Towards a Health Economic Simulation Model of Type 2 Diabetes in Sweden

Ahmad Kiadaliri, Aliasghar

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Towards a Health Economic Simulation Model of Type 2 Diabetes in Sweden

Aliasghar Ahmad Kiadaliri

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Ivar Sønbø Kristiansen

Professor of Public Health, Department of Health Management and Health Economics, University of Oslo, Norway

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Abstract

The aim of this thesis was to provide part of the data required in updating/developing computer simulation models (CSMs) for type 2 diabetes mellitus (T2DM) using data obtained from routine clinical practice in Sweden.

In paper I, evolution of five biomarkers (i.e., HbA1c, systolic blood pressure, BMI, LDL and total to HDL cholesterol ratio) over time was estimated using data on 5,043 newly diagnosed T2DM patients from the Swedish National Diabetes Register (NDR) and a dynamic panel data framework. The results indicated that difference between individuals with high and low biomarker values at the baseline was diminishing over time.

In paper II, we estimated and validated the risk equations for the first and second major macrovascular events after diagnosis during the five years of follow up using the data on 29,034 T2DM patients from the NDR. We used the Weibull proportional hazard regression to estimate these equations. We found within- and between-event heterogeneities in associations between explanatory variables and the risk of experiencing an event. Validation analysis indicated that all equations had reasonable predictive accuracy in the test sample.

In paper III, health utility weights associated with several T2DM-related complications were estimated using survey data on the Swedish version of EuroQol (EQ-5D) instrument among 1,757 T2DM patients collected by the NDR in 2008. The results indicated that history of kidney disorders (–0.114) and stroke (–0.111) had the highest negative effects on the UK EQ-5D index score. Using the UK and Swedish tariffs resulted in discrepant estimates, possibly leading to divergent results from cost–utility analyses.

In paper IV, an existing cohort model of T2DM in Sweden was updated using equations from the papers II and III, and was used to estimate the lifetime costs and benefits of three second-line treatment alternatives, i.e., GLP-1 agonists, DPP-4 inhibitors, or NPH insulin, as add-ons to metformin among T2DM patients in Sweden failing to reach Hba1c $\leq$ 7% with metformin alone. The results indicated that assuming a willingness to pay of SEK 500,000 per QALY gained in Sweden, treatment strategy with GLP-1 can be considered cost-effective compared to DPP-4 or NPH insulin as second line treatment.

The results indicated the importance of developing and refining the equations required in CSMs as new data become available. The data presented in the current thesis are representative of the current clinical practice in Sweden and hence it is suggested that using these data in economic evaluations of T2DM treatment strategies might provide more relevant and accurate results for policy-making in Sweden.

Key words: Copmuter simulation model, panel data, survival analysis, EQ-5D, Sweden, type 2 diabetes mellitus, cost–utility analysis, incretin-based therapies.

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To my parents

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List of publications

This thesis is based on the following papers, which are referred to in the text by their Roman numerals. The papers are reprinted with the permission of the publishers:

I. Ahmad Kiadaliri A, Clarke PM, Gerdtham UG, Nilsson P, Eliasson B, Gudbjörnsdottir S, Steen Carlsson K. Predicting Changes in Cardiovascular Risk Factors in Type 2 Diabetes in the Post-UKPDS Era: Longitudinal Analysis of the Swedish National Diabetes Register. J Diabetes Res 2013; 2013:241347.

II. Ahmad Kiadaliri A, Gerdtham UG, Nilsson P, Eliasson B, Gudbjörnsdottir S, Carlsson KS. Towards renewed health economic simulation of type 2 diabetes: risk equations for first and second cardiovascular events from Swedish register data. PLoS One 2013; 8(5): e62650.

III. Kiadaliri AA, Gerdtham UG, Eliasson B, Gudbjörnsdottir S, Svensson AM, Carlsson KS. Health Utilities of Type 2 Diabetes-Related Complications: A Cross-Sectional Study in Sweden. Int J Environ Res Public Health 2014; 11(5):4939-52.

IV. Kiadaliri AA, Gerdtham UG, Eliasson B, Carlsson KS. Cost-utility analysis of GLP-1 compared with DPP-4 or NPH basal insulin as add-on to metformin in type 2 diabetes in Sweden. Submitted.

