Lipid-modifying and glucose-lowering therapies in clinical practice: The impact of guidelines and changing reimbursement schemes

Billie Pettersson

Division of Health Care Analysis
Department of Medical and Health Sciences
Linköping University, Sweden
To my late parents Naser and Aida Kanngo:
I felt your support all the way

Thinking: the talking of the soul with itself.
Plato (427-347 BC)
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ABSTRACT

Preventive medicine has evolved in recent decades as an important way of reducing the risk of cardiovascular disease, which is still a major cause of death that creates large burdens to society in terms of costs and morbidity. Dyslipidemia and type 2 diabetes mellitus are the main risk factors for cardiovascular disease, and national and international guidelines recommend lipid-modifying and glucose-lowering treatments for prevention. In 2010, about 836,000 (9% of the population) and 372,000 patients respectively were treated with these therapies in Sweden.

Various pharmaceutical policies aimed at improving the efficiency of drug use have been introduced over the years. Health technology assessment (HTA) was introduced in Sweden in 2002 as a foundation for informing pricing and reimbursement decisions by the Dental and Pharmaceutical Benefits Agency (TLV).

Following HTA reviews, new reimbursement schemes for lipid-modifying and glucose-lowering therapies were introduced in 2009 and 2010 respectively. To assess the impact of the changing reimbursement schemes on the use and costs of these therapies, we analyzed data from the Swedish drug registry, using a quasi-experimental design and interrupted time series analyses.

Our results showed that the new reimbursement scheme for lipid-modifying treatment had a major effect on use; following the implementation of this scheme, there was a substantial increase in both discontinuation and switching to higher doses. Conversely, the new reimbursement scheme for glucose-lowering therapies had overall only a minor effect on use. Larger savings in the lipid market were anticipated but not fully realized, while even the minor anticipated changes in costs in the glucose-lowering market were not realized due to increased costs for insulins. We found that changes in reimbursement schemes might lead to unintended effects, which should be considered before implementation. Softer demand-side policies,
such as recommendations and guidelines, might be a better option under some circumstances.

Clinical and national guidelines are other policies aimed at improving quality of care and drug use. We assessed the impact of guidelines on the quality of lipid-modifying therapies, defined as proportions of patients attaining goal/normal levels according to guidelines for lipid management. A longitudinal retrospective observational study was carried out, covering time periods before and after initiation of lipid-modifying treatment. The findings show that about 40% of the patients attained the recommended low-density lipoprotein cholesterol goals following treatment, but only 18% attained goals/normal levels in all lipid parameters. Improvement in triglycerides was moderate, and low levels of high-density lipoprotein cholesterol persisted, showing only modest improvement following therapy. Treatment patterns were found to have a better degree of adherence to guidelines regarding low-density lipoprotein cholesterol as compared to other lipid parameters.

The overall objective of treatment of type 2 diabetes mellitus is to improve glycemic control without negatively affecting quality of life. Hypoglycemia is a common side effect of intensive blood glucose control, mostly seen in patients treated with insulins. Earlier studies have suggested that hypoglycemia has a negative impact on quality of life, even in patients treated with oral glucose-lowering therapies. We carried out a cross-sectional retrospective study to assess the impact of self-reported experience of hypoglycemia on quality of life in Swedish adult patients with type 2 diabetes mellitus treated with a combination of metformin and sulfonylureas. The results showed that about 40% of the patients achieved the goal of glycemic control. About 19% reported experience of moderate or more severe hypoglycemia, and these patients were found to have lower quality of life than those patients reporting no or mild hypoglycemia, as measured by EQ-5D, a generic quality of life instrument. This could be important to consider in clinical practice.
LIST OF PAPERS


ABBREVIATIONS

CVD      Cardiovascular disease  
CHD      Coronary heart disease  
DCCT     Diabetes Control and Complications Trial  
DDD      Defined daily doses  
EQ5D     EuroQol  
GLT      Glucose-lowering therapies  
HbA1c    Glycated hemoglobin  
HDL-C    High-density lipoprotein cholesterol  
HTA      Health technology assessment  
LDL-C    Low-density lipoprotein cholesterol  
LMT      Lipid-modifying therapies  
NCD      Non-communicable disease  
P&R       Pricing and reimbursement  
QoL      Quality of life  
SU       Sulphonylureas  
QALY     Quality-adjusted life year  
TGs      Triglycerides  
TIM      Thousand inhabitants per month  
TLV      The Dental and Pharmaceutical Benefits Agency  
T2DM     Type 2 diabetes mellitus
1. INTRODUCTION

Preventive medicine has evolved in recent decades as an important way of reducing the risk of cardiovascular disease (CVD). In the OECD countries, life expectancy has increased by 10 years since 1960, and CVD mortality has decreased substantially but is still the main cause of death in Europe [1]. Technological change has had a major impact on both health care outcomes and the quality of care. The introduction of lipid-lowering drugs has contributed significantly to the 50% reduction in cardiovascular mortality observed in many countries during the last two decades [2, 3]. However, CVD-related morbidity still constitutes a major burden to society, in both economic and human terms. In 2006, the costs related to CVD were estimated at around 10% of total health care expenditures in Sweden [1].

Technological change has been a major driver of health care spending over the post-war period [4, 5]. Pharmaceuticals represent around 15% of overall health expenditure in the OECD countries, and increasing expenditures have led to the introduction of different policies aimed at improving the efficiency of drug use [6].

In recent decades in Sweden, such policies have been introduced at a regional and national level [7], leading to major reformation and changes in the pharmaceutical market. Pharmaco-economic assessments in support of listings of publicly-funded benefits were initiated in Australia in 1993 [8], and have now been introduced in many OECD countries, in one form or another [9]. In Sweden, health technology assessment (HTA) has emerged as an important foundation for guiding decision-making and allocating resources in health care. HTA was introduced in 2002 as the basis for pricing and reimbursement (P&R) of new drugs as well as older drugs, within the framework of the reviews of the Swedish P&R agency, the Dental and Pharmaceutical Benefits Agency (TLV). HTA is increasingly used for production of clinical, national, and regional guidelines.
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In preventive medicine in particular, private demand could be influenced by market failures such as asymmetric information and moral hazard, and so the use of preventive medicines could be other than the socially desired level. While prevention is widely recommended by public health professionals as a strategy for improving health, there is an increasing recognition of resource constraints, which has led to the introduction of various pharmaceutical policies to control costs. Pharmaceutical policies such as P&R and guidelines are instruments employed by governments to steer demand and use of medicines towards a desirable level.

A review by Green et al. (2010)[10] concluded that policy measures should be carefully designed and should be based on research quantifying the harm and benefit profiles of the target and alternative drugs; otherwise there may be unwanted health system and health effects, particularly where drugs are not interchangeable. Furthermore, the authors concluded that removing restrictions on drugs that prevent complications of disease might remove barriers to access, resulting in a desired increase in their use as well as cost savings [10]. It has also been shown that guidelines accompanied by a change in reimbursement rules had a significant influence on the prescribing of lipid-lowering drugs [11].

It is therefore of particular interest to study the impact and effectiveness of emerging P&R policies and guidelines to steer use of preventive medicines. This dissertation focuses on lipid-modifying and glucose-lowering therapies, which are preventive therapies for two of the most prevalent risk factors for CVD. About 9% of the population in Sweden is prescribed a lipid-modifying therapy, and the prevalence of type 2 diabetes mellitus (T2DM) in Sweden has been estimated at around 4.5% [12, 13], affecting more than 400,000 individuals.
1.1. Health policy for prevention

CVD mortality has decreased substantially, but is still the main cause of death in the European region, causing over two million deaths per year [1]. In Sweden, CVD mortality is about 40% of total mortality, though the rate of death form heart disease and stroke is decreasing for both women and men[14], see figure 1.

Figure 1. Number of deaths from heart disease and stroke in women and men per 100 000 in Sweden 1952-2008.

The European division of the World Health Organization has a vision of a health-promoting Europe free of preventable non-communicable diseases (NCD), premature death, and avoidable disability; this vision is laid out in the European Strategy for the Prevention and Control of NCD [15]. The goal of this strategy is to avoid premature death and significantly reduce the disease burden from NCD by taking integrated action, by improving quality of life, and by making healthy life expectancy more equitable within and between Member States.

In 2003, a new national public health strategy for Sweden was presented, one of its objectives being health and medical care that more actively promotes good health. This strategy stated that: “A health-promotion and disease-prevention perspective shall be an integral part of the whole health and medical care service and be a
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palpable component of all care and treatment” [16]. Improving preventive care and using the potential of prevention was also highlighted in the objectives of the WHO strategy: “To take integrated action on risk factors and their underlying determinants across sectors” and “To strengthen health systems for improved prevention and control of NCD” [15].

1.1.1. Economics of prevention

Prevention is a broad concept, and a standardized approach identifies three categories of intervention: primary, secondary, and tertiary. Primary prevention consists of actions that reduce the occurrence or incidence of disease, secondary prevention consists of actions that reduce or eliminate the health consequences of a disease given its occurrence, and tertiary prevention consists of actions that reduce the disability associated with a chronic illness [17].

Use of preventive medicine depends on individual decisions and the functioning of the private markets; it is also affected by relevant market failures, such as moral hazard, asymmetric information, and other externalities on prevention decisions.

Moral hazard is one type of market failure related to asymmetric information. It refers in general to those actions of the insured which alter the accident probability but are not observable by the insurer [18]. One example in the field of health care is that health insurance for curative care might reduce incentives for prevention [19], mainly because the individuals subjective estimated risk of morbidity is in general lower than an objective estimation done by experts[20, 21]. However, other factors might create further private incentives for prevention, because in many cases the uninsurable utility loss from health risks, for example pain and suffering, far exceeds the insurable monetary loss; that is, the coverage is incomplete. Furthermore, despite

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insurance for curative care, prevention remains attractive because in cases when complete cure is not possible, the choice is between completely preventing disease or incompletely curing it.

Another source of failure for consumers to make optimal prevention decisions arises from lack of (correct) information on a wide variety of primary and secondary prevention activities [18, 22]. When this occurs, the decision is heavily influenced by the recommendation from the physician, who is in turn influenced by factors such as clinical guidelines and recommendations. In a publicly-financed health care system, incentives for prevention are partly shifted away from the insured onto the providers of insurance. The public sector has a general incentive to encourage prevention; the challenge is then to internalize this incentive to relevant agents who can influence consumer preventive behavior in order to steer the use of preventive drugs towards an optimal and cost-effective level. Removing restrictions for drugs that prevent complications of disease has been suggested to result in a desired increase in their use as well as cost savings [10].

Health science research and the development of new medical technologies are other important factors in determining trends in health as in cost and quality of medical care [23].

1.1.2. Prevention of cardiovascular risk factors

Cardiovascular disease – disease of the heart and blood vessels – has three major manifestations: coronary heart disease (CHD), transient ischemic attack, stroke and peripheral arterial disease [24]. The underlying pathology for CVD is atherosclerosis, which develops over many years and is usually advanced by the time symptoms occur, generally in middle age.

Prevention and modification of risk factors can reduce clinical events and premature death in people with established CVD as well as in those who are at high
Introduction

cardiovascular risk due to one or more risk factors [25]. A cardiovascular risk factor is a condition that is associated with an increased risk of developing CVD [26]. The concept of risk factors has evolved over the past 45 years, and new factors are periodically added to the list as comprehension of the disease process grows [26]. Box 1 lists the currently accepted cardiovascular risk factors classified as factors that cannot be changed, factors that can be changed, and factors that are protective. Cigarette smoking, diabetes, hyperlipidemia, and hypertension have been established as independent risk factors for CHD and are often labeled as “conventional” risk factors because of the strength of evidence supporting their role in the pathogenesis of CHD [27]. There is clear evidence that the four conventional risk factors and their resulting health risks are largely preventable by a healthy lifestyle [28].

Total risk estimation is a crucial tool to guide patient management, and has been a cornerstone of guidelines. Individual risk factors should be evaluated against total cardiovascular risk, since the combined effects of several risk factors may interact [29]. Targets for individual risk factors are problematic in that they will always be open to debate, they are not always achievable, and they seem to promote a single risk factor approach to prevention [29]. There is, however, a consensus that the risk increases continuously as blood pressure rises from levels that are considered to be within the normal range [29].
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Box 1. Cardiovascular risk factors

<table>
<thead>
<tr>
<th>Risk factors that cannot be changed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
</tr>
<tr>
<td>Gender</td>
</tr>
<tr>
<td>Heredity</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Risk factors that can be changed</th>
</tr>
</thead>
<tbody>
<tr>
<td>High blood pressure</td>
</tr>
<tr>
<td>Elevated serum cholesterol</td>
</tr>
<tr>
<td>Lipoprotein (a)</td>
</tr>
<tr>
<td>Cigarette smoking</td>
</tr>
<tr>
<td>Obesity</td>
</tr>
<tr>
<td>Glucose intolerance</td>
</tr>
<tr>
<td>Diabetes</td>
</tr>
<tr>
<td>Fibrinogen</td>
</tr>
<tr>
<td>Left ventricular hypertrophy</td>
</tr>
<tr>
<td>Cocaine</td>
</tr>
<tr>
<td>Behavioral factors (stress, type A)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Protective factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>HDL cholesterol</td>
</tr>
<tr>
<td>Exercise</td>
</tr>
<tr>
<td>Estrogen</td>
</tr>
<tr>
<td>Moderate alcohol intake</td>
</tr>
</tbody>
</table>

Adapted from Black, Yale University School of Medicine Heart Book [26].

