{S}_i$ could for example be estimated with the life-table method as well. In principle, any consistent estimator of the survival probabilities could be used. If we have good reason to assume that survival will follow some specific distribution, such as the exponential or the gamma distribution, then a parametric approach is more efficient than a non-parametric one like the Kaplan-Meier method. A parametric analogue to the KMSA estimator would be

$$AC = \int_0^T \hat{S}(t)\,\bar{c}(t)\,dt, \tag{8}$$

where $\hat{S}(t)$ is the survival function, $\bar{c}(t)$ the average cost per unit of time, and $T$ the maximum possible survival time.

Apart from efficiency considerations, a further advantage of the parametric method is that it can be used as a basis for modelling, e.g. extrapolating survival beyond the longest follow-up time.

## 3. Data sources

### 3.1. Survival and medical resource-utilization data

The survival and medical resource-utilization data encompass all cases of head and neck cancer in Sweden diagnosed during a ten-year period (from 1986 to 1996). A total of 2 174 cases of primary head and neck cancer were diagnosed during this time period. The data, which was obtained from the Cancer register of the National Board of Health and Welfare, show all hospital admissions for head and neck cancer after an initial index admission when the cancer was first diagnosed. (The admissions concern head and neck cancer as the primary diagnosis). The data file contains patient data on the follow-up time, the number of hospital admissions and their timing, and the number of hospital days for each admission. There are also data on whether the patient was alive or not at the end of follow-up. The cause of death is indicated with a code. Background variables include age, sex, calendar year of initial diagnosis, and a code representing the clinic.

In the database, it is not indicated how many hospital days that were associated with the index admission. However, for the index admission a DRG cost can be used instead.[1] Neither is there any indication of how far the cancer had progressed at the time of diagnosis. If the cancer is small and localized when detected, the prognosis is much better than if it is locally advanced and perhaps even metastatic (Stupp et al., 2000). The

specific location of the cancer in the head and neck region was not specified either. This kind of information is not needed in this study, since it would not affect the average cost, but it could be potentially valuable by providing explanatory factors in an extended survival and cost analysis.

### 3.2. Cost data

The cost data have been taken from hospitals in southern and western Sweden. Both per diem costs and DRG-based costs per admission have been used for the cost calculations. All costs were discounted at a real discount rate of 3%, with the index admission as the point of reference (Lipscomb et al., 1996). This is called the incidence approach to cost measurement, since the date of diagnosis is the starting point for the analysis.[2] An alternative of estimating the costs attributable to a disease is the prevalence approach, where costs are collected during a specific year. The latter approach is more suitable for long-term chronic diseases like multiple sclerosis or diabetes (Henriksson, 2001).

The cost per day in 2001 was estimated to be SEK 3 546, based on price lists for Malmö and Lund. The cost per admission was estimated to be SEK 30 646, based on DRG 64 for Malmö and Lund. (The price for the Gothenburg region is about the same, SEK 31 047). DRG 64 concerns malignant tumours of the ears, nose, mouth and neck. It does not correspond exactly to the slightly broader notion of head and neck cancer, but seems to be the DRG that comes closest to represent the disease.

For some of the admissions, the number of hospital days was zero according to the database. I am not sure how this is to be interpreted, but a reasonable assumption is that this refers a to single medical consultation, or perhaps radiation therapy, where the patients do not stay at the hospital. As a reasonable approximation, the cost for a "zero day" was set to SEK 1890. This is based on an average of prices for medical visits within the oncology area in Gothenburg, Lund, and Malmö. Sources: Västra Götalandsregionen (2001), Södra Sjukvårdsregionen (2001). In any case, these admissions

[1] DRGs = Diagnosis-related Groups, a system for measurement and reimbursement of health care charges. See, e.g., Folland et al. (1997, p.452ff).
[2] Incidence = The frequency of new cases.

account for only about 2.5% of all admissions, and about 1.5% of the total costs, so for practical purposes they could perhaps have been omitted.

I have not made any attempt to estimate the costs for outpatient care or nursing home care for head and neck cancer patients. However, outpatient costs are likely to be substantially lower than inpatient costs for cancer treatment. According to a study by Ragnarson, Tennvall & Karlsson (1998), the inpatient cost represented 79% of total treatment costs for cancer in 1995. Although the proportion of costs accounted for by outpatient care and pharmaceuticals have increased over time, inpatient care is still dominating in health care costs due to cancer. Nursing home care costs could be important, since the patients may become more dependent of home help and nursing home services with the disease than they would have been without it. The problem is that only very limited information on how specific diseases affect costs for home help and nursing homes seems to be available in Sweden.

## 4. Results

### 4.1. Patient characteristics and basic facts

In table 1 below, some facts from the database are shown. Note the difference between survivors and non-survivors. Since the data are censored, the survival time and the resource consumption for survivors is at least as large as the averages within the follow-up time.