Abbreviations

DM	Diabetes mellitus
IDF	International Diabetes Federation
T2DM	Type 2 diabetes mellitus
T1DM	Type 1 diabetes mellitus
CSM	Computer simulation model
CEA	Cost-effectiveness analysis
CUA	Cost-utility analysis
CBA	Cost-benefit analysis
QALY	Quality-adjusted life year
RCT	Randomized controlled trial
ADA	American Diabetes Association
CVD	Cardiovascular disease
MI	Myocardial infarction
DALY	Disability-adjusted life year
YLD	Years live with disability
HRQoL	Health-related quality of life
NPH	Human neutral protamine Hagedorn
NDR	The Swedish National Diabetes Register
GLP-1	Glucagon-like peptide-1
DPP-4	Enzyme dipeptidyl peptidase-4
UKPDS	United Kingdom Prospective Diabetes Study
DCCT	Diabetes Control and Complications Trial
EQ-5D	EuroQol
HbA1c	Glycated haemoglobin
BP	Blood pressure
HDL	High-density lipoprotein
LDL	Low-density lipoprotein
BMI	Body mass index
AMI	Acute myocardial infarction
HF	Heart failure
NAIHD	Non-acute ischaemic heart disease
OLS	Ordinary Least Squares
GMM	Generalized Method of Moments
PWP-GT	Prentice, Williams, and Peterson gap time
HU	Health utility
IHECM-T2DM	Institute for Health Economics Health Economics Cohort Model for T2DM
ICER	Incremental cost-effectiveness ratio
WTP	Willingness to pay

Abstract

Due to high prevalence and associated economic burden, type 2 diabetes mellitus (T2DM) and its related complications are considered a global major health concern. In response to this concern, economic evaluations of treatment alternatives using computer simulation models (CSMs) have widely applied in recent years. These models aim to provide valuable information to aid informed decision-making in health care systems and to improve T2DM management. To meet this aim, the structure of these models and their input data must be representative and relevant to the setting where their results will be used. The CSMs in TD2M generally need three main types of data: biomarkers and their evolution over time, the risk of developing T2DM-related complications, and health utility weights and costs associated with these complications. To our best knowledge, there is a lack of evidence on parts of these data in Sweden and the aim of the current thesis was to partly fill this gap by estimating equations required to develop or update a CSM of T2DM using data from routine clinical practice in Sweden.

In paper I, evolution of five biomarkers (i.e., HbA1c, systolic blood pressure, BMI, LDL and total to HDL cholesterol ratio) over time was estimated using data on 5,043 newly diagnosed T2DM patients from the Swedish National Diabetes Register (NDR) and a dynamic panel data framework. The results indicated that difference between individuals with high and low biomarker values at the baseline was diminishing over time. In addition, the results indicated that BMI was a significant predictor of other biomarkers. The estimated equations had better performance than the commonly used equations in the CSMs of T2DM.

In paper II, the risk of experiencing the first and second major macrovascular events after diagnosis was estimated during the five years of follow up. The data on 21,775 (training sample) and 7,259 (test sample) patients from the NDR were used to develop and validate these risk equations. The Weibull proportional hazard regression was used to estimate these equations. The results showed within- and between-event heterogeneities in associations between explanatory variables and the risk of experiencing an event.

In addition, there were nonlinear relationships between several biomarkers and time to event. Older age at diagnosis was generally related to a higher risk of experiencing both first and second events during the follow up. Longer duration of diabetes at the time of the first event was generally associated with higher risk

of a second event. For all complications, while the risk of a first event increased with duration of diabetes, the risk of experiencing a second event decreased as more time elapsed after the first event. Validation analysis indicated that all equations had reasonable predictive accuracy in the test sample.

In paper III, health utility (HU) weights associated with several T2DM-related complications were estimated. We used the survey data on the Swedish version of EuroQol (EQ-5D) instrument among 1,757 T2DM patients, collected by the NDR in 2008. The UK and Swedish tariffs were used to calculate the EQ-5D index score. The results indicated that the history of kidney disorders (–0.114) and stroke (–0.111) had the highest negative effects on the UK EQ-5D index score. With the Swedish tariff, the history of stroke (–0.059) and heart failure (–0.042) were associated with the lowest scores. While history of microvascular complications had the highest negative effect on HU among women, among men, history of macrovascular complications was associated with the greatest decline in HU. Using the UK and Swedish tariffs resulted in discrepant estimates, possibly leading to divergent results from cost–utility analyses.

In paper IV, the lifetime costs and benefits of three second-line treatment alternatives, i.e., GLP-1 agonists, DPP-4 inhibitors, or NPH insulin, as add-ons to metformin among T2DM patients in Sweden failing to reach Hba1c $\leq$ 7% with metformin alone. An existing cohort model of T2DM in Sweden was updated, using the equations developed in papers II and III, to conduct a cost-utility analysis. Information related to 12,172 patients on metformin monotherapy and an HbA1c > 7% was collected from the NDR and used as the baseline characteristics in the model. The results indicated that the treatment strategy with GLP-1 can be considered cost-effective compared to DPP-4 or NPH insulin as second-line treatment, assuming a willingness to pay of SEK 500,000 per quality-adjusted life year gained in Sweden.

In sum, the results of this thesis provided part of the data required to develop/update a CSM of T2DM for application in the Swedish setting. Using data from routine clinical practice in Sweden implies the representativeness and relevance of the findings of this thesis to policy-makers in Sweden. Therefore, we suggest that these data should be used in quantifying the lifetime costs and benefits of T2DM alternative treatment strategies. Estimating the risk of microvascular complication and the effects of a number of complications on the health utility are subjects for future research.