1.2. Health technology assessment

HTA is increasingly used in many countries to assist decision-making regarding the optimal use of competing health technologies. It has been defined as “a multi-disciplinary field of policy analysis, studying the medical, economic, social and ethical implications of development, diffusion and use of health technology” [30]. The declared purpose of HTA is to support the process of decision-making in health care at policy level by providing reliable information; in this respect, HTA can be seen as a bridge between the world of research and the world of decision-making [31].

HTA originated from growing concerns in the 1970s about the expanding costs of new medical technology and the ability to finance them [32-35]. During the subsequent decades, there has been substantial demand for well-founded information from HTA to support decisions on the development, uptake, and
diffusion of health technologies. This has led to a massive growth and development in HTA, with the subsequent establishment of HTA programs in almost all European countries, either in new agencies or institutes or in established academic units [9, 35]. While European HTA agencies share many of the same basic objectives, their structures and how they operate differ widely across countries [9, 36]. Decision-makers in most European countries have increasingly relied on the use of HTA to support P&R decisions regarding existing and new pharmaceuticals, prioritization, development of clinical guidelines, and the direction of resources to the most cost-effective treatments in health care [9, 37]. HTA can therefore play a major role in various phases in the use and diffusion of a health technology, notably when the decision on reimbursement of the technology is taken (or revised) and when recommendations on its use are made to the professionals using the technology.

1.2.1. Economic evaluations in HTA

Economic evaluations are important components of HTA. Economic evaluations have been defined as the comparative analysis of alternative courses of action in terms of both their costs and consequences. The general approach in full economic evaluations is to compare the consequences of health care programs with their costs, while partial evaluation might compare only consequences or only costs. The basic tasks of any economic evaluation are to identify, measure, value, and compare the costs and consequences of the alternatives being considered.

The main forms of full economic evaluations are tabulated in Table 1. All forms of economic evaluations analyze costs in the same way, but differ in the way that the consequences of health care programs are measured and valued. A general rule when assessing two programs, A and B, is that the difference in costs is compared with the difference in consequences, in an incremental analysis. Incremental analysis means that difference between the costs of the two treatments to reach the defined outcome, is divided by the difference in their effectiveness:
\[ C_A - C_B = \Delta C \]
\[ E_A - E_B = \Delta E \]

Table 1. The main forms of full economic evaluations.

<table>
<thead>
<tr>
<th>Type of evaluation</th>
<th>Measurement/valuation of costs in both alternatives</th>
<th>Identification of consequences</th>
<th>Measurement/valuation of consequences</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Cost-minimization analysis</td>
<td>Monetary</td>
<td>Identical in all relevant aspects</td>
<td>None</td>
</tr>
<tr>
<td>2. Cost-effectiveness analysis</td>
<td>Monetary</td>
<td>Single effect of interest but achieved to different degree</td>
<td>Natural units (e.g. life-years gained, points of blood pressure reduction)</td>
</tr>
<tr>
<td>3. Cost-utility analysis</td>
<td>Monetary</td>
<td>Single or multiple effects, not necessarily common to both alternatives</td>
<td>Health years or quality-adjusted life-years (QALYs)</td>
</tr>
<tr>
<td>4. Cost-benefit analysis</td>
<td>Monetary</td>
<td>Single or multiple effects, not necessarily common to both alternatives</td>
<td>Monetary</td>
</tr>
</tbody>
</table>

Adapted from Drummond et al. [38].

Cost-minimization analysis deals only with costs and can therefore be regarded as a partial form of economic evaluation. When the consequences of two or more alternatives are considered to be equivalent, cost-minimization can be used to compare the costs; hence, this analysis is a special form of cost-effectiveness analysis (CEA). In CEA, the consequences are measured in the most appropriate natural effects or physical units, such as life-years gained or units in any efficacy surrogate.
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parameter, such as blood pressure or lipid values. In cost-utility analysis (CUA), the consequences of programs are measured in physical units as in CEA, but adjusted by health state preference scores or utility weights. This gives the possibility to assess the gain in quality of life and gain in life-years in one single outcome measure, the quality-adjusted life year (QALY).

One severe limitation of CEA and CUA is that these analyses cannot provide information on whether a program is efficient or worthwhile; that is, whether the benefits exceed the costs. It is possible only to compare the cost-effectiveness ratios of various options [22]. In cost-benefit analysis (CBA), however, the consequences are valued in monetary terms and so can be directly compared to the costs related to a program [38]. CBA can therefore be used to evaluate whether the beneficial consequences of a program justify its costs.

1.2.1.1. Capturing quality of life in economic evaluations

Quality of life (QoL) has been defined as the “value assigned to duration of life as modified by the impairments; physical, social, and psychological functional states; perceptions; and opportunities that are influenced by disease, injury, treatment, or policy” [39]. QoL is a subjective, multidimensional, and dynamic concept, and therefore it is argued that QoL should be reported by patients whenever relevant and appropriate, under the premise that the best way to find out about the effectiveness of a certain treatment is to ask the patient [40]. QoL weights are fundamental in health economic evaluations aimed at estimating the cost of QALYs gained, and they play a major role in valuing the benefit of drugs where QALYs are used as the basis for P&R decisions [41].

The QALY methodology is preferred by the TLV and many other HTA agencies, because the outcome measure combines the dimensions of quantity of life (mortality) and quality of life (morbidity), thus allowing comparison between different disease areas with different clinical outcomes. In the QALY approach, the quality adjustment
is based on a set of quality weights that represent the health-related quality of life of the health state under consideration. The weights (utilities) are derived from consumer preferences, and so the consumers play a crucial role in valuing outcomes in QALY methodology.

The concept of the QALY is illustrated in Figure 2. QoL weights are shown on the vertical axis, with 0 representing death and 1 representing perfect health, and the quantity of life (mortality) is shown on the horizontal axis. In this example, the QALY gained by a treatment is illustrated in area A and B and it can be calculated as \(((0.8 \times 1 + 0.7 \times 1) - (0.4 \times 1)) = 1.1\) QALY compared to no treatment. Area A shows the gain in QoL, and area B shows the gain in both QoL and life-years from the treatment.

![Figure 2. The concept of the QALY.](image)

Utility and values are different types of preferences. Preferences can be measured using direct or indirect methods/techniques. The three most widely used techniques for directly measuring the preferences of individuals for health outcomes are the rating scale, the standard gamble, and the time trade-off [38]. A simpler alternative to these direct methods is to use one of the existing pre-scored multi-attribute health
status classification systems, for example Quality of Well Being, Health Utility Index, or EuroQol (EQ-5D), to measure QoL and weights related to health status. These methods and instruments have become widely accepted in health economics, and are therefore considered a standard [41].

1.2.1.2. Guidelines in economic evaluations

The results from economic evaluations and analyses are heavily influenced by the fundamentals and methodological choices related to costs and consequences. For instance, if the analysis takes a health care perspective, then only the costs and consequences arising for the health care sector are considered and included in the cost analysis, while a societal perspective would allow for all costs and consequences to be considered in the analysis. The employment of economic evaluations differs between countries [42]. In Sweden, the TLV takes the following preferred approach to drawing up a health economic analysis [43]:

- The health economic analysis should be done from a social economic perspective. Among other things, this means that all relevant costs and revenues for treatment and ill health should be considered, irrespective of the payee (county council, local authority, state, patient).
- The information must describe the situation in Sweden.
- The costs and health effects of using the drug in question should be compared with the most appropriate alternative treatment in Sweden. This could be drug treatment, another treatment, or no treatment at all.
- The analysis should include the whole patient population to which the subsidy application refers. Separate calculations should be made for different patient groups where the treatment is expected to have different cost-effectiveness.
• An estimation of the number of persons in each patient group in Sweden should be attached.

• All relevant costs associated with treatment and illness should be identified, quantified, and evaluated. The production loss for treatment and sickness should also be included (estimated using the human capital method).

• Cost-effectiveness analysis is recommended, with QALYs as the measure of effect. Cost-effectiveness ratios should be calculated based on the differences in costs and effects (QALYs) that exist between treatment alternatives (incremental analysis).

• QALY weightings should be based either on direct methods such as the standard gamble or time trade-off methods or on indirect measurements (where a health classification system such as EQ-5D is linked to QALY weightings).

1.2.1.3. Theoretical foundation of economic evaluations

The theoretical foundation of economic evaluations is rooted in welfare economics, a branch of normative economics that analyzes the desirability of different changes or policies. Welfare economics is concerned with providing criteria to rank different alternative changes or policies, with the aim of defining the optimal allocation of resources [18]. The most widely used criterion for evaluating resource allocation is Pareto efficiency, which states that a change is desirable if it makes some individual(s) better off without making any other individual(s) worse off. Hence, a situation is Pareto optimal if it is impossible to improve the situation of any individuals(s) without making at least one other individual worse off [18, 22].
Two key assumptions of the Pareto principle and the welfare approach are that 1) social welfare is made up from the welfare (or utilities) of each individual member of society; and 2) individuals are the best judges of their own welfare [41].

A reinterpretation of the Pareto principle, a potential Pareto improvement, was provided by Kaldor and Hicks in the compensation test [18, 22]. Potential Pareto improvements or compensation tests (Kaldor-Hicks criterion) refer to the situation of a policy that creates gainers and losers in welfare; if gainers in that situation could compensate the losers and remain better off themselves after the change, then society as a whole has benefited [41]. The reinterpretation of the Pareto principle and the compensation tests form a basis for CBA to be operationalized, with program benefits being valued using a compensation test based on the principle of willingness to pay.

The approach of extra-welfarism has emerged from critics of the traditional welfare economics, mainly due to the narrow focus on individual utilities for resource allocation that is implied by the key assumptions of traditional welfarist view [44]. Extra-welfarism is considered as a pragmatic approach, taking as its theoretical framework the aim of optimizing health benefits from a given budget; the evaluation is aimed at informing decision-makers rather than prescribing what decisions should be made [45]. The most prominent differences between extra-welfarism and welfarist economics are that extra-welfarism allows elements other than individual utility to be considered in the analysis, it allows other sources of valuation of the relevant outcomes, and it allows for interpersonal comparisons [44]. The extra-welfarist approach has however been criticized for its lack of theoretical framework, as it is not embedded in standard welfare economic theory [46]. While CBA has its theoretical roots in welfare economics, CUA and CEA are frequently referred to as non-welfarist, decision-maker, or extra-welfarist approaches [45]. Hence the two latter types of analysis are criticized for having weak theoretical foundations in comparison to CBA [45, 46].
1.3. Pharmaceutical policy

Pharmaceutical policies are the instruments used by governments to control the development, distribution, subsidization, pricing, and use of drugs in the communities they govern [47]. While each OECD country has a unique mix of pharmaceutical policies, their policy environments share several common features that have implications for the resulting market dynamics [6]. These common features comprise supply-side policies such as intellectual property rights and regulation for market authorizations, and demand-side policies aimed at promoting affordable access to medicines through various models for range and scope of subsidies through P&R policies. The net effect of intellectual property rights and market authorization is to raise prices by limiting competition, while the net effect of demand-side policies is to lower prices to consumers for pharmaceuticals through reduction or elimination of out-of-pocket costs paid by the consumer [6].

Pharmaceutical expenditures in Sweden have been rising since the early 1990s, as in many other countries [6, 48-51], see Figure 3.

Figure 3. Public expenditures on pharmaceuticals including medical devices and other in the pharmaceutical benefits in 2010 years prices.

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The main factor behind the escalation in drug costs in Sweden between 1990 and 2000 has been suggested to be the change from old to new and more innovative and expensive drug therapies [51]. Increasing pharmaceutical expenditures have led to the introduction of a variety of mainly demand-side policies aimed at restricting the escalation [48, 49, 52]. These policies can be divided into those aimed mostly at promoting cost-effectiveness and those aimed mostly at containing costs. Figure 4 presents the most important reforms in the Swedish pharmaceutical market since 1997 and the extent to which their purpose has been primarily to contain costs or to promote cost-effectiveness.

Figure 4. Major pharmaceutical reforms introduced in Sweden 1997-2004.

Cost-effectiveness

- Formulary committees (1997)
- Decentralised drug-budgets (1998)
- Changed user-charges (1997)
- Parallel trade (1997)

Cost-control

- Pharmaceutical Benefits Board (1st October 2002)
- Generic substitution (1st October 2002)

1997 2004

Adapted from Anell and Persson 2005[48].

Increased user charges (co-payments), parallel trade, and the introduction of generic substitution have been oriented towards cost containment, while other reforms have been oriented towards promoting a rational and cost-effective use of pharmaceuticals [48].

The reforms to encourage rational use of prescription medicines at a regional level have gathered pace, with drug budgets devolved to the counties as of 1998. These reforms include measures operated via regional Drug and Therapeutic Committees, such as the production of regional guidelines, academic detailing, benchmarking,
prescribing targets, and incentives [7]. A variety of such initiatives have been introduced in Sweden [53-55]. These can be categorized under one or more of the following four “E”s [54]: Education (programs that influence prescribing through dissemination of material, which can be passive or active), Engineering (organizational or managerial interventions), Economics (changes in insurance and reimbursement, patient contributory payment, financial interventions, etc.), and Enforcement (regulations including those enforced by law).

The reforms aimed at promoting a rational and cost-effective use of drugs at a national level involved already-established organizations in Sweden, but also led to the establishment in October 2002 of the Pharmaceutical Benefits Board (Läkemedelsförmånsnämnden/LFN), which was renamed in 2008 to the Dental and Pharmaceutical Benefits Agency (Tandvårds- och läkemedelsförmånsverket/TLV) [53]. The establishment of this agency markedly changed the principles of P&R of drugs in Sweden.

Reforms involving increased co-payments were found to have limited effects on expenditure and utilization of prescribed pharmaceuticals in Sweden, while policies using indirect pricing, reference-based pricing, and generic substitution were associated with decreased cost per volume; generic substitution was also associated with a decrease of total pharmaceutical expenditure [49, 52].