**Table 1.** *Comparison between survivors and non-survivors in the database.*

| **Patient characteristics** | **Non-survivors** | **Survivors** | **All** |
|---|---|---|---|
| Number of patients | 1210 | 964 | 2174 |
| Percentage of men | 61% | 58% | 60% |
| Mean age at diagnosis | 68.1 | 61.3 | 65.1 |
| Average follow-up time (years) | 1.28 | 1.48 | 1.37 |
| Average number of admissions | 8.0 | 5.7 | 7.0 |
| Average number of hospital days | 72.1 | 32.9 | 54.7 |
| Average cost 1 (SEK) – base-case | 279 600 | 138 300 | 216 900 |
| Average cost 2 (SEK) | 248 900 | 107 600 | 186 300 |
| Average cost 3 (SEK) | 240 700 | 166 200 | 207 700 |

1: Average cost based on hospital days with DRG cost for index admission.
2: Average cost based on hospital days without index admission.
3: Average cost entirely based on admissions (DRG).

The cost estimations have been performed by multiplying the number of hospital days for each patient with the per diem cost (SEK 3 546), according to the formula

$$TC = \sum_{i=1}^{N} c \cdot d_i \cdot \mathrm{e}^{-rt_i}\,, \tag{9}$$

where $TC$ stands for total cost during the follow-up period, $c$ is the cost per bed day, $d_i$ is the number of hospital days for admission $i$, and $t_i$ is the timing of admission $i$ with the index admission as point of departure. The admissions run from $i = 1$ to $N$, and the discount rate $r$ is equal to 3%. A cost of SEK 30 646 was also added for the index admission. For the average cost entirely based on admissions, the term $c \cdot d_i$ was replaced by a unit cost per admission (SEK 30 646).

One conclusion that can be drawn immediately from the cost estimation is that the expected average cost per patient diagnosed with head and neck cancer is at least SEK 216 900, if the cost estimate based on hospital days with an added cost for the index admission is used. The average cost for non-survivors is estimated to SEK 279 600. However, the only thing we know about the average cost for survivors is that it is at

least SEK 138 300. The question is how further costs for the survivors beyond the follow-up period can be estimated.

It is interesting to note that for those who do not survive, the treatment costs are not so much a function of time from diagnosis as a function of time to death.

**Table 2.** *The proportion of total inpatient costs as a function of time to death.*[*]

| Time to death (months) | 1 | 2 | 3 | 6 | 12 | 24 | 36 |
|---|---|---|---|---|---|---|---|
| Proportion of total costs | 18% | 32% | 42% | 60% | 78% | 89% | 94% |

* Costs based on hospital days with index admission added.

### 4.2. Kaplan-Meier analysis and cost estimation

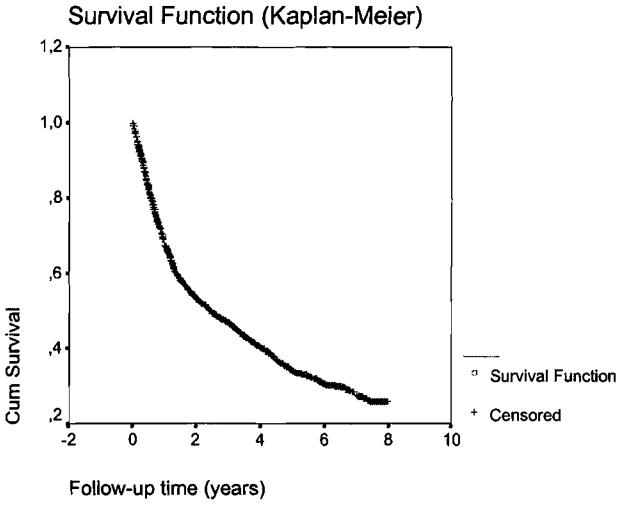
The first step in the estimation of the average cost is a Kaplan-Meier analysis of the survival time. It is the probabilities from this estimate that will be used for the KMSA estimator presented in the methods section.

**Table 3.** *Kaplan-Meier analysis of the survival time.*

| Number of Cases: 2174 | Censored: 964 ( 44.34%) | Events: 1210 |
|---|---|---|
| Survival Time (years) | Standard Error | 95% Confidence Interval |
| Mean: 3.611 (Limited to 7.984 ) | 0.076 | (3.462; 3.760) |
| Median: 2.442 | 0.163 | (2.123; 2.761) |

The survival function for head and neck cancer obtained by the Kaplan-Meier method is shown below.

**Figure 1.** *Survival function for head and neck cancer.*




The next step is to combine the survival probabilities from the Kaplan-Meier analysis with the average treatment costs for each interval of time defined by the Kaplan-Meier analysis. In table 4, a part of the calculation of the KMSA estimate of the average treatment cost is shown. In column 1, the Kaplan-Meier (K-M) estimates of the survival probabilities at different points in time (column 2) are shown. For each period of time, the average cost is obtained by dividing the total cost within each interval of time (column 3) with the number of remaining patients (column 4). The expected average cost (AC) is then calculated by multiplying the K-M probability with the average cost for each interval.