Introduction

In recent years, rising diabetes mellitus (DM) prevalence and associated costs have evolved to become a major health concerns among policy makers in health care systems worldwide. The International Diabetes Federation (IDF) estimated that globally around 382 million people aged 20–79 years had DM in 2013 [1]. Due to an aging population, population growth, increasing urbanization, increasing obesity, and changing lifestyles (e.g. increasing physical inactivity), this figure is predicted to rise up 55% by 2035 [1]. DM and DM-related complications not only incur substantial costs on society as a whole but also impose considerable economic burdens on individual patients and their families. For example, treatment of DM and its complications took up 8% of total health care expenditure in Sweden in 2010 [2]. Increasing DM prevalence means that costs on DM will continue to grow over coming decades.

Putting health resources scarcity into the perspective, we confront a dilemma. On one hand, health resources available for spending on DM are limited, and on the other hand need and demand for these resources are increasing due to growing prevalence of DM. This dilemma implies that choices must be made about allocating and distributing these limited health resources among DM population and alternative prevention and treatment strategies. Health economics is the discipline that deals with these choices [3]. Actually, health economics, especially economic evaluation as one of its topics, has been emerged as tools to aid informed decision-making on resource allocation in health care. In the following sections, first I briefly define health economics discipline and methods of economic evaluation. In the second section, I describe epidemiology and management of type 2 diabetes mellitus (T2DM). In the third section, I review the application of economic evaluation in the T2DM context.

Health economics is a branch of economics concerned with the application of economic theories and models to phenomena and problems associated with health and health care. It takes into account the issues of resource scarcity, opportunity costs, and broader social objectives such as efficiency and equity [3].

Alan Williams [4] defined eight distinct topics covered in the discipline of health economics: health determinants, health measurement and valuation, health care demand, health care supply, (micro) economic

evaluation, market equilibrium, evaluation at the whole system level, and planning, budgeting, and monitoring mechanisms.

Economic evaluation

To set priorities and obtain maximum benefits from scarce health resources through transparent and justifiable decisions, a health decision-maker needs comprehensive and accurate data not only on the effectiveness of interventions, but also on their costs. Economic evaluation is based on the recognition of these data requirements. Economic evaluation has been defined as a method to identify, quantify and compare the costs and outcomes of alternative decision options [5]. In practice, economic evaluations have increasingly become important criteria in decisions about health resources allocation, and policy formulation across health sectors worldwide.

Three main methods of economic evaluation can be distinguished by how they measure the outcomes of health interventions: cost–effectiveness analysis (CEA), cost–utility analysis (CUA), and cost–benefit analysis (CBA). In CEA, the health outcomes are measured in single natural units (e.g., percentage of cholesterol reduction, and life years gained). In CUA, the quality of health outcomes is taken into account and health outcomes are measured using health utility weights (tariffs). The quality-adjusted life year (QALY) is the most common measure of outcome in CUA. In CBA, the health outcomes are valued in monetary terms.

The data on the costs and outcomes required to conduct economic evaluation can be collected from primary sources such as randomized controlled trials (RCTs) or secondary sources such as databases. When conducting an economic evaluation, these data can be used in two formats:

1. Using patient-level data from a single clinical trial, either RCT or observational study as a vehicle for economic evaluation [5, 6].
2. Using decision-analytic modelling as a framework for economic evaluation – There are situations in which clinical trials do not provide a sufficient basis for economic evaluation. For example, a single clinical trial might not compare all relevant options, or might not reflect all appropriate evidence. Under these circumstances, decision-analytic modelling could provide an alternative framework for

economic evaluation. Decision-analytic modelling synthesizes data from multiple sources to compare the expected costs and outcomes of decision options. Decision-analytic modelling is structured in the form of a computer simulation model (CSM) that combines mathematical equations with computer software to simulate disease progression over time [5, 6].

Despite the extensive application of CSMs in economic evaluation of health care programmes and strategies, several valid concerns have been raised. The quality of sources used to extract the estimates applied in a CSM might be questioned. In other words, these estimates might be prone to bias due to sample selection, confounding bias, measurement errors, etc. In any modelling application, various key assumptions have to be made about disease progression, data extrapolation, and mathematical relationships between variables; and there may be varying degree of uncertainty around such model inputs. For example, many clinical trials are followed for only a limited duration; CSMs then use data from these trials to extrapolate the outcome beyond follow-up duration. Validity of assumptions used for such extrapolation might be questioned [7, 8]. CSM transparency and the power of the modeller in deciding on the model inputs and assumptions are other common concerns regarding CSM application [9].