A review [10] found that under some circumstances, reimbursement restriction policies can ensure better use of medicines with reduced costs and without an increase in the use of other health services; this occurs, for example, when the relevant drugs are aimed at targeting symptoms and have cheaper yet still effective alternatives. On the other hand, relaxing reimbursement rules for drugs used for prevention might remove barriers to access and increase use towards a desirable level [10]. Green et al. concluded that policy measures should be carefully designed and should be based on research quantifying the harm and benefit profiles of target
and alternative drugs. Otherwise, there is a risk of unwanted health system and health effects, particularly where drugs are not interchangeable.

A review by Cheah et al. (1998) found that there is considerable uncertainty whether clinical guidelines will improve or influence clinical practice [56]. Another review by Worrall et al. (1997) found that there is little evidence that the use of clinical guidelines produces significant changes in clinical outcomes in primary care [57].

There is only limited knowledge about the impact of guidelines on quality and the impact of the new Swedish P&R environment on use of medicines. This dissertation will focus on these two policy instruments and their effects on the use of preventive treatment with lipid-modifying and glucose-lowering medicines.

1.3.1. Guidelines

Regional and national clinical practice guidelines are developed by medical specialists, national authorities, and regional authorities as a guide to physician decision-making. HTA is an important cornerstone in the production of national guidelines to steer health care decision-making. The main aim and focus of the national guidelines are to steer towards an equal and cost-effective care across the country [58].

There are four national organizations in Sweden involved in producing and issuing guidelines and recommendations and making decisions that influence the use and quality of pharmaceuticals [53]: the Medical Products Agency (Läkemedelsverket/LMV), the Swedish Council on Health Technology Assessment (Statens Beredning för Medicinsk Utvärdering/SBU), the National Board of Health and Welfare (Socialstyrelsen/SoS), and the TLV. The LMV produces recommendations for pharmaceutical treatments, the SBU produces HTA reports and issues recommendations, the SoS produces and issues national guidelines on health care, and the TLV makes P&R decisions.
1.3.1.1. Lipid-modifying therapies

Dyslipidemia is one of the major risk factors for CVD and CHD [27, 59]. Low-density lipoprotein cholesterol (LDL-C) has been established as a key causative factor in the progression of CHD [60-62]. Independently of levels of LDL-C, there is an inverse association between high-density lipoprotein cholesterol (HDL-C) and increased risk for CHD [62-65] and CVD [66]. T2DM and CVD are associated with increased risk of metabolic syndrome, which includes dyslipidemia [67]. Dyslipidemia in metabolic syndrome is characterized by hypertriglyceridemia and low levels of HDL-C [68, 69]. Low levels of HDL-C have been shown to be predictive of and an independent risk factor for developing CHD [70-72].

Recommended thresholds for LDL-C and total cholesterol (TC) and normal levels of HDL-C and triglycerides (TGs) as per the Swedish guidelines are outlined in Box 1 [73].

Box 2. Swedish guidelines for treating dyslipidemia.

**Recommended lipid levels:**

<table>
<thead>
<tr>
<th>Lipid</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>TC</td>
<td>&lt;5.0 mmol/L (very high risk: &lt;4.5 mmol/L)</td>
</tr>
<tr>
<td>LDL-C</td>
<td>&lt;3.0 mmol/L (very high risk: &lt;2.5 mmol/L)</td>
</tr>
</tbody>
</table>

**Indications for increased risk:**

<table>
<thead>
<tr>
<th>Lipid</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>TGs</td>
<td>&gt;1.7 mmol/L</td>
</tr>
<tr>
<td>HDL-C</td>
<td>&lt;1.0 mmol/L (men), and &lt;1.3 mmol/L (women)</td>
</tr>
</tbody>
</table>

The average cholesterol level in the population in Sweden has decreased in recent decades, see Figure 5. A large cohort study in northern Sweden [74] showed that mean TC lipid levels decreased significantly during 1986-2004, from 6.4 to 5.8 mmol/l in men and 6.3 to 5.5 mmol/l in women aged 25-64 years, and from 6.4 to 5.5 mmol/l in men and 7.1 to 6.2 mmol/l in women in men and women aged ≥65 [75, 76].
from the Västerbotten Intervention Programme [77] has shown declining lipid levels in the population since the introduction of the new guidelines in 1999 [78]. However, from 2004 onwards there has been a tendency to an increase in mean TC lipid levels among both men and women [79].

Figure 5. Age-adjusted levels of total cholesterol in the population of northern Sweden, 25–64 years old, 1986–2004.

Adapted from Eliasson et al. 2006[75].

1.3.1.2. Glucose-lowering therapies

The risk of developing CVD is increased twofold to fourfold in patients with T2DM, independently of other concomitant risk factors [80]. Glycemic control in these patients reduces the risk of developing complications [81, 82]. International [83] and Swedish national guidelines recommend that glycated hemoglobin (HbA1c) level is used as a treatment target. The Swedish standard is a level of <6% on the Mono S scale [84, 85], which is comparable to the <7% standard used in the Diabetes Control and Complications Trial (DCCT) and the <52 mmol/mol threshold recommended by the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) [86]. Most patients require pharmacological treatment to reach these
treatment goals. Even so, only 50% of all T2DM patients in Sweden reach the goal of HbA1c <6% [87], with goal attainment varying widely between regions in the range of 40–60% [88].

However, while intensive glycemic control reduces the risk of microvascular complications and non-fatal myocardial infarction, it increases the risk of hypoglycemia [82]. Failure to achieve the treatment goals could, among other reasons, be due to poor adherence because of the side effects of certain antidiabetic treatments [89]. Hypoglycemia has been suggested to be the main limiting factor in achieving adequate glycemic control [90]. Furthermore, hypoglycemia episodes induce costs, the annual cost in Sweden of managing hypoglycemic events is estimated at around 50 million SEK [91].

T2DM is a progressive disease [81], and so most patients will sooner or later become candidates for an add-on treatment [84]. In the new international and Swedish national guidelines (introduced in 2010) [83-85], sulfonylureas (SUs) are recommended for use as a second-line treatment in patients not adequately controlled on metformin. Thus SUs are seen as an alternative to neutral protamine Hagedorn (NPH) insulin treatment, and although they are known to induce hypoglycemia [92, 93], they are recommended before newer treatments such as thiazolidinediones (glitazones), dipeptidyl peptidase-4 (DPP-4) inhibitors, and glucagon-like peptide-1 (GLP-1) analogues [84, 85].

The overall objective of diabetes treatment is to maintain good QoL while avoiding acute and long-term complications [94]. A study in France showed that hypoglycemia induced by oral antidiabetic agents has a negative effect on QoL [95]. A study of Swedish patients found similar results, but 43% of the patients were treated with insulin [96], why the results might not be appropriate to generalize to patients treated with oral therapies. There is, therefore, still limited knowledge of how QoL is affected in Swedish patients with T2DM in general; this was confirmed by a recent evaluation of the national guidelines [97]. In particular, there is a lack of
knowledge of how Swedish patients with T2DM treated with oral antidiabetic agents experience hypoglycemia.

This lack of knowledge could be due to a lack of clarity in the stated goal for QoL. While the objective of glucose control is a fairly clear goal, the objective of avoiding deteriorating QoL is somewhat vague and therefore difficult to evaluate. A TLV review states: “Acute serious events in T2DM are unusual, however even less serious symptoms caused by either hyper or hypoglycemia should be avoided to retain good quality of life” (freely translated into English) [98]. Swedish national guidelines also emphasize QoL: “In the clinical situation one has to make individual assessment of the remaining life expectancy and quality of life. In particular, the latter (QoL) requires care and responsiveness vis-à-vis the individual it concerns” (freely translated into English) [84].

1.3.2. Pricing and reimbursement

In 2002, the Swedish parliament passed a new pharmaceutical benefits reform aimed at promoting cost-effective use of publicly-financed pharmaceuticals and ensuring equal drug benefits throughout the country. Following the reform, HTA was introduced as a foundation for P&R decision making and the LFN was established as a new government body. As previously mentioned, the LFN was later transformed and renamed to the TLV after its responsibility was extended to include reimbursement decisions for dental care.

The establishment of the LFN/TLV produced significant changes in the P&R of pharmaceuticals in Sweden. The assigned task of the P&R agency was to make decisions on new prescription pharmaceuticals to be included in the public pharmaceutical benefits scheme, and to review all pharmaceuticals already included

3 Page 16.
4 Pages 14-15.
in this scheme [7, 99, 100]. The primary purpose of the establishment of TLV was to replace the former system that “automatically” subsidized pharmaceuticals with market authorization by a system that employed HTA coupled with economic efficiency criteria (i.e. marginal cost-effectiveness) and ethical principles for prioritization in health care as the basis for reimbursement [48], as stated in law. These ethical principles are: 1. human dignity, 2. need and solidarity, and 3. cost-effectiveness. The aim was to improve the rational and cost-effective use of medicines.

Economic evaluations which provide evidence on the cost-effectiveness of a product have since been a central foundation for the decisions made by the TLV. The guidelines and practices for these evaluations are of major importance for the whole functioning of the market for pharmaceuticals (see section 1.2.1.2.Guidelines in economic evaluations).

The universal coverage scheme in Sweden acts as a combined pharmaceutical subsidy and de facto nationwide price regulation mechanism for the subsidized products [6]. A company applies for reimbursement of a pharmaceutical at a given price, and TLV’s evaluation of whether the product is cost-effective is normally based on documentation enclosed in this application. The same principle also applies for TLV’s pharmaceutical reviews, which evaluate those pharmaceuticals that were included in the pharmaceutical benefits according to the old system. From its establishment until 2010, the TLV was following a priority plan for reviewing nearly 2,000 drugs included in the national reimbursement scheme prior to the new system, employing the same principles as in the new reimbursement system [99, 101, 102]. This plan was recently abandoned for a more flexible process and sequence for the reviews, where TLV can initiate reviews in any area at any time in order to improve the efficiency of the reviews [101].
1.3.2.1. Lipid-modifying therapies

The TLV review of the lipid-modifying market was presented in a report published in February 2009. Following this review, the new reimbursement scheme was implemented on 1 June 2009 [103]. The review concluded that regardless of the statin used, a decrease in LDL-C is correlated to the risk of CVD. Consequently, the reimbursement for each lipid-modifying medicine was continued, restricted, or halted on the basis of the medicine’s marginal cost-effectiveness on documented decrease in LDL-C. TLV estimated that the new reimbursement scheme could result in savings of 170 million SEK per annum (= €18 million at a rate of 1 SEK = €0.104, June 2011).

An evaluation of the initial effects of the review estimated that likely savings within the reimbursement scheme amounted to 47 million SEK (= €5 million) for the first 6 months, a large part of which was related to lower prices for generic simvastatin rather than changes in reimbursement status [104].

1.3.2.2. Glucose-lowering therapies

The TLV review of glucose-lowering therapies (GLT) was presented in a report published on 2 December 2009, which concluded that use of GLT in Sweden was cost-effective, with a few exceptions [101]. Consequently, all glucose-lowering therapies were assigned one of the following four reimbursement statuses in the new reimbursement scheme: retained, restricted, no reimbursement, or no reimbursement for new courses. This new reimbursement scheme was introduced on 1 March 2010 [105]. TLV estimated that the decisions made in the review could result in cost savings of at least 12 million SEK per annum [105] (=€ 1.3 million at a rate of 1 SEK = € 0.11, 5 November 2011).
An independent evaluation of the initial effects of the new GLT reimbursement scheme showed that savings at constant volumes based on data for the first six months following the new scheme were in line with those estimated by TLV [106].

### 1.4. Use of preventive medicines

#### 1.4.1. Lipid-modifying therapies

International and Swedish guidelines recommend control and management of dyslipidemia for primary and secondary prevention in patients at risk of CVD [58, 73, 107, 108]. There is wide documentation on the protective effects of lipid-modifying therapies (LMT), mostly statins, for various patient groups in clinical trials [61, 109], and on their cost-effectiveness for primary as well as secondary prevention [24, 110-112].

Statins are widely and increasingly used in many countries, though their use varies extensively. Use in Sweden is at an average level in comparison with other Nordic and western European countries [113, 114]. About 8.7% (816,000) of the population in Sweden in 2010 were dispensed a statin, an increase from 6.7% in 2006 [115]. The total number of patients treated with lipid-modifying drugs in 2010 was about 836,000 (98% receiving statins), an increase of about 32% since 2006, while the increase in defined daily doses (DDD) was about 55% over the same period [115].

There have been considerable price differences between patented and off-patent statin substances since the Swedish patent for Zocord (simvastatin) expired in 2003. Prices for the off-patent versions can now be about 90% lower, as is the case in many other countries [116], and since the patent expiration there has been a sharp increase in use defined in DDD and substantial decrease in costs, see Figure 6. While over 610,000 (83%) patients were treated with simvastatin and 100,000 (14%) were treated
with atorvastatin in 2008 in Sweden, these two drugs accounted for 30% and 60% of total costs, respectively [103]. Statins have therefore been a particular target for various types of cost containment measures [117-121], mostly through demand-side mechanisms enforced by law [122, 123].

Figure 6. Defined daily dose (DDD) and costs (Swedish crowns: SEK) per thousand inhabitants/day 2000-2008.

New restrictive regulations were introduced in Norway in 2005 and in Finland in 2006. Following these new regulations, about 40% of the users of the more expensive statins in Norway switched to simvastatin [117]. In Finland, 58% of those using atorvastatin and 49% of those using rosuvastatin before the restriction switched to a less expensive statin [118]. In both countries, the policies were considered successful in reducing the overall cost of statins [117, 118].