**Table 4.** *The KMSA estimator.*

| K-M Probabilities | Time of event | Tot cost within time interval | Remaining patients | Expected AC within interval |
|---|---|---|---|---|
| 1,000 | 0,000 | 200 227 | 2 174 | 92 |
| 0,999 | 0,003 | 2 768 044 | 2 172 | 1 273 |
| 0,998 | 0,008 | 1 963 083 | 2 170 | 903 |
| 0,997 | 0,011 | 2 440 711 | 2 167 | 1 123 |
| 0,997 | 0,014 | 1 223 330 | 2 165 | 563 |
| 0,995 | 0,016 | 1 536 427 | 2 161 | 707 |
| 0,994 | 0,019 | 1 853 757 | 2 159 | 853 |
| 0,993 | 0,022 | 1 365 814 | 2 157 | 629 |
| 0,993 | 0,025 | 2 639 734 | 2 154 | 1 216 |
| 0,992 | 0,030 | 2 211 543 | 2 152 | 1 020 |
| 0,990 | 0,033 | 2 490 767 | 2 147 | 1 149 |
| 0,988 | 0,036 | 507 691 | 2 140 | 234 |
| 0,985 | 0,038 | 3 214 893 | 2 134 | 1 484 |
| . | . | . | . | . |
| . | . | . | . | . |
| . | . | . | . | . |
| 0,270 | 7,236 | 14 179 | 76 | 50 |
| 0,266 | 7,247 | 172 469 | 75 | 612 |
| 0,262 | 7,354 | 101 948 | 61 | 438 |
| 0,257 | 7,425 | 363 390 | 57 | 1 641 |
| 0,000 | 7,784 | | 25 | |
| TC in database | | 404 978 691 | KMSA[1] | 226 982 |
| TC initial admission | | 66 624 404 | CIA[2] | 30 646 |
| TC | | 471 603 095 | TAC[3] | 257 628 |

1) Kaplan-Meier Sample Average estimate of average cost.

2) Cost of initial admission.

3) Total average cost.

If the Kaplan-Meier sample-average estimator discussed in the methods section is used, a mean value of SEK 226 982 is obtained. To this amount should be added the DRG cost for the index admission, which is equal to SEK 30 646. The estimate of the average inpatient treatment costs is thus equal to SEK 257 628.

### 4.3. Life-table approach

Another way of calculating the mean cost is to start from admissions instead of hospital days and then apply a life-table approach to the survival analysis. The same formula as above is used, but both costs and survival probabilities are calculated in a different way. The survival probabilities are calculated by partitioning the follow-up times for all patients into equally long intervals of time (here months). For each interval a survival probability is calculated by dividing the number of deaths with the population at risk. The probabilities $S_i$ are finally calculated by multiplying the survival probabilities for

the intervals together in order to obtain the cumulative survival probabilities. The mean costs are calculated by multiplying the cost of admission with the number of admissions that occurred within the interval and then dividing by the mean population at risk within the interval.

If the life-table approach is used in combination with the cost per admission, the discounted mean cost per patient is estimated to be SEK 265 925. This is very close to the figure above, which is not surprising given that the number of patients in the analysis is large. The life-table estimate of survival probabilities would then be close to the Kaplan-Meier estimate, and the DRG-cost would be close to the cost of an average admission based on the number of hospital days.

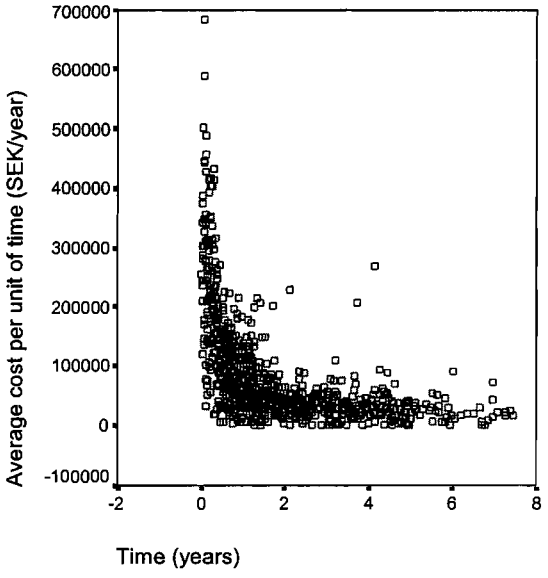
### 4.4. A parametric technique

As mentioned earlier, parametric methods can also be used for estimating the average treatment cost. It is difficult to capture both costs and survival in one single parametric model, but we can use a parametric analogue to the KMSA estimator. The first step is to specify a certain functional form of the survival function, and then fit the parameters to the data at hand. If the average cost per unit of time also can be expressed in parametric form, the total average cost can be estimated by the integral in equation (8) in the methods section.

If an exponential survival function is fitted to the head and neck data, the survival function takes the form $\hat{S}(t) = e^{-0.25t}$, where 0.25 is the hazard rate per year. See Lee (1992, p.202f) for details. The next step is to estimate a parametric function for the average cost per unit of time, as a function of time. In figure 2, the relationship between follow-up time and cost per unit of time is illustrated. In order to produce figure 2, I used time intervals from the Kaplan-Meier analysis, since these happened to be available. (In principle, any interval length that is fine enough can be used.) I divided the average cost for each interval with the length of the interval in order to calculate the average cost per unit of time. I then plotted the average cost per unit of time against the follow-up time to see how the costs evolve over time. A clear pattern emerges. The

closer we come to the beginning of follow-up (i.e. the point of diagnosis), the higher is the average cost per unit of time.