In spite of these concerns, in some situations the availability and generalizability of information from clinical trials are limited and evidence has to be collected and synthesized from multiple sources. In these situations, CSMs might be helpful to overcome these limitations by reducing bias and uncertainty in economic evaluation through identifying all relevant evidence. From a decision-maker perspective, a CSM might improve decision-making under uncertainty by a clear structuring of the decision problem and providing information on expected long-term outcomes of different alternatives. One such situation is chronic diseases in which clinical and economic outcomes evolve over a long period and it is difficult to conduct clinical trials to collect all relevant data. One of these chronic diseases which impose substantial economic burden on societies is DM. DM can result in multiple micro- and macrovascular damages, leading to several systemic complications. In response to the limitations of clinical trials and significant economic burden of DM, there has been growing interest over the last decade in developing and applying CSMs in the DM context [10]. Recognizing the importance of CSMs in decision making, the American Diabetes Association (ADA) published a guideline for developing CSMs [11]. Moreover, to improve the performance, promote the

transparency, and identify key aspects of the future development of diabetes-related CSMs, the Mount Hood Challenge meetings have been held since 2000 [10, 12].

Definition, classification and prevalence of DM

DM is a group of heterogeneous disorders characterized by hyperglycaemia and glucose intolerance resulting from insulin deficiency, impaired insulin sensitivity, or both. Based on the aetiology and clinical presentation of the disease, DM is classified in four general categories: type 1 diabetes mellitus (T1DM), type 2 diabetes mellitus (T2DM), gestational diabetes mellitus, and other specific types [13]. Of these, T2DM is the most common form of DM worldwide. T2DM is characterized by insulin resistance and relative insulin deficiency resulting in increased blood glucose levels. Although this form of DM was traditionally described as adults diabetes (usually at an age greater than 40 years), it is globally increasingly being diagnosed in younger people [14]. T2DM frequently goes undiagnosed for many years because the hyperglycaemia develops gradually and at earlier stages it does not cause overt symptoms of DM [13]. The IDF estimated that 439,000 people aged 20–79 years (6.4% of the same population age group) were living with DM in Sweden in 2013, and this figure will rise to 498,000 (6.6% of the same population age group) by 2030 [1].

Micro- and macrovascular complications

T2DM is an established risk factor for several fatal and non-fatal microvascular (e.g., nephropathy, neuropathy, and retinopathy) and macrovascular (e.g., myocardial infarction, and stroke) complications. A recent multinational study reported that micro- and macrovascular complications were present in approximately 27% and 53%, respectively, of 66,726 participants with T2DM [15]. A pooled analysis based on 8.49 million person-years at risk indicated that DM is associated with a two-fold excess risk of cardiovascular diseases (CVDs) [16]. Moreover, the risk of death from any cause in people with DM is 1.8 times higher than in people without DM [17]. Specifically, people with DM are 1.25 times more likely to die from cancer and 2.32 times more likely to die from vascular causes [17]. In Sweden, the Northern Sweden MONICA study demonstrated that long-term survival after a first stroke and myocardial infarction (MI) is markedly lower among people with DM than among people without DM [18, 19].

Burden of disease

The IDF estimated that approximately 5.1 million people aged 20–79 years died from DM in 2013, accounting for 8.4% of global all-cause mortality among people in this age group, about half (48%) of these occurred in people under the age of 60 years [20]. The Global Burden of Disease Study recently estimated disability adjusted life years (DALYs) and years live with disability (YLD) for 289 diseases and injuries and found that DM was the 14th and 9th leading cause of global DALYs and YLD, respectively, in 2010 [21, 22].

This high morbidity resulted in a significant deterioration in health-related quality of life (HRQoL), and people with DM report lower HRQoL than do people without DM [23, 24]. In addition, among people with DM, people with a history of diabetes-related complications have lower HRQoL [25-27]. Significant morbidity, decreased HRQoL, and premature mortality translate into a major economic burden on individuals, families, and societies. The IDF estimated that DM taking up approximately USD 548 billion dollars in health spending globally in 2013, i.e., 11% of total worldwide health expenditures [20]. Besides these direct medical costs, considerable productivity losses are caused by DM, as people with DM are less likely to work and more likely to have health-related work limitations than are people without DM [28-30].

Management of T2DM

It is well-documented that good glycaemic control is one of the cornerstones of T2DM care [31, 32]. While the association between improved glycaemic control and reduced risk of microvascular complications is well-established, results regarding the role of glycaemic control in reducing the risk of macrovascular complications are inconclusive [33-37]. The ADA recommends glycated haemoglobin (HbA1c) < 7.0% as the treatment goal in most patients to reduce the incidence of T2DM-related complications [38]. Lower (6–6.5%) and higher (7.5–8%) HbA1c targets might be considered in sub-groups of T2DM patients [39, 40]. The guidelines from the National Board of Health and Welfare in Sweden advocate similar treatment goals for the newly diagnosed, people diagnosed at a younger age, and people with a low risk of CVD [41].