Therapeutic reference pricing strategies have not been proven conclusively successful as a cost containment tool [124]. In Hungary, such strategies caused increased use of higher doses of statins, which increased overall expenditure [119]. Including statins in the German reference pricing scheme resulted in total savings ranging from €94.4 million to €108.7 million in 2005, but also led to higher
contributory payments for patients, which might explain the higher discontinuation rates for patients initially treated with atorvastatin [121].

1.4.2. Glucose-lowering therapies

Use of glucose-lowering therapies has increased over time in many European countries, but at different rates and levels. In Sweden, the number of patients treated with GLT in 2010 was 372,000, an increase of 17% since 2006. Of these, 183,000 were treated with insulins and 265,000 with oral GLT, representing an increase of 15% and 19% respectively since 2006 [115]. In total, 76,000 patients were treated with both insulins and oral GLT during 2010, either at the same time or due to a change of therapy.

Until 2000 the use of insulin was highest in Sweden, in a comparison of ten European countries, while the use of oral GLT was on an average level [125]. The prevalence of T2DM has been estimated at around 3.5%-4.5% in Sweden [12, 126], and around 3% on average among European countries, ranging from 1.7% in the Netherlands to 4.2% in Germany [127]. Earlier findings suggest, however, that this variation is overestimated and due more to variation in factors related to definitions, detection, and registration, among others [128]. The variation in prevalence does not, therefore, fully explain the variation in use of GLT. Another factor that has been suggested to explain the variation is differences in reimbursement schemes [125]. Insulins are fully reimbursed for individuals in Sweden, the county councils being responsible for covering the co-payments, while the costs of oral GLT are covered by individuals within the regular co-payment scheme [129].
2. AIMS OF THE THESIS

The main purpose of this thesis was to analyze the impact of changes in reimbursement schemes and guidelines on use, costs, and quality of preventive treatment with lipid-modifying and glucose-lowering therapies.

The purposes and aims of the specific papers were:

Paper I: To compare use, costs, and switching behavior regarding LMT before and after the implementation of the new reimbursement scheme in June 2009.

Paper II: To estimate the prevalence of dyslipidemia and attainment of goal/normal lipid levels in patients treated with LMT.

Paper III: To compare use and costs of GLT before and after the implementation of the new reimbursement scheme in March 2010.

Paper IV: To evaluate the experience of hypoglycemia in patients treated with metformin in combination with SUs, and the impact on patients' QoL and level of worry about hypoglycemia.
3.METHODS AND MATERIALS

3.1. General design

A quantitative, deductive approach using an observational or quasi-experimental design was adopted for all four studies.

3.1.1. Observational studies

A basic distinction in quantitative research is that between experimental and non-experimental (observational) research. Experimental studies involve some type of intervention, while non-experimental or observational studies do not. In an observational study, the investigator observes and evaluates the results that occur without intervention. Randomized controlled trials are considered the most scientifically rigorous method for hypothesis testing, yielding high internal validity for the association between exposure and outcome [130, 131], due to the highly controlled settings in which they operate. This type of setting, however, is also a limitation when it comes to generalizing the findings to reflect real-life clinical practice; this is in contrast to observational studies. The performance of medicines in real-life clinical practice is of crucial importance to inform decision-makers about the effectiveness of a treatment [41].
3.1.2. Quasi-experimental studies

In quasi-experimental or experimental study designs, the investigator allocates or controls the exposure of interest in an attempt to isolate the effect of the exposure only; in this way, causal associations can be better established [130]. Quasi-experimental studies, like true experiments, involve an intervention. However, the quasi-experimental design lacks the randomization that is the signature of a true experiment [131]. Quasi-experimental designs are useful in guideline implementation research for evaluating the effects of interventions when it is difficult to randomize or identify an appropriate control group [132].

The three most commonly used designs in guideline implementation studies are uncontrolled before-and-after studies, time series designs, and controlled before-and-after studies [132].

Interrupted time series design is the strongest quasi-experimental approach for evaluating the longitudinal effects of interventions. Segmented regression analyses of interrupted time series data are often used to assess how an intervention changed an outcome of interest [133]. Segments in a time series are defined when the sequence of measures is divided into two or more portions at change points, with two parameters defining each segment: the level and the trend (or slope) [133]. The level is the value of the series at the beginning of a given time interval, and the trend is the rate of change of a measure during a segment.
3.2. Papers I-IV

Table 2. Overview of the design and methods of each study.

<table>
<thead>
<tr>
<th>Title</th>
<th>Paper I</th>
<th>Paper II</th>
<th>Paper III</th>
<th>Paper IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Title</td>
<td>Utilization and costs of lipid modifying therapies following health technology assessment for the new reimbursement scheme in Sweden</td>
<td>Prevalence of lipid abnormalities before and after introduction of lipid modifying therapy among Swedish patients with dyslipidemia (PRIMULA)</td>
<td>Utilization and costs of glucose lowering therapies following health technology assessment for the new reimbursement scheme in Sweden</td>
<td>Self-reported experience of hypoglycemia among adults with type 2 diabetes mellitus (Exhype)</td>
</tr>
<tr>
<td>Aims</td>
<td>The aim of this study was to compare utilization, costs and switching behavior in patients treated with LMT before and after the new reimbursement scheme.</td>
<td>To estimate the prevalence of dyslipidemia and attainment of goal/normal lipid levels in patients treated with lipid modifying therapy (LMT).</td>
<td>To compare utilization and costs of GLT for type 2 diabetes Mellitus (T2DM) before and after the implementation of the changed Reimbursement schemes</td>
<td>To evaluate the experience of hypoglycemia in patients treated with metformin in combination with sulphonylureas (SUs) and the impact on patients’ quality of life (QoL) and worry about hypoglycemia.</td>
</tr>
<tr>
<td>Methods and materials</td>
<td>A quasi-experimental study using data on dispensed LMT and costs from a database on dispensed individual prescriptions in Sweden. Segmentated regression analyses were used to assess utilization and costs of LMT.</td>
<td>Longitudinal retrospective observational study covering time periods before and after treatment. Data were collected from 1994-2007 electronic patient records in public primary healthcare centers in Uppsala County, Sweden.</td>
<td>This was a quasi-experimental study using data on dispensed GLT and costs from a database on dispensed individual based prescriptions in Sweden. Segmentated regression analyses were used to assess utilization and costs.</td>
<td>A national, cross-sectional, multicenter study. Patients with type 2 diabetes treated with metformin and SU dual therapy were recruited by 54 investigators between January 2009 and August 2009. The patients were asked to complete a QoL instrument, (EQ5D) and the Hypoglycemia Fear Survey (HFS-II) questionnaire.</td>
</tr>
</tbody>
</table>
3.2.1. Paper I

This was a quasi-experimental study [132] using a segmented time series [133] design to analyze the use and costs of LMT. The study consisted of two time periods: before and after the new reimbursement scheme (the intervention) was implemented.

Under the new reimbursement scheme, each drug was assigned to one of the following three reimbursement statuses: continued, restricted, or excluded, Table 3.

1. **Continued full reimbursement**: generic pravastatin and simvastatin.

2. **Restricted reimbursement**: atorvastatin (Lipitor) and rosuvastatin (Crestor) in higher strengths (>10 mg and >5 mg respectively) are reimbursed as a new treatment only if generic simvastatin has been tried and the patient has not reached the treatment objectives. Patients who have previously used atorvastatin 10 mg or rosuvastatin 5 mg should first have tried simvastatin before higher doses of atorvastatin and rosuvastatin may be prescribed with reimbursement. Ezetimibe is reimbursed if generic simvastatin has been tried and the patient has not achieved the treatment objectives, or if it has been established that the patient does not tolerate statins.

3. **Excluded from the reimbursement scheme**: atorvastatin 10 mg, rosuvastatin 5 mg, fluvastatin, pravastatin, cholestyramine, and branded simvastatin (Zocor) for all packages except 80 mg in packs of 49 tablets (this refers only to the patented Zocord 80 mg in 49 tablets pack, since this pack was deemed to have an acceptable price/tablet [134]).
Table 3. The new reimbursement status for respective products following the TLV review for LMT.

<table>
<thead>
<tr>
<th>Name of medicine</th>
<th>Name of substance</th>
<th>1. Continued</th>
<th>2. Restricted</th>
<th>3. Excluded</th>
</tr>
</thead>
<tbody>
<tr>
<td>Statins</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Generic pravastatin*</td>
<td>pravastatin</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pravachol</td>
<td>pravastatin</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Generic simvastatin*</td>
<td>simvastatin</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Zocor, 80 mg, 49 tabl</td>
<td>simvastatin</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lipitor, 10 mg atorvastatin</td>
<td>atorvastatin</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Lipitor, 10 mg</td>
<td>atorvastatin</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Crestor, 5 mg rosuvastatin</td>
<td>rosuvastatin</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Lescol, Lescol Depot fluvastatin</td>
<td>fluvastatin</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Cholesterol absorption inhibitors</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ezetimibe</td>
<td>Ezetimibe</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bile acid sequestrants</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lescol</td>
<td>colestipol</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Questran, Questran 1x</td>
<td>cholestyramine</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Bile acid sequestrants</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bezafibrate, Bezafibrate retard</td>
<td>bezafibrate</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lipanthyl</td>
<td>fenofibrate</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lipid + generic</td>
<td>fenofibrate</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Niacin acid</td>
<td>niacin acid</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Niacin acid and lamipiptan</td>
<td>niacin acid and lamipiptan</td>
<td>X</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Individual products and packages which contain any of these substances lose their reimbursement.

* These medicines are not reimbursed for the indication blood lipid disorder.

Drug dispensing data were collected from the Swedish prescribed drug register held by the National Board of Health and Welfare [115]. The register is described elsewhere [135], but in short, it contains data for all dispensed prescriptions covering the whole population of Sweden (9.5 million inhabitants). It contains patient-specific data (personal identifier, age, gender, place of residence) as well as drug data such as the Nordic article number (which provides the trade name, pharmaceutical form, strength, and package size), number of packages, Anatomical Therapeutic Chemical (ATC) code, amount in DDD [136], prescription category, reimbursement code, prescribing date, dispensing date, and price. It covers all prescribed drugs purchased at Swedish pharmacies, but not drugs used in hospitals or purchased over the counter, and it does not contain clinical information on diagnoses/indications for treatment. Use of LMT was defined in volumes, expressed in terms of thousand inhabitants per month (TIM) as number of patients/TIM or DDD/TIM. Costs were measured in SEK and all analyses were carried out for total costs (reimbursed expenditure and patient contributory payment) and converted to Euros (SEK, 1 SEK ≈ € 0.104, June 2011).
**Methods and materials**

Linear segmented regression analyses were used to analyze the changes in the levels and trends in use and costs before and after the intervention. Number of patients, DDD, and costs were entered as dependent variables. A dichotomous indicator variable for the intervention was entered as an independent variable in the regression models. The regression models allowed for a slope for the time period preceding the intervention and a slope and a level shift to account for the change after the intervention. Separate models were constructed for the total group and for each reimbursement category. Any shifts in level (intercept) or slope related to the regulation with p<0.05 were considered statistically significant.

Switching behavior was assessed as the number of individuals initially treated with atorvastatin 10 mg or rosuvastatin 5 mg (at least the two last consecutive dispensations but dispensation of other statin before the two subsequent dispensations possible) during a one year period prior to the intervention (May 2008-May 2009) and the first dispensation during a six-month period following the intervention. The same analyses were carried out for a reference period using a corresponding time period of one year before the intervention (May 2007-May 2008).

All analyses were performed using version 16.0 of the SPSS Statistical Package for Windows and version 9.1.3 of the SAS software package (SAS Institute Inc., North Carolina, USA).

**3.2.2. Paper II**

This was a longitudinal retrospective observational study covering time periods before and after LMT. The study consisted of a baseline period (15 months prior to initiation of LMT) and a follow-up period (12 months following LMT). Data were collected retrospectively (1994-2007) from electronic patient protocols using a search engine to scan patient protocols in 26 out of 30 public primary health care centers.
serving 77% of the total population in the county of Uppsala, Sweden (total population: 322,043 in 2007).

The study included patients >35 years of age whose lipid values indicated dyslipidemia, who had initiated LMT (ATC code C10: Lipid modifying agents) [136] between May 1994 and June 2006, and who had complete lipid profiles at baseline and at follow-up. Treatment gaps of up to 6 weeks were allowed during the follow-up period except for the first 6 weeks post index date (initiation of LMT). A total of 5,424 patients met the criteria and were included in the study.

Normal and goal lipid levels were defined according to Swedish guidelines (see section 1.3.1.1.Lipid-modifying therapies). Mixed dyslipidemia was defined as abnormal levels of more than one lipid fraction. High-risk groups were defined as those with CHD, T2DM without CHD, and 10-year CHD risk>20% without CHD or T2DM. Patients with T2DM and those with CHD were identified from the International Classification of Disease (ICD) diagnostic codes. Patients with 10-year CHD risk>20% were identified by calculating risk per Framingham Risk Score [137].

Descriptive analyses were performed to evaluate baseline patient characteristics and the prevalence of dyslipidemia and goal attainment, mixed dyslipidemia, and treatment patterns, using thresholds for dyslipidemia according to clinical guidelines. These analyses were carried out for the total study population as well as for subgroups. Chi-squared tests were used to detect significance in differences in proportions between groups at the level of \(p<0.05\) (two-tailed). Multivariate logistic regressions were used to evaluate factors associated with attainment of goal/normal lipid levels.
3.2.3. Paper III

This was a quasi-experimental study [132] using a segmented time series [133] design to analyze the use and costs of GLT in Sweden following the new reimbursement scheme. The study consisted of two time periods: before and after the new reimbursement scheme (the intervention) was implemented. We studied 38 separate months in the period between February 2008 and March 2011 (25 months before and 13 months after the intervention on March 1, 2010).