**Figure 2.** *Average cost per unit of time, as a function of time since diagnosis.*




The question is which kind of parametric model that will represents the pattern above best. I tested several models (log-linear, polynomial, exponential, and inverse), and the model that seems to work best is a model based on the gamma distribution, but with a cost parameter $c$ added for scaling purposes. The empirical distribution of average cost per unit of time was fitted to the following expression:

$$\bar{c}(t) = c \cdot f_T(t, \alpha, \beta) = c \cdot \frac{\beta}{\Gamma(\alpha)} (\beta t)^{\alpha-1} e^{-\beta t}, \tag{10}$$

where $t$ is the follow-up time, and $\alpha$ and $\beta$ parameters in the gamma distribution. The symbol $\Gamma$ stands for the gamma function, which is defined by the integral

$$\Gamma(\alpha) = \int_0^\infty t^{\alpha-1} e^{-t} dt, \tag{11}$$

which is well known for its use in probability theory. (For general mathematical properties of the gamma function, see, e.g., Arfken & Weber, 1995. For a discussion of the gamma distribution, see, e.g., Wackerly et al., 1996.)

The parameters $c$, $\alpha$, and $\beta$ in the gamma model (10) were estimated by applying the method of least squares to the data shown in figure 2. The following values were obtained: $c$ = SEK 246 042, $\alpha = 0.8608$, and $\beta = 1.1799$. The discount rate is 3% as before, and the hazard rate $\lambda = 0.25$.

If we combine the gamma model for the average cost with the exponential survival function, and apply continuous discounting with discount rate $r$, we get the following integral expression:

$$AC = \int_0^\infty \hat{S}(t)\,\bar{c}(t)\,e^{-rt}\,dt = \int_0^\infty e^{-\lambda t} \cdot c\frac{\beta}{\Gamma(\alpha)}(\beta t)^{\alpha-1}e^{-\beta t} \cdot e^{-rt}\,dt = \tag{12}$$

$$= c\frac{\beta^\alpha}{\Gamma(\alpha)}\int_0^\infty t^{\alpha-1}e^{-(\alpha+\beta+r)t}\,dt = 246\,042 \cdot \frac{1.1799^{0.8608}}{\Gamma(\alpha)} \cdot 0.722022 \cdot \Gamma(\alpha) = 204\,839.$$

Integrating the function given above is a bit tricky, since the solution is expressed as an infinite series. However, the integral can be evaluated numerically or symbolically by using a mathematical software package like Mathematica. A comment about the upper integration limit is perhaps in place here. In principle, it is clearly not realistic to use infinity as the upper integration limit, since we are dealing with follow-up times. In practice, the results above would change very little even if the maximum follow-up time would be limited to, say, 30 years.

Just as for the KMSA estimator, a cost must also be assigned to the initial admission. The cost per admission is SEK 30 646 per patient as before. The total average cost is thus estimated to SEK 235 485. This is slightly lower than the KMSA estimate, probably because the exponential function does not represent the survival function well enough.

# 5. Discussion

## 5.1. Modelling as an alternative approach

The disease progression could also have been analysed through a modelling approach, e.g., a Markov model (Sonnenberg & Beck, 1993; Briggs & Sculpher, 1998), or a more general simulation model. The advantage of the Markov model as compared to survival analysis techniques is that the assumptions are more explicit. The effect of different assumptions regarding post-censoring survival and costs on the estimate of the average costs could be explored, for example. The advantage of statistical techniques is that they are less *ad hoc* and that their properties can be studied in a more rigorous fashion (see Lin et al., 1997, and Bang & Tsiatsis, 2000).

In order to create a realistic model, an extensive analysis of the empirical data would still be required. Some regularities in the data that could be used for modelling purposes are shown in the appendix. The parametric survival and cost functions estimated above could also be used as a basis for stochastic modelling, for example, if we wanted to estimate the remaining lifetime and cost beyond the follow-up time for survivors in a clinical trial involving head and cancer patients.

## 5.2. Kaplan-Meier estimator applied directly to costs

Fenn et al. (1995) discusses the treatment of censored cost data in economic evaluations in health care. They argue that survival analysis techniques can be applied not only to censored survival times but also to censored medical costs. The method that Fenn et al. (1995) propose is a Kaplan-Meier estimator for estimating the cost intensity in the same way as it is used for calculating a mortality hazard.

The Kaplan-Meier estimate of the mean within-trial survival time is $T = \sum_{t=1}^{L} S(t)$, where $T$ represents the area under the Kaplan-Meier curve up to $L$ days. Instead of estimating Kaplan-Meier survival probabilities and average costs separately, the costs are used directly in the Kaplan-Meier estimator. In order to obtain the Kaplan-Meier estimate of the mean program costs we simply substitute the number of days in the expression above for the costs.

However, this estimator is biased, as is shown by Hallstrom and Sullivan (1998). The crucial assumption of independence is not satisfied. By using the Kaplan-Meier technique for the costs, censoring is informative in the sense that cost at censoring time is usually positively correlated to cost accumulated to the time of death. As a consequence, a Kaplan-Meier estimator for costs will overestimate the true cumulative cost. For the head and neck cancer data, the average cost per patient is estimated to be SEK 358 600 by the Kaplan-Meier cost hazard method, an estimate that is upward-biased by a considerable amount.