Lifestyle modifications are the foundation of typical T2DM treatment strategies. Such modifications mainly comprise education, dietary interventions, and exercise. Due to the progressive nature of T2DM, adding oral

anti-hyperglycaemic agents (e.g., metformin, sulphonylureas, thiazolidinediones, and incretin-based therapies) or insulin to the lifestyle modifications eventually becomes necessary.

Metformin, the most commonly used first-line T2DM drug, is an orally administered drug used to lower blood glucose concentrations [42]; its use is associated with stable or slightly decreased body weight in the long-term and does not raise the risk of hypoglycaemia [43]. While the sulphonylureas are effective in glycaemic control, their use is associated with a risk of hypoglycaemia and weight gain [44, 45]. The efficacy of thiazolidinediones in terms of HbA1c reduction is comparable to that of metformin and sulphonylureas; however, their use is associated with weight gain, water retention with an increased risk of oedema and/or heart failure and bone fractures [46, 47]. In addition, concerns regarding increased risk of myocardial infarction and bladder cancer have been reported [48-50].

Insulin therapy for T2DM

The progressive nature of T2DM, characterized by gradual deterioration in pancreatic beta-cell function, necessitates the use of insulin therapy for many patients. Typically, insulin therapy is initiated with basal insulin alone [51-53]. There are several basal insulin options: human neutral protamine Hagedorn (NPH) insulin, which is intermediate-acting, and long-acting basal insulin analogues (e.g., insulin glargine and insulin detemir). As the disease progresses, it may become necessary to further intensify insulin therapy to maintain patients at target HbA1c levels. Prandial insulin therapy with rapid-acting insulin analogues (e.g., aspart, lispro, and glulisine) and regular insulin are available options [54]. Premix insulin is another available intensification option. Several premix insulin products are available (e.g., biphasic insulin aspart 70/30 and biphasic insulin lispro). Both prandial and premixed insulin therapy options are associated with a greater reduction in HbA1c than is basal insulin therapy [55].

Despite treatment guidelines and the availability of a range of therapies, many T2DM patients fail to achieve and maintain the treatment goals, mainly due to the progressive nature of the disease and the inadequacy of conventional treatments [56]. For example, in Sweden, data from the Swedish National Diabetes Register (NDR) indicate that about half of patients with T2DM did not achieve HbA1c $\leq$ 7% in 2009–2012 (https://www.ndr.nu/). There is therefore a need for new therapies with better efficacy and fewer side effects including incretin-based therapies, which have emerged in recent years and attracted growing interest.

Incretin-based therapies for T2DM

Glucagon-like peptide-1 (GLP-1) hormone released from the small intestine in response to nutrient ingestion, stimulates insulin secretion in a glucose-dependent manner. In addition, GLP-1 reduces glucagon secretion, delays gastric emptying, and reduces appetite. These features imply that GLP-1 is an option for T2DM treatment. However, the enzyme dipeptidyl peptidase-4 (DPP-4) rapidly breaks down and inactivates native GLP-1, limiting its circulating half-life and subsequent biological effects on pancreatic beta cells. This has prompted the development of longer-acting GLP-1 receptor agonists that are DPP-4 resistant. Similarly, DPP-4 enzyme inhibitors have also been developed that allow native GLP-1 to accumulate, prolonging the half-life of GLP-1 [57, 56]. Besides providing good glycaemic control, incretin-based therapies offer two main clinical advantages over other glucose-lowering agents: 1) low risk of hyperglycaemia and 2) no weight gain [58-60]. The main side effects of incretin-based therapies are nausea and vomiting; moreover, concerns about acute pancreatitis and pancreatic cancer have been raised [61, 62].

The availability of multiple therapeutic options for T2DM implies that a choice has to be made in allocating limited health resources to these therapies. This requires assessing the impact of these treatment strategies based on survival, disease progression, complications, comorbidities, HRQoL, and cost [31, 63]. These requirements and the chronic nature of T2DM have resulted in the increasing application of CSMs, especially by health economists, to aid informed decision-making in the T2DM context.

CSMs in the T2DM context

CSMs of T2DM start by defining patient characteristics including demographic features (e.g., age, diabetes duration) and biomarkers (e.g., HbA1c, systolic blood pressure). Then the models simulate the incidence of T2DM-related complications over a series of discrete time periods (cycles) based on transition probabilities. These transition probabilities are calculated based on the value of biomarkers and demographic variables using survival analysis. Costs and health utilities are attributed to every complication and based on these and transition probabilities, the required data for cost-effectiveness analysis including expected QALYs and costs are calculated. This process continues until the time horizon of analysis is reached or the patient dies. The same process is performed for all patients included in a study.

Figure 1 shows a schematic of a typical CSM in the T2DM context. As can be seen, a CSM usually consists of three main modules: the biomarker, complication, and health utility/cost module. The biomarker module requires an understanding of how risk factors change over time, as these changes influence the progression of the disease and the risk of complications. The complication module involves projecting the risk of developing T2DM-related complications. The utility/cost module involves estimating the effects of T2DM-related complications and therapies on costs and patients' health utility.