The TLV review of GLT included all drugs in group A10 of the ATC classification [138]. Under the new reimbursement scheme, each drug was assigned to one of the following four different reimbursement statuses: retained, restricted, excluded, and excluded for new courses of treatment, see Table 4.
Table 4. Reimbursement categories in the new reimbursement scheme for glucose-lowering therapies.

<table>
<thead>
<tr>
<th>Category</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Retained</strong></td>
<td>Insulins: Rapid-acting human insulin, rapid-acting insulin analogues, intermediate-acting human insulin (NPH), intermediate-acting insulin with rapid onset (2-step). Oral: Biguanides (generic metformin), SUs (Mindiab, generic glimepiride, generic glibenclamide, Amaryl).</td>
</tr>
<tr>
<td><strong>Restricted</strong></td>
<td>Insulins: For T2DM patients the coverage of long-acting insulin analogues, insulin glargine, and insulin detemir is restricted to patients for whom other insulin treatment is not sufficient to reach the treatment objectives due to recurring hypoglycemic episodes. (The restrictions did not apply for patients with type 1 diabetes.) Insulin detemir used to be restricted to patients with type 1 diabetes from 2004 until June 19, 2007, when the restriction was lifted [139]. Oral: Acarbose, rosiglitazone, pioglitazone, sitagliptin, vildagliptin, repaglinide, exenatide, and combinations of these with metformin, will only be reimbursed for patients who have first tried metformin, SUs, or insulin, or if these treatments are not suitable.</td>
</tr>
<tr>
<td><strong>Excluded</strong></td>
<td>Oral: Nateglinide (Starlix) is no longer covered by the benefit scheme. Glibenclamide sold under the trade name of Daonil is excluded while generic products with glibenclamide are retained. The combination of rosiglitazone and glimepiride is excluded from the reimbursement scheme, while the active substances as separate substances are retained.</td>
</tr>
<tr>
<td><strong>Excluded for new courses of treatment</strong></td>
<td>Oral: Glibenclamide (Glibenklamid Recip) is excluded for incident patients but retained for patients already treated with the drug.</td>
</tr>
</tbody>
</table>

The analyses were carried out on total effects from the intervention for oral and for insulin therapies respectively. Oral GLT were analyzed in total and for each of the four reimbursement statuses. Insulin therapies were analyzed in total and for reimbursement statuses ‘retained’ and ‘restricted’.
Methods and materials

As in Paper I, drug dispensing data were collected from the Swedish prescribed drug register held by the National Board of Health and Welfare [115].

Use of GLT was defined as volumes expressed as number of patients/TIM. We used a cut-off age of >40 years at the time of dispensation as a proxy for patients with T2DM, since indications are not available in the registry and the onset of T2DM usually occurs in patients >40 years [126]. Costs were measured in SEK and all analyses were carried out for total costs (reimbursed expenditure and patient co-payment). We converted to Euros using current exchange rates (1 SEK = € 0.11, 5 November 2011).

Linear segmented regression analyses were used to analyze the changes in the levels and trends in use and costs before and after the intervention. Number of patients and costs were entered as dependent variables. A dichotomous indicator variable for the intervention was entered as an independent variable in the regression models. The regression models allowed for a slope for the time period preceding the intervention and a slope and a level shift to account for the change after the intervention. Separate models were fitted for oral GLT and for insulin-based GLT in total and for each reimbursement category. Shifts in level (intercept) or slope related to the intervention with $p<0.05$ were considered statistically significant.

Total costs were computed one year before (March 2009-February 2010) and one year after (March 2010-February 2011) the new reimbursement scheme was implemented, and the results were used to analyze cost savings following the intervention.

All analyses were performed using version 16.0 of the SPSS Statistical Package for Windows and version 9.1.3 of the SAS software package (SAS institute Inc., North Carolina, USA).
3.2.4. Paper IV

This was a cross-sectional, multicenter study. Patients were recruited by their general practitioner (GP). After consenting to participate in the study, patients received a self-administered questionnaire. Data on patient characteristics and medical record data were entered into an online form by the physician or a research nurse. A sample of GPs and diabetologists from 54 sites in Sweden recruited patients consecutively during their usual GP visit between January 2009 and August 2009. Patients with T2DM aged 35 years or older, male or female, on treatment with metformin and SU for the last six months were enrolled. Medical data were collected from the patient’s records.

The patients were asked to complete questionnaires covering QoL and worry about hypoglycemia during the past 6 months, demographics, and experience of hypoglycemia. The specific questionnaires used were Experience of Low Blood Sugar, EuroQol-5 Dimensions (EQ-5D), and the Hypoglycemia Fear Survey (HFS-II). The form concerning experience of low blood sugar (hypoglycemia) has been used in previous studies [95] and contains 10 items on the frequency and seriousness of hypoglycemic events in the patient’s history. Mild symptoms of low blood sugar were defined as causing “little or no interruption of your activities, and you didn’t feel you needed assistance to manage symptoms”, moderate symptoms caused “some interruption of your activities, but [you] didn’t feel you needed assistance to manage symptoms”, severe symptoms were described as “[you] felt that you needed the assistance of others to manage symptoms (for example, to bring you food or drink)”, and very severe symptoms “needed medical attention (for example, called an ambulance, visited an emergency room or hospital, or saw a doctor or nurse)”.

QoL was evaluated with EQ-5D, a generic instrument for use as a measure of health outcome covering the following dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression [140]. The EQ-5D consists of 5 items scored on a 3-point Likert scale plus a visual analogue scale (VAS). Summary score
Methods and materials

calculated from the responses ranges from 0 to 1, where 1 is perfect health and 0 is death. Scores were weighted using published weights from the UK population [141]. Worry about hypoglycemic symptoms was quantified using the Worry subscale of HFS-II [142, 143]. This subscale consists of 18 items scored on a 5-point Likert scale ranging from 0 (never) to 5 (very often). Scores on the worry subscale range from 0 to 72, with 0 representing the least worry.

Descriptive statistics were computed for all quantitative and qualitative variables. Hypoglycemia was dichotomized into none/mild or moderate/severe/very severe. Between-group comparisons on continuous variables were carried out using a t-test (or ANOVA if more than 2 groups) or the Mann-Whitney-Wilcoxon test (or Kruskal-Wallis if more than 2 groups) if the requirements for the t-test were not met. For categorical variables, the comparisons between groups were carried out using a Chi squared test, or a Fisher exact test if the requirements for the Chi squared test were not met. Age-adjusted p-values were calculated using ANCOVA for continuous variables and Cochran's Mantel-Haenszel for categorical variables. A p-value <0.05 was considered statistically significant.
4. RESULTS

4.1. Lipid-modifying therapies

4.1.1. Use and costs of lipid-modifying therapies

Results from the regression analyses on the number of patients/TIM treated with LMT before and after the intervention are shown in Figure 7 A-D. Looking at total LMT, before the intervention there was a slightly increasing trend in number of patients/TIM (p=0.0007) (Figure 7 A), with no statistically significant differences following the intervention. In the “continued” category (Figure 7 B), the number of patients/TIM was slightly increasing before the intervention (p=0.0002), with no statistically significant differences in level or trend following the intervention. The “restricted” category (Figure 7 C) also showed an increase prior to the intervention (p=0.002), and there was a statistically significant increase in level following the intervention (p=0.0336). Finally, in the “excluded” category (Figure 7 D), the trend was slightly negative before intervention (p=0.0001) and there was a negative shift in level following the intervention (p<0.0001).
Results

Figure 7 A-D. Segmented regression analyses of number of patients/1000 inhabitants treated with LMT in all and in respective reimbursement categories before and after implementation of the intervention.

Switching behavior for all patients and for a subgroup of patients with diabetes (patients treated with glucose-lowering drugs) initially treated with atorvastatin 10 mg during a reference period and the period after the intervention is shown in Table 5.

Table 5. Switching of all patients and patients with diabetes initially treated with atorvastatin 10 mg, reference period and period after introduction of the new reimbursement scheme.

<table>
<thead>
<tr>
<th>Initial treatment</th>
<th>10 mg atorvastatin</th>
<th>Diabetes coprescription</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Period before</td>
<td>Period after</td>
</tr>
<tr>
<td></td>
<td>n=38443</td>
<td>n=32751</td>
</tr>
<tr>
<td>Remain on initial treatment</td>
<td>87.3% (87.1 - 87.6)</td>
<td>20.6% (20.2 - 21.0)</td>
</tr>
<tr>
<td>Switch to higher dose of initial treatment</td>
<td>1.2% (1.1 - 1.3)</td>
<td>19.8% (19.4 - 20.2)</td>
</tr>
<tr>
<td>Switch to simvastatin 10 mg</td>
<td>0.3% (0.3 - 0.4)</td>
<td>6.5% (6.3 - 6.7)</td>
</tr>
<tr>
<td>Switch to simvastatin 20/40/80 mg</td>
<td>1.2% (1.1 - 1.3)</td>
<td>29.3% (28.9 - 29.8)</td>
</tr>
<tr>
<td>Switch to other</td>
<td>0.4% (0.4 - 0.5)</td>
<td>3.5% (3.3 - 3.7)</td>
</tr>
<tr>
<td>Discontinuation</td>
<td>9.4% (9.2 - 9.7)</td>
<td>20.2% (19.9 - 20.6)</td>
</tr>
</tbody>
</table>
An alternative view is shown in Figure 8. The proportion of patients initially treated with atorvastatin who remained on the same strength following the intervention was 21%, while the corresponding figure for the reference period was 87%. Of all patients, 20% switched to higher doses of atorvastatin following the intervention compared to 1% in the reference period. Switching to higher doses (20/40/80 mg) of simvastatin from atorvastatin 10 mg was increased from 1% to 30% following the intervention. In the reference period, 10% of patients discontinued treatment, while the corresponding figure following the intervention increased to 20%.

Figure 8. Switching of patients initially treated with 10 mg atorvastatin before and after the introduction of the new reimbursement scheme.
Results

Costs

Results from the regression analyses are shown in Figure 9 A–D. In total, the costs/TIM decreased significantly following the intervention by about 1,122 SEK/TIM (=€0.12/TIM) (p<0.0001). This corresponds to a total saving of 125 million SEK/year (=€13 million/year) (figures not shown). This was predominately reflected in the “no reimbursement” category (p<0.0001) (Figure 9 D). In the “restricted reimbursement” category, neither level nor trend showed a statistically significant difference following the intervention (Figure 9 C).

Figure 9 A-D. Segmented regression analyses of total cost/1000 inhabitants in all and in respective reimbursement categories before and after implementation of the intervention.

In summary, the new reimbursement scheme had a dramatic effect on the use of LMT. Patients initially treated with low doses of statins that were eventually excluded from the reimbursement scheme, switched to higher doses or discontinued to a much greater extent compared to a reference period. However, the new reimbursement scheme had only a moderate decreasing effect on costs, and the expected savings were not realized.
4.1.2. Quality aspects of lipid-modifying therapies

Among the 5,424 patients included, the prevalence of dyslipidemia (≥1 lipid abnormality) was 100% by definition at baseline, and 82% at follow-up. At baseline, 60% had elevated LDL-C combined with low HDL-C and/or elevated TGs, while the corresponding figure at follow-up was 36%. Low HDL-C and/or elevated TGs at follow-up remained at 69% for patients with T2DM, 50% among patients with CHD, and 66% among patients with 10-year CHD risk >20%. At baseline, there were large differences between different high risk groups in terms of prevalence of elevated TGs, low HDL-C, and mixed dyslipidemia, while no major differences were seen concerning elevated TC or LDL-C. The most prominent differences were in the prevalence of dyslipidemia in the group with T2DM compared to those with CHD. At follow-up, differences in TC and LDL-C were most prominent in the group with 10-year CHD risk >20%, where they persisted in about 70%. The prevalence of elevated TGs, low HDL-C, and combinations decreased modestly and persisted to a greater extent in the groups with T2DM and with 10-year CHD risk >20%, Table 6.

Table 6. Prevalence of dyslipidemia at baseline (BL) and follow-up (FU) by riskgroups and p-values for comparison of proportions.