### 5.3. Regression techniques

An important factor to consider is the way in which efficacy and costs vary in relation to potential predictor variables such as age and sex of the patient, his or her lifestyle, and health status on admission. These are all factors that may affect treatment paths and outcomes. Multivariate techniques for subgroup analysis may therefore be valuable. The Kaplan-Meier estimator is unsuitable for this purpose, because separate survival distributions would have to be calculated for each predictor variable, one at a time.

By instead using a special regression technique, the Cox proportional hazards model, developed by Cox (1972) and others, multivariate analysis of the independent variables (usually called covariates) can be performed in a way that takes account of censored observations. Here, the hazard function is defined as a function of time as well as characteristics of the individual patient and his treatment. If it is assumed that the time-related component of the hazard function is independent of the individual's characteristics $X$, then a proportional hazards model can be constructed as

$$h(t;x) = h_0(t)e^{\beta' X}, \tag{13}$$

where $h_0(t)$ is the baseline hazard, $X$ is a vector of characteristics such as age (continuous variable), sex (categorical variable), or health status at the time of diagnosis, and $\beta'$ is a vector of regression coefficients. No distributional assumptions for the hazard function are specified in the standard formulation of the model, but the hazards for

different covariate values are assumed to be proportional with a ratio that is constant over time.

The problem is that the Cox method also requires that the observations be independent. Otherwise the individuals still under observation within the groups formed by the covariate $X$ will not be representative of the population at risk in each group. This means that if two groups accrue costs at different rates, the proportional hazards assumption of a constant cost hazard will not be valid, and the method will be biased (Etzioni et al., 1999).

Unfortunately, neither the Kaplan-Meier estimator nor the Cox proportional hazard model can be applied directly to cumulative costs without serious problems of bias, unless quite restrictive assumptions hold. An urgent task for future research is thus to develop robust regression methods, which can take account of explanatory variables that explain differences in average cost between censored and uncensored cases. Poisson models may be useful in this respect.[3]

Recent advances in applying regression methods to censored survival and costs data are reported in Lin (2000), and Carides et al. (2000). However, these methods are technically more demanding and require that one writes separate computer programs for carrying out the analysis. The KMSA estimator, by contrast, can be applied by using standard statistical program packages and/or spreadsheet programs. With respect to the average cost for all patients, the regression estimators and the KMSA estimator give practically identical results. In the absence of explanatory variables, the KMSA estimator can be used equally well. The only disadvantage is that it is slightly less efficient from a statistical point of view, i.e. the variances will be larger.

[3] Anders Odén, personal communication. See Greene (1997) for a brief introduction to Poisson models.

# 6. Concluding remarks

## 6.1. Catch-up effect

Which conclusions can be drawn from the study? I believe that the Kaplan-Meier sample average estimate of SEK 257 600 is a fairly accurate estimate of the average inpatient treatment cost. Let us compare this result with the base-case figures in table 1. Not surprisingly, the KMSA estimate lies between the average cost for all within the follow-up time (SEK 216 900), and the average cost for those who died within the follow-up time (SEK 279 600).

The intuition behind this is that a catch-up effect is at work. In fact, it is reasonable to expect a catch-up effect. As we saw in table 2, the major part (78%) of the total costs occurs during the last year of life. Many of the patients who survived during the follow-up time will eventually succumb to the disease. They will then catch up in terms of costs, and accumulate total costs that probably are similar in size to the costs for those who died within the follow-up time. On the other hand, some of the survivors will be cured, and will then have no further costs for this particular disease. The average cost for all could therefore be expected to be slightly lower than for those who died within the follow-up time. However, better survival in head and neck cancer increases the probability of having other diseases later on, so lifetime health care expenditures may still be higher for this group.

## 6.2. Usefulness of cost-of-illness estimates

This study is in a sense a cost-of-illness study, albeit an incomplete one, since only the direct cost for inpatient care has been taken into account. It has often been argued that cost-of-illness studies are of no use, since they do not tell us whether or not more resources should be allocated to the diseases concerned (see, e.g., Drummond, 1992). While it is true that no conclusions regarding the cost-effectiveness can be drawn from a cost-of-illness study alone, an accurate estimation of costs is an important step in a subsequent economic evaluation (Henriksson, 2001). With additional information regarding outpatient costs, pharmaceutical costs, and health outcomes from a clinical study comparing different head and neck cancer therapies, the results of the present study could be used in a model-based economic evaluation of different treatment

strategies. In particular, the parametric estimate of costs and survival could be used in order to extrapolate costs and health effects beyond the end of follow-up of a clinical study. Extrapolation of costs and health effects is frequently necessary, since clinical studies are usually carried out within a rather short time frame (Ekman et al., 2001). A parametric estimate also makes it possible to explore uncertainty by using stochastic modelling of remaining lifetime and expected costs. The results of the present study are thus not so much of interest in themselves. They rather serve the purpose of providing building blocks for further studies of costs, effects, and, ultimately, cost-effectiveness. Estimates of the cost related to the incidence of the disease may also be valuable in economic evaluations of preventive programs aimed at reducing the number of new cases, or to find them at an earlier stage.