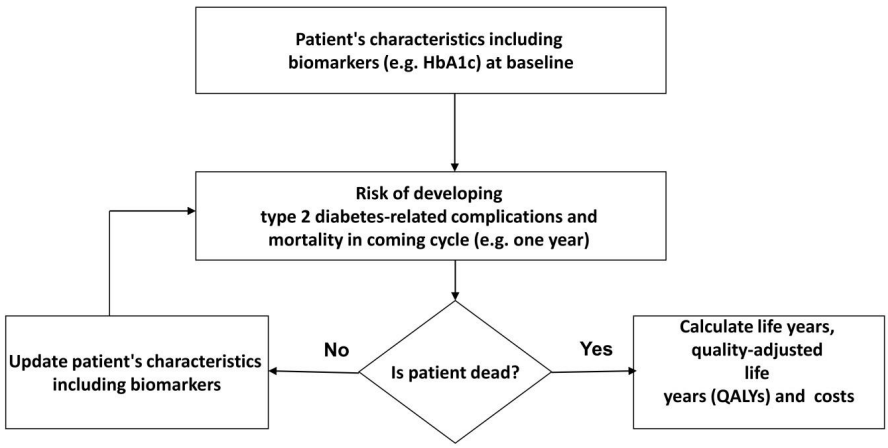
It should be noted that this is a simplified example of a CSM used in the T2DM context. Such CSMs are more sophisticated in reality: for example, interrelationships between biomarkers, endogeneity problem between treatments, biomarkers, and complications, capturing time-varying biomarkers when estimating the risk of developing complications, interdependence between complications when one complication increases the likelihood of another, handling competing complication risks, and handling uncertainty in CSMs are a number of issues that make CSM development a demanding task [64].

Several CSMs in the T2DM context have been previously described [65, 12, 10]. Many of these models have been examined in the Mount Hood Challenges, in which computer modellers of DM discuss and compare models and their performance against clinical trial and observational data. Since the first Mount Hood Challenge in 2000, six more challenges have been held.

The results of the fifth Mount Hood Challenge indicated that the models performed well in predicting the relative benefits of interventions, but less well in estimating the absolute risk of T2DM-related complications [10]. In addition, several limitations are associated with the data source used to develop these models [65, 66]. First, these models have generally used the results of the Framingham cohort study [67], the United Kingdom Prospective Diabetes Study (UKPDS) [68], and the Diabetes Control and Complications Trial (DCCT) [69]. The UKPDS and DCCT are RCTs and, like all RCTs, the generalizability of their results might be limited. The patients participating in these trials might not be representative of current people with DM, as factors such as new treatment patterns including improved hypertension and dyslipidemia management, as well as population life styles have changed since these trials were conducted. The Framingham study was conducted in the USA and included only a small number of patients with DM (n = 337), which limits the accuracy and generalizability of its results for DM patients and to other settings [70].

Earlier T2DM models used DCCT results for people with T2DM, while this trial was conducted among patients with T1DM. Moreover, while the recurrence of events is a feature of T2DM-related complications [71], a number of models failed to capture this effectively [10]. In addition, there are between-country differences in terms of population demographics, socioeconomic status, clinical practice patterns, and disease epidemiology, which limit transferability of the results of a CSM to a new setting. Therefore, a crucial aspect of a CSM is using representative and relevant structure and input data to the place where the model will be applied.

Figure 1. Schematic of a typical computer simulation model used in the type 2 diabetes context.



It seems that the availability of longitudinal data on a large sample of T2DM patients from routine clinical practice in a country might effectively address a number of these limitations. In Sweden, such data are available through register-based longitudinal data from the NDR. In the current thesis, we used the data from the NDR to provide representative and relevant input data for developing/updating a CSM of T2DM. In addition, these data can also be used in conducting cost-utility analyses alongside clinical trials data. We hope that using these country-specific data will provide better aid to inform decision-making by health policy-makers in Sweden.

Aims and objectives

General aim

The overall aim of this thesis was to estimate and provide part of the data required to develop/update a CSM of T2DM based on data from routine clinical practice for application in the Swedish setting.

Specific aims

- To estimate the time path of five cardiovascular risk factors (i.e., HbA1c, systolic blood pressure, body mass index, total to HDL cholesterol ratio, and LDL cholesterol) among T2DM patients in Sweden (Paper I).
- To estimate the risk of developing first and second occurrences of four CVD events (i.e., acute myocardial infarction, heart failure, non-acute ischemic heart disease, and stroke) among T2DM patients in Sweden (Paper II).
- To estimate the health utilities associated with a range of T2DM-related complications in Sweden (Paper III).
- To apply the results of the first three studies, through a CSM, in estimating and comparing the long-term costs and benefits of three second-line therapies for T2DM in Sweden: glucagon-like peptide-1 (GLP-1) receptor agonists, dipeptidyl peptidase-4 (DPP-4) inhibitors, and neutral protamine Hagedorn (NPH) insulin (Paper IV).