<table>
<thead>
<tr>
<th></th>
<th>T2DM (n = 1280)</th>
<th>CHD (n = 528)</th>
<th>10-year CHD risk &gt; 20%</th>
<th>Difference (T2DM vs CHD)</th>
<th>P-value</th>
<th>Difference (T2DM vs 10-year CHD risk &gt; 20%)</th>
<th>P-value</th>
<th>Difference (CHD vs 10-year CHD risk &gt; 20%)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elevated TC</td>
<td>BL  51%</td>
<td>FU  67%</td>
<td>BL  40%</td>
<td>FU  64%</td>
<td>&lt;0.001</td>
<td>0.51</td>
<td>0.381</td>
<td>0.058</td>
<td>0.251</td>
</tr>
<tr>
<td>Elevated LDL-C</td>
<td>92%  92%</td>
<td>2%  6%</td>
<td>92%  65%</td>
<td>92%  65%</td>
<td>&lt;0.001</td>
<td>0.211</td>
<td>&lt;0.0001</td>
<td>0.208</td>
<td>0.052</td>
</tr>
<tr>
<td>Elevated TGs</td>
<td>72%  59%</td>
<td>4%  6%</td>
<td>72%  84%</td>
<td>72%  84%</td>
<td>&lt;0.001</td>
<td>0.305</td>
<td>0.054</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Low HDL-C</td>
<td>47%  42%</td>
<td>35%  2%</td>
<td>47%  51%</td>
<td>47%  51%</td>
<td>&lt;0.001</td>
<td>0.223</td>
<td>0.043</td>
<td>&lt;0.0001</td>
<td>0.017</td>
</tr>
<tr>
<td>Low HDL-C and/or elevated TGs</td>
<td>80%  69%</td>
<td>60%  50%</td>
<td>80%  63%</td>
<td>80%  63%</td>
<td>&lt;0.001</td>
<td>0.345</td>
<td>0.284</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Elevated LDL-C and low HDL-C and/or elevated TGs</td>
<td>73%  41%</td>
<td>53%  32%</td>
<td>73%  41%</td>
<td>73%  41%</td>
<td>&lt;0.0001</td>
<td>0.157</td>
<td>0.045</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Elevated LDL-C and low HDL-C and/or elevated TGs</td>
<td>100%  88%</td>
<td>100%  83%</td>
<td>100%  89%</td>
<td>100%  89%</td>
<td>0.123</td>
<td>0.342</td>
<td>0.481</td>
<td>0.008</td>
<td></td>
</tr>
</tbody>
</table>

Results from multivariate regression models (Table 7) to determine attainment of goal/normal levels in TC, LDL-C, TGs, and HDL-C suggested a slight positive association between age and attainment of goal/normal levels in all lipid parameters.
Results

Female compared to male gender was associated with significantly lower odds of attaining normal levels in HDL-C (odds ratio [OR]: 0.07; 95% confidence interval [CI]: 0.05-0.08). Patients with T2DM had significantly lower odds of attaining lipid goals/normal levels in any lipid parameter than patients without T2DM. Patients with a history of CHD had significantly lower odds of reaching goal/normal level in TC or LDL-C, compared with patients without history of CHD. Baseline lipid values were strongly associated with attainment of goal/normal levels in all lipid parameters. For each 0.1 mmol/l increase in TC or LDL-C at baseline, the odds of attaining goal levels decreased by about 7% for TC and for LDL-C respectively (OR: 0.93; 95% CI: 0.92-0.93) and (OR: 0.93; 95% CI: 0.92-0.94). For each 0.1 mmol/l increase in TG at baseline, the odds of attaining normal levels were about 15% lower. Baseline HDL-C values were strongly and positively associated with attainment of normal levels, as the odds increased by more than 200% for each 0.1 mmol/l increase in baseline value (OR: 2.15; 95% CI: 2.06-2.25). Duration of statin therapy was associated with lower odds of attaining goal/normal levels of TC, LDL-C, and TG. For each year on statin treatment, the odds of attaining TC or LDL-C goal were about 15% lower and the odds of attaining normal levels of TGs were 6% lower.
Table 7. Logistic regressions on goal/normal lipid level attainment.

<table>
<thead>
<tr>
<th>Dependent variable</th>
<th>Odds ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>TC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>1.02</td>
<td>1.01-1.03</td>
</tr>
<tr>
<td>Gender</td>
<td>0.99</td>
<td>0.78-1.21</td>
</tr>
<tr>
<td>T2DM</td>
<td>0.73</td>
<td>0.63-0.85</td>
</tr>
<tr>
<td>CHD</td>
<td>0.55</td>
<td>0.45-0.69</td>
</tr>
<tr>
<td>TC</td>
<td>0.93</td>
<td>0.92-0.94</td>
</tr>
<tr>
<td>Time on statin</td>
<td>0.85</td>
<td>0.83-0.87</td>
</tr>
<tr>
<td>LDL-C</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>1.02</td>
<td>1.01-1.02</td>
</tr>
<tr>
<td>Gender</td>
<td>1.20</td>
<td>1.06-1.36</td>
</tr>
<tr>
<td>T2DM</td>
<td>0.75</td>
<td>0.65-0.85</td>
</tr>
<tr>
<td>HDL-C</td>
<td>0.53</td>
<td>0.42-0.64</td>
</tr>
<tr>
<td>Time on statin</td>
<td>0.86</td>
<td>0.84-0.88</td>
</tr>
<tr>
<td>TGs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>1.01</td>
<td>1.01-1.02</td>
</tr>
<tr>
<td>Gender</td>
<td>1.05</td>
<td>0.92-1.20</td>
</tr>
<tr>
<td>T2DM</td>
<td>0.63</td>
<td>0.73-0.86</td>
</tr>
<tr>
<td>TGs</td>
<td>0.94</td>
<td>0.84-0.95</td>
</tr>
<tr>
<td>Time on statin</td>
<td>0.94</td>
<td>0.92-0.97</td>
</tr>
<tr>
<td>HDL-C</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>1.01</td>
<td>1.00-1.02</td>
</tr>
<tr>
<td>Gender</td>
<td>0.70</td>
<td>0.07-0.08</td>
</tr>
<tr>
<td>T2DM</td>
<td>2.15</td>
<td>2.06-2.25</td>
</tr>
<tr>
<td>HDL-C</td>
<td>1.02</td>
<td>1.01-1.03</td>
</tr>
</tbody>
</table>

TC = total cholesterol, LDL-C = low-density lipoprotein, TG = triglycerides, HDL-C = high-density lipoprotein. The basic model included age and gender. Smoking, hypertension, baseline lipid values, history of diabetes, history of CHD and time on statin therapy (years). Insignificant variables were then stepwise excluded. Age, gender and time on statin are considered important to keep in model even if non-significant in some models. Gender: Male = 1 (female have higher odds to attaining LDL-C goals and lower odds for attaining goals of HDL-C compared to males). Risk factors: T2DM = 1, no T2DM = 0. Having CHD = 1, No CHD = 0 (Example: having T2DM is associated with lower odds of attaining goal in any lipid parameter and having CHD is associated with lower odds of attaining goals in TC and LDL-C).

In summary, we found that the majority of patients (98%) were treated with statins, and 40% of the patients attained goal levels of LDL-C but only 18% attained goal/normal levels on all three lipid parameters. Improvement in TGs was moderate. Low HDL-C persisted, showing only modest improvement following therapy, and this was most notable in patients with T2DM. These findings show that treatment patterns were fairly well in line with treatment guidelines concerning LDL-C, but less in line in treatment of other lipid parameters.
4.2. Glucose-lowering therapies

4.2.1. Use and costs of glucose-lowering therapies

Use of glucose-lowering therapies

*Insulins*

Results from the regression analyses of number of patients/TIM treated with insulin-based GLT before and after the intervention are shown in Figure 10 A–C. There was an accelerated increasing trend in total number of patients/TIM treated with insulins following the intervention (p=0.0027) (Figure 10 A); this was the case for insulins with retained reimbursement as well as for restricted insulins (Figure 10 B–C).

Figure 10 A–C. Segmented regression analyses of number of patients/1000 inhabitants treated with insulin in total and in respective reimbursement categories before and after implementation of the intervention.
Results

Oral glucose-lowering therapies

Results from the regression analyses of number of patients/TIM treated with oral GLT before and after the intervention are shown in Figure 11 A-E. There were no significant differences when the total group of drugs was considered (Figure 11 A). There was a negative trend in number of patients/TIM treated with products with restricted reimbursement ($p<0.0035$) (Figure 11 C) and a negative shift in products that were excluded from the reimbursement scheme following the intervention ($p<0.0001$) (Figure 11 D).

Figure 11 A-E. Segmented regression analyses of number of patients/1000 inhabitants treated with oral glucose lowering therapies in total and in respective reimbursement categories before and after implementation of the intervention.
**Results**

**Costs**

Total costs in the year following the intervention (March 2010–February 2011) amounted to 1.1 billion SEK (≈€ 121 million), an increase of 58 million SEK (≈€6.4 million) compared to a reference period one year before the intervention (March 2009–February 2010). Total costs for insulins increased by 60 million SEK (≈€ 6.6 million), while costs for oral GLT decreased by 2 million SEK (≈€ 0.22 million) (data not shown).

**Insulins**

Regression analyses showed accelerated increasing trends in total costs (Figure 12 A), both for insulins with retained reimbursement and for insulins with restricted reimbursement, following the intervention. There was an increase of 100 SEK/TIM (≈€ 11/TIM); of this, 60 SEK (≈€6.6) was for products with retained reimbursement and 40 SEK (≈€4.4) was for restricted products (data not shown).

**Oral glucose-lowering therapies**

There were negative trends in costs for oral GLT in total (Figure 12 B) and for drugs which were retained or restricted in the new reimbursement scheme. There was a negative level shift in products excluded from the reimbursement scheme (p<0.0001) (data not shown).
Results

Following the changed reimbursement status, there was an accelerated increasing trend in the number of patients treated with restricted or retained insulins, as well as in costs for insulin-based GLT. No impact was detected in the total number of patients treated with oral GLT, but there was a slightly negative trend in total costs for oral GLT following the intervention.

In summary, we found the new reimbursement scheme for GLT had a minor impact on use and costs of oral GLT. Despite restricted reimbursement for patients with T2DM, the use of insulin-based GLT and related costs increased faster following the intervention.
4.2.2. Quality aspects of glucose-lowering therapies

The study included a total of 430 Swedish adult patients with T2DM treated with a combination of metformin and SUs. Their mean age was 69, and 60% of them were men, Table 8. All patients were treated with metformin, with a mean daily dose of 1862 mg, and SUs (glibenclamid [64%], glimepirid [10%], and glipizid [26%]).

The goal of <6% HbA1c was attained by 40% of the total population, with 39% of patients reporting no or only mild hypoglycemia, and 48% of patients reporting experience of moderate or more severe hypoglycemia (p=0.14 between the latter two groups). Mean HbA1c was lower in the group reporting moderate or worse hypoglycemia compared to patients reporting no or mild hypoglycemia (6.1 mmol/l and 6.4 mmol/l respectively, p=0.03), Table 8.

| Table 8. Patient characteristics in all patients and study groups with no/mild hypoglycemia and moderate/worse hypoglycemia, mean (SD), percentage. |
|---|---|---|---|---|---|
| Total (n = 412) | No/mild (n = 332) | Moderate/worse (n = 80) | p-Value* |
| Age (years), mean (SD) | 69.0 (5.5) | 69.8 (9.1) | 64.6 (9.9) | 0.001 |
| Male gender | 61% | 60% | 63% | 0.38 |
| Smoking | | | | |
| Never smoked | 41% | 41% | 35% | 0.52 |
| Smoking | 12% | 12% | 11% | 0.64 |
| Diabetes duration > 7 years | 71% | 71% | 71% | 0.51 |
| Microvascular events | 20% | 20% | 14% | 0.50 |
| Macrovascular events | 33% | 32% | 33% | 0.32 |
| Major medical events | 23% | 24% | 22% | 0.87 |
| Medical procedures | 10.7% | 11.5% | 7.5% | 0.67 |
| Glycated hemoglobin (HbA1C) [mmol/l] < 6% | 40% | 39% | 48% | 0.14 |
| Fasting blood glucose [mmol/l], mean (SD) | 8.4 (2.2) | 8.5 (2.3) | 7.9 (2.0) | 0.08 |
| Glycated hemoglobin (HbA1C) [mmol/l] mean (SD) | 6.3 (0.0) | 6.4 (0.8) | 6.1 (0.0) | 0.03 |
| BMI (kg/m²), mean (SD) | 28.7 (4.3) | 28.8 (4.4) | 28.5 (4.3) | 0.23 |
| Triglycerides [mmol/l], mean (SD) | 1.8 (0.8) | 1.8 (0.9) | 1.7 (0.9) | 0.21 |
| Cholesterol HDL [mmol/l], mean (SD) | 1.2 (0.4) | 1.2 (0.4) | 1.2 (0.3) | 0.53 |
| Cholesterol LDL [mmol/l], mean (SD) | 2.6 (0.8) | 2.6 (0.8) | 2.6 (0.7) | 0.64 |
| Diastolic blood pressure [mmHg], mean (SD) | 76.3 (13.1) | 76.3 (13.1) | 75.5 (9.7) | 0.04 |
| Systolic blood pressure [mmHg], mean (SD) | 137.1 (15.8) | 137.8 (16.3) | 134.4 (14.6) | 0.30 |

* Age adjusted.

In the total population, 34% reported that they had experienced hypoglycemia, with 19% experiencing moderate or worse hypoglycemia (17%, 1%, and 1% experienced moderate, severe, and very severe hypoglycemia, respectively). Experience of moderate or worse hypoglycemia was associated with a lower QoL measured by EQ-
5D summary scores (lower EQ-5D scores indicate lower QoL). Both the weighted and the unweighted EQ-5D summary scores were lower in the group reporting moderate or worse hypoglycemia than in the group with no/mild hypoglycemia (weighted: 0.81 vs. 0.88, p<0.001; unweighted: 0.75 vs. 0.83, p<0.001). The VAS score was lower for the group reporting moderate or worse hypoglycemia than for the group with no/mild hypoglycemia (0.71 vs. 0.76, p<0.01), Table 9.

Table 9. EQ5D scores, weighted and unweighted, visual analogue (VAS) scores and HFS-II worry score, mean (SD) in all patients and in group with no/mild and moderate or worse hypoglycemia.

<table>
<thead>
<tr>
<th></th>
<th>All patients (n = 430)</th>
<th>No/Mild (n = 332)</th>
<th>Moderate/worse (n = 88)</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>EQ-5D summary score-weighted</td>
<td>0.87 (0.2)</td>
<td>0.88 (0.18)</td>
<td>0.81 (0.26)</td>
<td>0.001</td>
</tr>
<tr>
<td>EQ-5D summary score-unweighted</td>
<td>0.83 (0.22)</td>
<td>0.83 (0.21)</td>
<td>0.75 (0.26)</td>
<td>0.001</td>
</tr>
<tr>
<td>EQ-5D Visual analogue scale (VAS) score</td>
<td>0.75 (0.17)</td>
<td>0.76 (0.16)</td>
<td>0.71 (0.18)</td>
<td>0.014</td>
</tr>
<tr>
<td>HFS-II Worry score</td>
<td>5.66 (0.99)</td>
<td>4.93 (0.55)</td>
<td>7.96 (10.93)</td>
<td>0.009</td>
</tr>
</tbody>
</table>

*p-Value adjusted for difference between group with no/mild and moderate to worse hypoglycemia.