### 6.3. Future research: incorporating explanatory variables

In the present study, no account is taken of the staging of the disease, or other explanatory variables such as age or sex. This is a problem, since the prognosis and the costs are dependent on age and sex, and above all on the size and localisation of the tumour. Such information would be valuable in order to explain variations in cost. It would also be potentially valuable for modelling in cost-effectiveness studies, since the patients in a particular clinical trial may differ from the general population of patients. We could then predict costs and survival for specific patient-group compositions in terms of age, sex, and severity of disease. However, when estimating the average cost for all patients, which was the purpose of this study, the Kaplan-Meier sample average estimator is sufficient.

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# Appendix

**Some regularities in the data and their implications for modelling**

The probability of further admissions seems to be fairly independent of how many admissions the patient has already gone through. The second column in table A shows the proportion of patients that reaches a specific number of admissions. The third column shows the conditional probability. Given that a patient has already had 4 admissions, for example, how large is the probability that he will also go through a fifth? This is calculated as the proportion remaining at the fourth admission divided by the proportion remaining at the fifth, i.e. 0.507/0.607 = 0.836. The conditional probability remains fairly constant at a value of about 0.83 for the first 30 admissions or so. (Thereafter the conditional probability starts to fluctuate, because there are so few patients left). From a modelling point of view, this means that we can set the probability of another admission to 0.83 and get a very good representation of the disease progression.

In the fourth column of table A, the mean number of hospital days for each admission is shown. The figures indicate that the number of hospital days per admission is fairly independent of the number of admissions a patient has gone through. On average, each admission is about 9-10 days long.

**Table A.** *Some interesting facts on admissions and hospital days.*

| Admission | Remaining proportion of the sample | Conditional probability | Mean number of hospital days |
|---|---|---|---|
| 1 | 1.000 | | 12.8 |
| 2 | 0.877 | 0.877 | 12.1 |
| 3 | 0.731 | 0.834 | 11.6 |
| 4 | 0.607 | 0.830 | 11.2 |
| 5 | 0.507 | 0.836 | 10.5 |
| 6 | 0.405 | 0.798 | 9.9 |
| 7 | 0.328 | 0.809 | 9.9 |
| 8 | 0.264 | 0.808 | 10.4 |
| 9 | 0.221 | 0.835 | 10.0 |
| 10 | 0,176 | 0.798 | 8.8 |
| 11 | 0,139 | 0.791 | 10.4 |
| 12 | 0.117 | 0.842 | 9.0 |
| 13 | 0.093 | 0.796 | 7.8 |
| 14 | 0.080 | 0.857 | 9.0 |
| 15 | 0.069 | 0.868 | 8.7 |
| 16 | 0.058 | 0.834 | 9.5 |
| 17 | 0.048 | 0.833 | 8.0 |
| 18 | 0.040 | 0.838 | 9.7 |
| 19 | 0.033 | 0.807 | 7.4 |
| 20 | 0.027 | 0.817 | 10.0 |
| 21 | 0,023 | 0.862 | 8.5 |
| 22 | 0.020 | 0.860 | 7.4 |
| 23 | 0.015 | 0.767 | 6.8 |
| 24 | 0.013 | 0.879 | 9.1 |
| 25 | 0.011 | 0.862 | 10.3 |
| 26 | 0.010 | 0.880 | 7.1 |
| 27 | 0.008 | 0.818 | 6.4 |
| 28 | 0.007 | 0.889 | 11.5 |
| 29 | 0.006 | 0.813 | 6.7 |
| 30 | 0.005 | 0.846 | 12.1 |

## Glossary

**Adverse selection.** A form of market failure usually resulting from asymmetric information in which individuals are able to purchase insurance at rates which are below actuarially fair rates. This phenomenon occurs because the insurance premiums are usually based on the average risk in a certain population. If there are individuals with different risks in the population and the individuals themselves know more about their risk than does the insurance company (asymmetric information), then the insurance will look most attractive to high risk individuals, thus resulting in an adverse selection of customers.

**Allocative efficiency.** See *Efficiency*.

**Asymmetric information.** A situation in which parties on the opposite sides of a transaction have differing amounts of relevant information.

**Bootstrapping.** A simulation method for deriving nonparametric estimates of variables of interest (e.g. the variance) from a data set.

**Consumer surplus.** The difference between the maximum amount consumers would be willing to pay for the quantity of the good that they demand and the amount that they actually pay. It is measured as the area between the demand curve and a horizontal line at the market price.

**Cost-benefit analysis (CBA).** A method for estimating the net social benefit of a program or intervention as the incremental benefit of the program less the incremental cost, with all benefits and costs measured in monetary terms.

**Cost-effectiveness analysis (CEA).** A method in which costs and effects of a program and at least one alternative are calculated and presented in a ratio of incremental cost to incremental effect. Effects are health outcomes, such as cases of a disease prevented, years of life gained, or quality-adjusted life years gained, rather than monetary measures as in cost-benefit analysis.