Material

This thesis is based on registry (papers I, and II) and survey (papers III, and IV) data from the NDR. The NDR was initiated in 1996 to enable local quality control and regional benchmarking against national treatment guidelines [72]. Individual-level demographic and clinical data on adults aged ≥18 years who have given informed consent to participate are reported to the NDR by trained nurses or physicians in all hospital diabetes outpatient clinics and primary health care centres at least once a year. In 2013, 90 outpatient clinics (100%) and 1,246 primary health care centres (≥ 90% of total) participated in the NDR (https://www.ndr.nu/). In addition, the NDR data are linked to the Swedish Cause of Death Register (http://www.Socialstyrelsen.se/register/dodsorsaksregistret/) and the Patient Register (http://www.socialstyrelsen.se/register/halsodataregister/patientregistret/) at the Swedish National Board of Health and Welfare. The Cause of Death Register includes information, collected by local parish registries, on age at death, date of death, specific cause of death obtained from the death certificate, and gender. The medical data in the Patient Register include main diagnosis, secondary diagnoses, external causes of injury and poisoning, and surgical procedures.

Paper I

Register data from the NDR were used for this study. We applied four general inclusion criteria to the data to select the original sample: (1) T2DM diagnosis in 2001–2004, (2) age 25–70 years at diagnosis, (3) a minimum of three observations from T2DM diagnosis to the end of 2008, and (4) no missing values for smoking or BMI in the year of diagnosis. In total, 5,043 newly diagnosed T2DM patients met these inclusion criteria and were included in the study. In addition, a sample of 414 patients aged 25–70 years diagnosed with T2DM in 2005 with follow up data in 2005–2008 were used as a test sample to validate the performance of the time-path equations developed for the original sample.

Paper II

Register data from the NDR with a linkage to the Swedish Cause of Death and Patient Registers were used for this study. Two general inclusion criteria were applied to the data: (1) age 30–75 years at diagnosis, and (2) no missing values for explanatory variables at baseline (year 2003). Altogether, 29,034 individuals with

T2DM met these criteria. This sample was randomly divided into two distinct subsamples: training (n = 21,775) and test (n = 7,259) samples. The training sample was used to develop the risk equations in the study and the test sample was used to validate the performance of the risk equations.

The IQ3 project (paper III)

In 2008, the IQ3 project was conducted by the NDR to improve knowledge of the quality of DM care in Sweden. The IQ3 project was a survey to collect data on patients' health-related quality of life using the Swedish version of the EuroQol (EQ-5D) instrument. Twenty-six primary health care centres participated in the IQ3 project. All patients who visited one of these centres during the recruitment period (1 February to 30 May 2008) were selected to participate, as long as they met the following inclusion criteria: (1) aged 18–80 years, (2) time since diagnosis greater than six months, and (3) not living under a protected identity. A total of 4,760 patients with T1DM or T2DM met these criteria, and were mailed the Swedish version of the EQ-5D questionnaire between June and August 2008. Of these, 2947 patients (1020 T1DM and 1927 T2DM) responded to the questionnaire. Of these T2DM patients eligible for inclusion in the study, we excluded 168 patients due to lack of data on history of events and two patients < 25 years old at diagnosis, resulting in a sample size of 1,757 for the study.

Paper IV

In 2009, the NDR conducted a population-based cross-sectional study among T2DM patients using non-pharmacological treatments and T2DM patients continuously using the 12 most common pharmacological treatment regimens who were registered in the NDR (n=163,121) [73]. Of these, 41,847 patients were on metformin monotherapy. For paper IV, we obtained the characteristics of the 29.9% of these patients who had an HbA1c level > 7% in this research cohort from the NDR. These data were included as cohort baseline characteristics in the CSM applied in paper IV. Table 1 presents the baseline characteristics of T2DM patients included in the four papers comprising the current thesis.

Table 1. Baseline characteristics of type 2 diabetes mellitus patients included in papers I–IV.