The proportion of patients reporting problems in the EQ-5D dimensions (mobility, self care, usual activities, pain/discomfort, anxiety/depression) are shown in Figure 13. More patients in the group with moderate or worse hypoglycemia reported problems in the dimensions “pain/discomfort” and “anxiety/depression” compared to the group with no/mild hypoglycemia symptoms (pain/discomfort: 56% vs. 43%, p<0.01; anxiety/depression: 36 vs. 22%, p<0.05).
Results

Figure 13. Proportion (%) of patients with no/mild and moderate or worse hypoglycemia indicating problems per EQ-5D dimension.

QoL measured by the VAS score decreased, while fear of hypoglycemia increased, with increasing severity of experienced hypoglycemia, Figure 14 and Figure 15.

Figure 14. EQ-5D VAS score by severity of hypoglycemia experienced.
In summary, only 40% of Swedish adult patients with T2DM treated with a combination of metformin and SUs attained the goal of <6% HbA1c, and patients reporting moderate or more severe hypoglycemia were found to have lower QoL than patients reporting no or mild hypoglycemia.
5. DISCUSSION

5.1. Main findings

5.1.1. Lipid-modifying therapies

About 836,000 patients in Sweden in 2010 were treated with lipid-modifying therapies, predominantly statins (98%). We found that changes following the new reimbursement scheme had a large effect on the use of LMT. Patients initially treated with low doses of statins that were eventually excluded from the reimbursement scheme switched to higher doses or discontinued to a much greater extent in a period following the new reimbursement scheme compared to a reference period. The new reimbursement scheme had a moderate decreasing effect on costs, but the expected savings were not realized.

The primary purpose of the reformed P&R system in Sweden is to improve the rational and cost-effective use of medicines. The TLV review of the lipid-modifying market concluded that regardless of the statin used, a decrease in LDL-C is correlated to the risk of CVD [103]. Consequently, the reimbursements for all lipid-modifying drugs were continued, restricted, or halted on the basis of their marginal cost-effectiveness on documented decrease in LDL-C. According to our findings, this approach accelerated the effect of reducing use of lower doses of atorvastatin and rosuvastatin, and increased use of generic simvastatin; however, it was paired with potentially less desirable effects related to switching behavior and discontinuation.

More patients initially treated with atorvastatin 10 mg and rosuvastatin 5 mg switched to higher doses. Similar results were shown in Hungary and in Germany,
where use of higher doses of statins was increased following the introduction of therapeutic reference pricing [119, 121]. Increased doses could be beneficial if therapeutically motivated, but high doses are also associated with more side effects [144, 145]. However, neither study can exclude the possibility that patients split the higher-dose tablets to spread their use over more than one day, for example using one 40 mg tablet split in half over two days instead of using two whole 20 mg tablets, a strategy which is sometimes used to reduce costs [146]. Switching to higher doses prior to the intervention could also have been influenced by the new treatment guidelines issued in 2008 [58], where the use of patented statins to attain target levels of LDL-C was recommended for secondary prevention in high-risk patients, as well as by the increased awareness of treatment objectives induced by the coming intervention. It has further been shown that guidelines accompanied by a change in reimbursement rules had a significant influence on the prescribing of lipid-lowering drugs [11].

Total costs decreased following the intervention despite increased volumes, but the expected savings were not fully realized. In addition, the calculated savings might be overestimates, as they do not take into account any long-term effects on costs of other health care resources that might be caused by the policy, such as costs for GP visits when patients switch, or costs for managing morbidity as a consequence of discontinuation. This is a limitation of the studies in the present thesis as well as other similar studies [117, 118]. On the other hand, evaluation of the health impact of a policy is more important where drugs are not interchangeable [10], which is not the case in LMT.

A full cost analysis should account for the total transition and other costs related to the new reimbursement scheme. It should also be evaluated against the accumulated savings generated over time, which may be substantial. The long-term effectiveness of lipid-lowering drugs in clinical practice is therefore of major interest, and is the subject of another ongoing project [147]. On the other hand, in this specific case, because the Swedish patent for atorvastatin expires during 2011, the savings
associated with low-dose atorvastatin over time might be limited if the price for generic atorvastatin was to follow that of generic simvastatin.

Economic evaluations, as employed in current practice in Sweden, use a static approach in cost-effectiveness analyses; they do not include assessment of products using data on the total life cycle of a particular treatment. This approach might not be an efficient resource allocation tool over time [148]. Lindgren et al. showed that if the cost-effectiveness data for statins were re-estimated taking into consideration the current availability of generics, the results would indicate savings for health care systems; the cost savings from reductions in events are greater than the cost of the drug [111], creating large social benefits over time. Producer surplus will only last for the limited time until patent expiration, while the social net benefits will not only increase with a reduction in price, but will also continue over a long time frame. The producer appropriated 20–43% of the value during the on-patent period, a figure dropping to 1% following loss of exclusivity. The total producer surplus between 1987 and 2018 will be 2–5% of the total social surplus. The major part of the social surplus generated comes from the value of improved quality-adjusted survival. The monetary value of the total surplus was estimated at between 2,368 and 1,135 million euros per million inhabitants, based on value of statistically saved life and QALY respectively. A review by Ward et al. of the cost-effectiveness of statins acknowledged the influence of prices on cost-effectiveness, as the analyses were pointed out as being sensitive to the cost of statins; the authors therefore advocated for reviewing the cost-effectiveness in the light of any significant changes in the price of statins [24]. In contrast to static efficiency, a dynamic approach, where the future value of a pharmaceutical is considered, is a more efficient criterion for resource allocation [148]. Another method that could be considered to satisfy the criterion of dynamic efficiency is to employ an anticipated average price of a pharmaceutical over its total life cycle for CEA, based on both the price of a product during the patented time and its price after patent expiration.
Due to increasing discontinuations and switching to higher doses, and the long term impact this might have on health outcomes and costs over time, we do not consider it possible to clearly judge if use of lipid-modifying therapies was improved following the new reimbursement scheme. It has been suggested that soft demand-side policies might be a more effective tool to promote a cost-effective use of drugs, since more restrictive regulations might lead to unintended effects [54].

**Quality aspects**

Our results show that in terms of the guidelines, about 40% of the patients attained goals in LDL-C following treatment, but only 18% attained goals/normal levels in all three lipid parameters. Improvement in TGs was moderate, and low HDL-C persisted, showing only modest improvement following therapy; this was most notable in patients with T2DM, which could be explained by the limited use of LMT targeting lipid parameters other than LDL-C.

Studies have shown that LMT targeting multiple lipid abnormalities provides additional benefits beyond statin monotherapy, where niacin was considered to be the most effective HDL-C modifying agent available [149, 150]. When used alone or in combination with other LMT, niacin has been associated with a significant reduction in cardiovascular events [151-153]. On the other hand, a recent study showed that there was no incremental clinical benefit from addition of niacin to statin ± ezetimibe therapy in patients at target LDL-C with established, non-acute, atherosclerotic cardiovascular disease, despite significant improvements in HDL-C and triglyceride levels. This creates doubt about the usefulness of niacin in reducing residual risk [154].

In the logistic regression analysis, we found duration of statin therapy to be negatively associated with attainment of goal/normal levels. For each additional year on statin treatment, the odds of attaining LDL-C goal decreased by about 10% (OR: 0.86; 95%CI: 0.84-0.87). This could indicate lower efficacy with increasing time on treatment; however, better medication possession ratio was found to be associated
Discussion

with a better goal attainment in TC and in LDL-C [155]. Half of all patients on statin treatment discontinue the medication by the end of the first year [156]. Our findings might be influenced by factors related to patient compliance with treatment and discontinuation. Patients in this study were assumed to be compliant with treatment, as they fulfilled the criteria of refilling their prescriptions for at least one year; however, this still might not accurately reflect real compliance with treatment. Another possible explanation could be related to dosing. Almost 94% of all patients in this study were treated with statins, of which 61% were treated with simvastatin. The mean dose for those patients treated with simvastatin was 16.74 mg; 43% were treated with 10 mg/day, 52% with 20 mg/day, 4.9% with 40 mg/day, and only 0.1% with 80 mg/day. This dosing is in the lower range of what is recommended for patients at high risk [73]. The doses of other statins were also in the lower ranges.

In a study assessing the impact of the new guidelines on lipid levels in a diabetes patient population participating in the Västerbotten Intervention Programme, Fährm et al. [78] showed that there was a marked decrease in mean plasma total cholesterol levels among patients with diabetes after introduction of the guidelines in 1999, from 5.79±1.21 mmol/l in 1995-1999 to 5.07±1.00 mmol/l in 2000-2004 (p<0.001). They found the trend in diabetes patients was influenced by increased use of lipid-lowering agents, even though only 25.3% of the diabetes patients received lipid-lowering treatment after the introduction of the new guidelines. We found the discontinuation rates following the new reimbursement scheme were similar for the total patient population and for a subpopulation of patients treated with glucose-lowering drugs; this indicates a non-desirable effect, since patients with diabetes are at higher risk for CVD than patients without diabetes.
5.1.2. Glucose-lowering therapies

The total number of patients treated with glucose-lowering drugs in 2010 was about 372,000, an increase of 17% since 2006. Of these, 183,000 were treated with insulins and 265,000 with oral GLT, representing increases of 15% and 19% respectively since 2006 [115].

We found the new reimbursement scheme had a minor impact on use and costs of oral GLT. Despite restricted reimbursement for patients with T2DM, the use and costs of insulin-based GLT increased more rapidly following the intervention. The use of insulin-based treatment in patients ≥45 years of age has been reported to be twice as high in Sweden as in its neighboring country Denmark [125], indicating wider use of insulin-based treatment for T2DM in Sweden compared to that in Denmark. This difference might partly be explained by differences in reimbursement system; in Sweden, insulins are reimbursed to 100% while the reimbursement of oral GLT was reduced in 1997. In Denmark, the reimbursement is the same for oral and for insulin-based GLT.

The TLV review concluded that that the overall use of glucose-lowering drugs was already considered cost-effective prior to the review, with a few exceptions, and so the new reimbursement scheme was not designed to alter the overall use. However, the proportion of use of insulin for T2DM might be excessive in Sweden [125], and the costs for insulin amount to the largest part of costs for GLT. The use of insulins could have been evaluated in the HTA review, with respect to cost-effectiveness. If the use was found to be excessive (not cost-effective) or could be steered toward cheaper oral treatment, this could have been a potential target to consider in the new reimbursement scheme. This would have better reflected the stated aim of the review: “The purpose of our reviews is to extract as much health as possible for each tax crown expended on medicines” [105].

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Discussion

Quality aspects

Failure to achieve the treatment goals could among other things be due to poor adherence because of the side effects of certain antidiabetic treatments [89]. Hypoglycemia has been suggested to be the main limiting factor in achieving adequate glycemic control [90], which might be explained by the impact on the patient’s QoL when experiencing hypoglycemia, as shown in earlier studies in Sweden and in France [95, 96].

About 50% of all patients with diabetes in Sweden reach the goal of HbA1c <6% [88] according to guidelines, while in our findings only 40% of Swedish adult patients with T2DM treated with a combination of metformin and SUs reached glycemic goal. However, a review by Hemmingsen et al. found that the risks of both mild and severe hypoglycemia were increased with intensive glycemic control, even if it was found to reduce the risk of microvascular complications and suggested to reduce the risk of non-fatal myocardial infarction in trials exclusively dealing with glycemic control in usual care settings [82].

Our findings confirm the results of earlier studies in which patients reporting experience of moderate or more severe hypoglycemia were found to have lower QoL summary scores, as measured using EQ5D and VAS. In health economic evaluations, even seemingly minor numerical improvements in QoL measured by EQ-5D might translate into considerable gain in QALYs [157].

According to guidelines, QoL aspects in GLT should be taken into consideration (see section 1.3.1.2.Glucose-lowering therapies). Our findings indicate further that socioeconomic factors could influence QoL; a larger proportion of patients reporting no or only mild hypoglycemia had elementary school as highest education, compared to the group of patients reporting experience of moderate or more severe hypoglycemia. This contradicts the usual view that lower socioeconomic status leads to lower QoL [158]. In this case, those patients with higher education seemed to report more hypoglycemia and subsequently lower QoL; this could be explained by
better disease control, which leads to hypoglycemia and lower QoL. The results are confirmed by higher HbA1c in the group reporting experience of no or only mild hypoglycemia. These findings could be interesting to consider from a health equity standpoint, to ensure fair and just distribution of health care.

### 5.1.3. Use of preventive medicines

Prevention can be a cost-effective and sometimes cost-saving component of managing established chronic conditions [159].

Use of preventive medicines depends on demand and supply. However, market failures such as moral hazard and asymmetric information might drive the private demand of use toward a non-optimal level (lower level) from a societal perspective. This might be even more evident in a publicly-financed health care system, since incentives for prevention might be partly shifted away from the insured to the insurers.

Effective preventive drugs for coronary heart disease and stroke have been shown to be underused globally, with striking variation between countries at different stages of economic development [160]. Variation in use of new drugs could be explained by macro-level or system-level determinants, service organization determinants, and clinical practice determinants; the most important determinants are spending on pharmaceuticals, the role and impact of health technology assessment, guidelines, and clinical culture and attitudes [161]. It has been suggested that relaxation of restriction of reimbursement policies for statins might increase their use [11, 117, 162].