**Cox's proportional hazards model.** In survival analysis the hazard function is the instantaneous likelihood of dying at a particular time, from which survival probabilities and survival curves are derived. The proportional hazards model is one algebraic form of the hazard funtion that assumes that the impact of risk factors (co-variates) is to multiply the baseline hazard fucntion by some factor. Hence their effect can be expressed as being proportional to the baseline hazard.

**Deterministic model.** For a health process, a model that computes quantities of interest (e.g., treatment effect, survival probabilities) directly by algebraic formulas. Such a model does not use event simulation techniques to model the process.

**Diagnosis-Related Groups (DRGs).** Each diagnosis-related group (DRG) represents patients with similar medical conditions and a similar treatments. To each DRG is assigned a relative weight that compares its costliness to the average for all DRGs.

DRGs are used for setting charges for prospective payment for health care services. Prospective payment here means that a flat rate is paid for all interventions classifies into a particular DRG, no matter what the actual cost is.

**Direct cost.** The value of all goods, services, and other resources that are consumed in the provision of an intervention or in dealing with side effects or other current or future consequences linked to it.

**Discounting - Discount rate.** The process of converting sums to be received at a future date to a present value. The interest rate that is used is called the discount rate.

**Efficiency.** *Technical efficiency* occurs when a firm produces the maximum possible output from a given set of inputs. *Allocative efficiency* occurs when inputs or outputs are put to their best possible uses in the economy, so that no further gains in output or welfare are possible. Allocative and technical efficiency are both prerequisites for Pareto efficiency.

**Ex ante.** A situation viewed from before hand, i.e. before the event occurs, before an action is taken, or before an outcome is known.

**Expected value.** A measure used with a probability distribution of returns. The expected value is the sum of each probability multiplied by its corresponding return.

**Ex post.** Opposite to *ex ante*.

**Externality.** An action by either producers or consumers that affects other producers or consumers, yet is not accounted for in the market price.

**Functional status.** An individual's performance or ability to perform in various everyday activities, e.g. to work, play, or maintain the house. Functional status can be divided into physical, emotional, mental, and social abilities.

**Gross domestic product (GDP).** The output produced by factors of production located in the domestic economy, whoever owns them.

**Hazard rate.** The instantaneous probability of mortality or morbidity at any point in time.

**Incremental cost.** The cost of one alternative less the cost of another.

**Incremental cost-effectiveness ratio.** The ratio of the difference in costs between two alternatives to the difference in effect between the same two alternatives.

**Indifference curve.** A graphical way of presenting all combinations of goods that provide the same level of utility.

**Indirect cost.** A term used in health economics to refer primarily to productivity gains and losses related to illness or death. In accounting it is used to describe overhead or fixed costs of production.

**Inpatient care.** Care that requires a stay in a hospital.

**Incidence.** The rate at which new cases occur in a population during a specified period of time. When the population at risk is roughly constant, the incidence is measured as Number of new cases/(Population at risk * Time during which cases are registered).

**Kaldor-Hicks criterion.** A program is considered to be welfare enhancing if those who gain from it would hypothetical be willing to pay enough for their gains to compensate the losers (potential Pareto improvement).

**Life-table methodology.** A methodology by which the mortality of a fixed population is evaluated within successive small time intervals so that the time dependence of mortality can be estimated.

**Marginal cost (MC).** The increase in total cost resulting from a one unit increase in output.

**Marginal rate of return.** The percent gain per time period (e.g., per year) from diverting $1 of consumption to investment. For example, if the marginal rate of return is 6% annually, a dollar invested today will yield $1.06 one year hence.

**Marginal rate of substitution (MRS).** The amount of one commodity given up per unit increase in another commodity while maintaining the same level of satisfaction.

**Marginal rate of transformation (MRT).** The slope of the production possibilities curve, and the rate at which society can transform one good into another.

**Medicare.** The US federal insurance program established in 1965 for the elderly and other selected groups.

**Moral hazard.** A situation in which an insured party can affect the probability or magnitude of an event against which he is insured. As a result of the disincentives created by health insurance, for example, the individual may fail to take measures that would reduce the amount of health care demanded.

**Morbidity rate.** The rate of incidence of disease in a particular population.

**Mortality rate.** The rate of incidence of death in a particular population.

**Opportunity cost.** The value of the best alternative which is forgone in order to get or produce more of a commodity.

**Outpatient care.** Care at a hospital or a clinic without the patient staying overnight.

**Poisson regression.** A data analysis technique in which event probabilities are assumed to be represented by the Poisson distribution with an event parameter expressed as a mathematical function of predictor variables. This technique is most often used in parametric survival analysis.

**Population at risk.** The group of people, healthy or sick, who would be counted as cases if they had the disease being studied.

**Prevalence.** The proportions of individuals in a population who are suffering from a disease or a condition at a specific point in time.

**Pareto efficiency.** (See also *Efficiency*). Situation in which it is impossible to improve the level of welfare of one individual without decreasing the welfare level of another individual. Situations in which the level of welfare of one or more individuals can be improved without hurting any other individual are Pareto improvements.

**Perfect competition.** A market structure in which there are (1) numerous buyers and sellers, (2) perfect information, (3) free entry and exit, and (4) a homogeneous product.