The level of use of statins in Sweden compared to other similar countries was found to be low during 2008-2009 [113] and medium during 1997-2003 [163]. In the PURE study, even in high-income countries (Sweden included), only 72.2% of patients with coronary heart disease and 52.2% of patients who had a stroke were treated with
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statins [160], which might be an indication of underuse of LMT for secondary prevention. On the other hand, overuse of statin therapy was found among 69% of patients undergoing primary prevention in the US [164], but that might differ substantially from the use in Sweden. Taylor et al. questioned the benefits of treatment with statins for primary prevention; they found only limited evidence that primary prevention with statins may be cost-effective and improve patient QoL [165], but acknowledged that cost-effectiveness should be reviewed in the light of changes in cost as suggested by Ward et al.

Underuse of preventive technologies might also arise from inadequate supply if market forces discourage investment in R&D for prevention compared to R&D for cure, for example if there are differences in the type of evidence required for market authorization or for reimbursement. It has been suggested that many public and private insurers use a double standard when evaluating new treatments; while the adoption of a curative treatment seems to require evidence of safety and efficacy at the least and cost-effectiveness at the most, adoption of a preventive treatment seems to require evidence of cost-effectiveness at the least and often also evidence of cost savings [166]. Furthermore, safety, efficacy, and cost-effectiveness data on prevention are likely to be more costly to gather compared to the process for cure, since the benefits of prevention tend to be diffused and take a long time to develop, so clinical trials of prevention require larger samples and longer durations than clinical trials of cure.

No generalizable pattern has emerged when comparing cost-effectiveness of technologies for prevention and cure [17]. However, it is possible that general methods in CEA, such as discounting of future health benefits, are less likely to promote a preventive program than a curative one [38, 167].

In contrast to what is sometimes argued, Russell (1986) suggested that in many cases prevention will not be cheaper than cure [168]. An analysis of 599 studies published between 2000 and 2005 revealed that spending more on prevention increased
medical spending over 80% of the time [169]. However, prevention is still attractive, since it will be a better option than cure in cases where cure is incomplete, and in many cases the uninsurable utility loss from health risks, for example pain and suffering, far exceeds the insurable monetary loss.

We found that the impact on use and costs from the new reimbursement schemes following the HTA reviews for LMT and GLT depended mostly on initial perception of the efficiency in the market place, timing (when the review was undertaken and implemented), and design (how precise it is), besides the characteristics of a specific market (e.g. if generics are available in the market, new entries, competition). In the HTA review of GLT, the TLV concluded that the overall use of glucose-lowering drugs was already cost-effective prior to the review, and so the new reimbursement scheme was not designed to alter the overall use. In contrast, the review of LMT was aimed at reducing the use of lower doses of patented statins in favor of equivalent doses of generic statins, which was considered to be more cost-effective. Consequently the new schemes differed in terms of design and precision. Timing of the reviews is an important factor that influences the effectiveness of a policy, because the potentials for savings might differ. This could be understood by the results in Papers I and III, since the impact of the new reimbursement scheme for LMT had a clearer effect on the market compared to the new reimbursement scheme for GLT, where there was no potential for major gains from increased use of generics. In a review, potential savings should be evaluated and weighted against the potential unintended effects that may emerge following new restrictive reimbursement schemes, as was shown in our studies. Soft demand-side policies might be more effective instruments under certain circumstances.
5.2. Methodological considerations

5.2.1. Papers I & III

Time series design

The three most commonly used designs in guideline implementation studies are uncontrolled before-and-after studies, time series designs, and controlled before-and-after studies [132]. While the before-and-after design uses two time points, one before and one after the intervention, the time series design makes use of multiple time points to evaluate the effect of an intervention. Before-and-after design might produce results confounded by other factors. One or both of the time points could be atypical apart from the new program or regulation, or could be influenced by other regulations or other factors such as introduction of new drugs, generic competition, changes in treatment policies, marketing activities, introduction of new treatment, and educational interventions by Drug and Therapeutic Committees. Even though the time series design does not eliminate all problems of interpreting changes in turnover rate, the extended time period strengthens the ability to attribute changes to the intervention [131].

Internal validity could be threatened by historical events, that is, some other event occurring at the same time as the intervention which could also explain the pattern of change over time. Another source threatening internal validity is related to collection of the data, if aspects of the record-keeping procedures may change at the same time as the intervention.

Interrupted segmented regression is best suited to testing immediate and sustained changes associated with the intervention while controlling for trends, and to capturing immediate effects. Capturing immediate effects could therefore be a
Discussion

problem using interrupted segmented regression if a program is implemented slowly over time.

**Drug utilization studies and the drug registry**

There are clear methodological issues related to drug utilization studies. In most of them, units of drugs available (purchased) are used as a proxy for the volume consumed. However, the quantity of prescribed drugs might differ widely from the quantity consumed by those for whom they were intended. Compliance with treatment differs between therapies, but in general is less than 100%, and the compliance rate might also be lower in asymptomatic diseases, because patients do not perceive an immediate need for their medication [170].

The indication for the prescription is not recorded in the database; it is therefore not possible to evaluate average dosage and adherence to treatment guidelines, nor is it possible to measure if the use of drugs is at an optimal level. It is further not possible to capture use of drugs in patients who may have switched to over-the-counter products.

**5.2.2. Paper II**

One possible limitation in the study on prevalence of lipid abnormalities was related to the selection of patients. Only those 5,424 who met all predefined inclusion and exclusion criteria were included in the analysis, comprising about 58% of the total study population ($n=5,424/9,384$). The inclusion criterion of complete lipid profiles caused an exclusion of about 21% ($n=1,933/9,384$); this may have resulted in selection bias, since patients with high CVD risk should have better documentation and thus a greater probability of selection in the cohort. The problem of incomplete lipid profiles has been reported by other researchers, and the analytical solution used in this study was adapted from their prior work [155]. In short, they compared baseline lipid values for those patients with complete lipid profiles to all included patients. If
baseline lipid profiles were similar, they concluded that those patients with complete profiles were representative of the entire cohort. Using the same methodology in this study, no major differences in baseline lipid values were found between excluded and included cases. Nonetheless, one should use caution when extrapolating these data to the general population of patients using LMT. Retrospective data do not permit controlling for a variety of confounding factors, thus limiting our ability to make inferences about associations observed in the results. Furthermore, all included patients should have had their LMT prescription refilled for at least one year as well as having complete lipid profiles, which might represent a best-case scenario of goal/normal lipid level attainment. Another possible limitation is that it was not possible to differentiate between fasting and non-fasting TG measurements in this study. To address this issue, LDL-C measurements were considered invalid if the triglyceride values were >4.5 mmol/L, since both fasting and non-fasting TG act as strong predictors of cardiovascular events [171].

5.2.3. Paper IV

Hypoglycemia was one of the main concepts in this study, but the literature shows a lack of consensus on the definition of hypoglycemia [21]. Hypoglycemia definitions may be heterogeneous between trials [82], which limits the possibility in general to compare and integrate findings across studies on hypoglycemia. However, the definition for hypoglycemia used in our study is consistent with the definitions used in a recent Cochrane review [82], where hypoglycemia was defined as mild (controlled by patient), moderate (daily activities interrupted but self-managed), or severe (requiring assistance).

Reasonable accuracy can be achieved when using a quantitative approach to study a phenomenon using physiologic measurements such as blood pressure or body temperature, but no comparable methods have yet been developed to measure psychological phenomena such as hope or self esteem [131]. Quantitative
methodology can thus be limited when it comes to explaining or giving in-depth insights into a phenomenon, which is important in research areas dealing with patients’ experience and views related to different treatments. Patient-reported outcomes have become increasingly important, and many instruments and questionnaires have been developed for use in different settings. However, using questionnaires instead of interviews can result in missing information that was never asked for in the questionnaire, while issues in general might more easily appear in the more flexible form of an interview as compared to the highly structured form of a questionnaire. This is also evident since the use of questionnaires is sometimes criticized by patient organizations, because these instruments are developed for a generic purpose and might not reflect the specific issues related to a disease area or therapy as perceived by the patients. Compared with questionnaires, interviews are superior in terms of response rates, audience, clarity, depth of questioning, providing complete information, order of questions, sample control, and supplementary data.

The study utilized an observational, cross-sectional, retrospective design. In a retrospective study, the response is recorded at entry and an attempt is made to look backwards in time for possible explanatory features [131]. Patients were asked about their experience of hypoglycemia during the past six months; the answers and hence the results were thus dependent on the patients’ ability to recall the episodes. While the recall of severe hypoglycemic episodes may be reliable over a longer time period, the reliable recall period for mild episodes is shorter than one week [25]. This is in general a problem with retrospective studies, since they are subject to biases of recall; but on the other hand they may often yield results much more quickly than corresponding prospective studies.

The cross-sectional design is a limitation, since observations taken at just one time point are likely to be less enlightening than those taken over time [131].

Another potential weakness is that generic instruments like the EQ-5D may not be sensitive enough to detect features specific to a certain disease outcome; this was
Discussion

acknowledged in a recent report evaluating QoL in Swedish patients with diabetes [97]. This may in fact be reflected by the fact that in our study the VAS score showed a dose-response relationship with hypoglycemia severity, which was not the case for the EQ-5D summary score.

Patients should have been prospectively and consecutively recruited to the study at their usual visit to their GP. However, many of the investigators had difficulties recruiting patients who were eligible for participation, and many potential study patients were excluded because they had been already been switched to other treatments. The QoL difference between the study groups might therefore be underestimated due to a selection bias, in that patients with more severe hypoglycemic problems had already been taken off their treatment as recommended. This may indicate that patients included in this study tolerated the treatment better than other patients, which would underestimate the problem of hypoglycemia.
6. CONCLUSIONS

The new pricing and reimbursement scheme for LMT had a substantial effect on the use of LMT. Patients initially treated with low doses of statins that were eventually excluded from the reimbursement scheme were switched to higher doses or discontinued to a much greater extent following the new reimbursement scheme. The new reimbursement scheme for GLT had a minor impact on the use and costs of oral GLT, while there was an accelerated increasing trend in the number of patients treated with restricted or retained insulins, as well as in costs for insulin-based GLT.

The effects of new reimbursement schemes depend mostly on the timing (when the review is undertaken and implemented) and design (how precise it is), besides the characteristics of a specific market.

Our findings show that about 40% of the patients attained goal levels for LDL-C following treatment, but only 18% attained goals/normal levels in all three lipid parameters. Improvement in TGs was moderate, and low HDL-C persisted, showing only modest improvement following therapy; this was most notable in patients with T2DM, which could be explained by the limited use of LMT targeting lipid parameters other than LDL-C.

These findings show that treatment patterns for LMT were more in line with treatment guidelines considering LDL-C compared to treatment of other lipid parameters.

Hypoglycemia was found to be associated with lower QoL in Swedish adult T2DM patients treated with GLT as a combination of metformin and SU. This should be considered in clinical practice.
7. IMPLICATIONS FOR THE FUTURE

Changes in P&R policies to steer use of pharmaceuticals should be carefully evaluated with respect to timing and design, in order to avoid unintended and unwanted effects; this should be weighted against potential savings. Softer demand-side policies might be a better option to steer more precisely towards a cost-effective use of medicines.

Independent follow-up is needed to assess the impact of new reimbursement decisions. At the same time, the TLV should have a follow-up plan to make their own assessments of the impact from their decisions, since our findings show that unintended effects might emerge.

Focusing dyslipidemia therapy on LDL-C reduction allows 40% of all patients to successfully achieve LDL-C goal and also helps reduce triglyceride levels, whereas HDL-C and/or triglyceride abnormalities mainly persist. About 60% of all patients starting statin therapy could be considered for addition of treatments that target multiple lipid disorders. This option is most urgent for patients with T2DM.

Experience of hypoglycemia was found to be associated with lower QoL in patients with T2DM on dual treatment with metformin and SU. This should be taken into consideration when selecting treatment for these patients in clinical practice, perhaps through introduction of a specific questionnaire at the regular visits with health care providers.
8. FUTURE RESEARCH

The effects of a policy on costs of health care resources other than drugs are often not accounted for; this constitutes a limitation of our studies as well as other similar studies [117, 118]. Employing a wider societal perspective might result in different conclusions when evaluating the cost-effectiveness of a treatment, since it would take into account all costs, whereas if only costs for drugs are included, the results generated might be inconclusive. A full cost analysis should account for the total transition and other costs related to the new reimbursement scheme, and should be evaluated against the accumulated savings generated over time, which may be substantial. Research on long-term effectiveness and cost-effectiveness of LMT is therefore of major interest.

The economist’s view that the optimal level of prevention is where the marginal benefits equal the marginal costs remains somewhat foreign and controversial to health professionals who encourage greater use of prevention [17], even if the opinion varies between countries. Primary prevention is heavily debated from both economic and ethical perspectives, since it may drive costs and be of only minor benefit for individuals that are actually healthy. However, recent research shows a substantial underuse of effective secondary prevention drugs despite the low costs of these drugs, which are generic in most parts of the world [160]. Further research on the causes of this underuse could give further information useful in determining the optimal level of prevention.

The outcomes of cost-effectiveness analysis where initial prices are used would differ widely compared to analysis using a price averaged over a product’s total life cycle. In the case of statins, where prices have dropped considerably since the Swedish patent for simvastatin expired in 2003, results on cost-effectiveness using a dynamic analytical approach showed that simvastatin generates considerable societal
Future research

surplus [111] if total life cycle value is captured, which is different to the static approach generally employed in economic evaluations [43]. Further research should consider using a dynamic approach to better inform on the cost-effectiveness of a therapy over time.

In health economic evaluations, even seemingly minor numerical improvements in QoL measured by EQ-5D might translate into considerable gain in QALYs [157]. Due to methodological challenges related to QoL studies in general, further research on methodological issues could help to better reflect the value and cost-effectiveness of medicines with benefits predominately related to QoL improvements.
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10. REFERENCES


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