**Present value.** (See also *Discounting*). The value of a stream of returns to be received at future dates, discounted to the equivalent of present dollars.

**Production possibilities curve.** A curve describing all combinations of two goods that can be produced with given quantities of input factors and the existing technology. The slope of the curve is the marginal rate of transformation, showing the quantity of one good that must be given up for a one unit increase in the other good.

**Quality-adjusted life years (QALYs).** A measure of health outcomes which assigns to each period of time a weight, ranging from 0 to 1, corresponding to the health-related quality of life during that period, where a weight of 1 corresponds to optimal health and a weight of 0 corresponding to a health state judged equivalent to death. These weights are aggregated across time periods.

**Quality of life.** A measure reflecting subjective or objective judgment concerning all aspects all an individual's life, including, health, economic, political, cultural, environmental, aesthetic, and spiritual aspects.

**Randomised clinical trial (RCT).** A clinical trial in which the treatments are randomly assigned to the subjects. The random allocation eliminates bias in the assignment of treatments to patients and establishes the basis for statistical analysis.

**Real value.** The dollar value of a good or service after correction for inflation.

**Shadow price.** The social *opportunity cost* of capital.

**Social rate of time preference.** The rate at which the social decision maker is willing to trade off present for future consumption. Frequently approximated by the real (inflation-adjusted) return on low risk government investments.

**Social welfare function.** A decision rule under which society ranks all possible distributions of goods and services.

**Stochastic model.** Health care process models that use computer-generated random numbers to simulate the occurrence of events over time.

**Survival probabilities.** The probability that a specified individual will be alive at the end of a given period of time.

**Time costs.** The money value of the time lost through travel or waiting when consuming a product or service.

**Utility.** The level of satisfaction that an individual gets from consuming a good or undertaking an activity. The problem is that the level of satisfaction as such is unobservable. In economic analysis, utility is therefore used in a more restrictive, but measurable, sense. Utility refers to relative preference rankings of baskets of goods.

**Utility function.** An algebraic expression stating that a decision maker's satisfaction is dependent on the types and amounts of commodities she consumes. Symbolically, $U = U(x_1, x_2, ...)$, where $x_1$, $x_2$, ... are tangible or intangible goods. According to expected utility theory, individuals behave so as to maximize the expected value of utility, subject to constraints.

**Validity.** The extent to which a technique measures what it is intended to measure.

**Welfare economics.** A normative branch of economics concerned with the development of principles for maximizing social welfare and economic output. It is based on the assumptions (1) that individuals maximise a well-defined utility function, and (2) that the overall welfare of society is a function of these individual preferences.

***Sources:*** In compiling this glossary, I have borrowed heavily from Folland et al., Ecoonomics of Health and Health Care, 2nd ed., Prentice-Hall, 1997; and Gold et al., Cost-Effectiveness in Health and Medicine, OUP, 1996. Some definitions have also been taken from Katz & Rosen, Microeconomics, 3rd ed., McGraw-Hill, 1998; Dornbusch, Fisher & Schmalensee, Economics, 2nd ed. McGraw-Hill, 1988; Pindyck & Rubinfeld, 4th ed., Prentice-Hall, 1998; and Varian, Intermediate Microeconomics, 4th ed., Norton, 1999.

## List of abbreviations

| | |
|---|---|
| AC | Average cost/s/ |
| ACE inhibitor | Angiotensin-converting enzyme inhibitor |
| AIRE | Acute Infarction Ramipril Efficacy |
| β blocker | Beta-adrenergic blocking agent |
| ΔC | Difference in average cost between two treatments |
| CHF | Congestive heart failure |
| CIBIS | Cardiac Insufficiency Bisoprolol Study |
| CONSENSUS | Cooperative New Scandinavian Enalapril Survival Study |
| DDD | Defined daily dose |
| DRG | Diagnosed-related group |
| ΔE | Difference in average effect between two treatments |
| GDP | Gross domestic product |
| GP | General practitioner |
| IC | Indifference curve |
| ICER | Incremental cost-effectiveness ratio = ΔC/ ΔE (same as R) |
| KMSA | Kaplan-Meier sample average |
| LIF | Läkemedelsindustriföreningen (Swedish Association of the Pharmaceutical Industry) |
| LY | Life year |
| MERIT-HF | Metoprolol Controlled-Release Randomised Intervention Trial in Heart Failure |
| MRS | Marginal rate of substitution |
| MRT | Marginal rate of transformation |
| NB | Net benefit = p · ΔE - ΔC, where p is WTP per LY or QALY |
| NBER | National Bureau of Economic Research |
| NPV | Net present value |
| NYHA | New York Heart Association |
| OECD | Organisation for Economic Co-Operation and Development |
| PPC | Production possibilities curve |
| QALY | Quality-adjusted life year |
| R | Incremental cost-effectiveness ratio = ΔC/ ΔE (same as ICER) |

| | |
|---|---|
| SAVE | Survival and Ventricular Enlargement |
| SCB | Statistiska Centralbyrån (Statistics Sweden) |
| SOLVD | Studies of Left Ventricular Dysfunction |
| TC | Total cost/s/ |
| WTP | Willingness to pay |

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*1998*

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