Variable	Paper I	Paper II	Paper III	Paper IV
Sample (*n*)	5,043	29,034	1,757	12,172
Age (years)	56.4 (8.9)	65.1 (9.7)	66.1 (8.8)	64.7 (11.6)
Diabetes duration (years)	0	9.0 (7.1)	9.5 (7.1)	5.6 (4.6)
Male (%)	58.8	57.9	56.7	57.5
Smoker (%)	21.7	14.7	17.0	17.5
HbA1c (%)	7.0 (1.4)	7.4 (1.2)	7.2 (1.1)	7.7 (0.8)
Systolic BP (mmHg)	139 (18)	142 (18)	136 (16)	137 (16)
Diastolic BP (mmHg)	81 (10)	78 (9)	76 (9)	79 (9)
Total cholesterol (mmol/l)	5.3 (1.1)	5.0 (1.0)	4.5 (1.0)	4.9 (1.1)
HDL (mmol/l)	1.3 (0.4)	1.3 (0.4)	1.3 (0.4)	1.2 (0.3)
LDL (mmol/l)	3.2 (1.0)	2.9 (0.9)	2.5 (0.8)	2.8 (0.9)
Triglycerides (mmol/l)	2.1 (1.4)	1.8 (1.0)	1.8 (1.1)	2.1 (1.3)
BMI (Kg/m^2)	30.3 (5.8)	29.2 (5.0)	29.8 (5.3)	30.9 (5.3)

Definition of variables

T2DM is defined in the NDR as treatment with diet or oral hypoglycaemic agent (OHA) only regardless of the age at onset of diabetes, or treatment with insulin alone or in combination with OHA and age ≥ 40 years at onset of diabetes.

Currently, HbA1c is measured using the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) reference method and the high-performance liquid chromatography (HPCL) Mono-S method in the NDR. At the time of conducting the current thesis, HbA1c values were measured using HPCL Mono-S method and were transformed to the Diabetes Control and Complications Trial (DCCT) standard levels using the following formula [74]:

$$\text{HbA1c (DCCT)} = (0.923 \times \text{HbA1c [HPCL Mono-S]}) + 1.345$$

Systolic/diastolic blood pressures (BPs) are recorded as the mean value of two readings (Korotkoff 1-5) in the supine position in the NDR.

The total cholesterol to high-density lipoprotein (HDL) ratio was calculated by dividing total cholesterol by HDL, both measured in millimoles per litre (mmol/l) of blood at local laboratories.

Low-density lipoprotein (LDL) was measured in millimoles per litre (mmol/l) of blood at local laboratories.

Microalbuminuria is defined as urine albumin excretion of 20–200 µg/min in two of three consecutive tests.

Macroalbuminuria is defined as urine albumin excretion of > 200 µg/min in two of three consecutive tests.

The body mass index (BMI) is a measure of body fat based on an individual's weight and height and is calculated according to the following formula: weight (kg) / (height (m))^2

Smoking status was defined as a binary variable (i.e., smoker vs. non-smoker). A smoker was defined as an individual who smoked at least one cigarette per day or smoked a pipe daily, or who had stopped smoking within the previous three months.

T2DM-related complications are defined according to the International Classification of Disease, 10th revision (ICD-10) codes and were retrieved by data linkage with the Swedish Cause of Death and Patient Registers. Any episode of hospitalization was considered an event (papers II and III). The ICD-10 codes for these complications are as follows:

- Acute myocardial infarction (AMI): I21, R96.0, and R96.1;
- Heart failure (HF): I50;
- Non-acute ischaemic heart disease (NAIHD): I22, I24.8, and I24.9 including stable and unstable angina: I20.0, I20.1, I20.8, and I20.9;
- Stroke: I61, I63, I64, and I67.9;
- Kidney disorders: N00-N08, N10-N16, N28.9, E11.2, E14.2, Z49.1, Z49.2, Z99.2, Z94.0, N17, N18, and N19;
- Retinopathy: H35.0, H35.2, H35.6, H35.9, H36.0, and E11.3; and
- Amputation: ankle (S98.0), lower leg (S88), hip (S78.0), and pelvis (S38.3).

Methods

Paper I

The current values of five biomarkers (i.e., HbA1c, systolic BP, BMI, LDL and total to HDL cholesterol ratio) over a maximum of seven years after diagnosis were used as outcome variables. Each outcome variable was modelled as a function of the one-year lag of its own value and a number of other explanatory variables. To do so, we considered a dynamic fixed-effects model in the following form:

$$Y_{i,t} = \alpha Y_{i,t-1} + \beta \dot{X_{i,t}} + \mu_i + \varepsilon_{i,t} \qquad (1)$$

where $Y_{i,t}$ represents the value of a biomarker for the *i*th patient ($i = 1, \ldots, n$) in year *t* after diagnosis of T2DM, $Y_{i,t-1}$ is the one-year lag of the biomarker, $X_{i,t}$ is a (K–1)×1 vector of exogenous explanatory variables, μ_i is a fixed effect (i.e., patient-specific effect allowed to vary between patients but constant within patients), and $\varepsilon_{i,t}$ is the identically and independently distributed (i.i.d.) error term with a mean of zero and a variance of σ_ε^2. In equation 1, the fixed effect is correlated with $Y_{i,t-1}$ implying that the ordinary least squares (OLS) estimator of α is inconsistent which is called the "dynamic panel bias" [75]. One way of dealing with this problem is to use the first difference transformation to eliminate μ_i as follows:

$$(Y_{i,t} - Y_{i,t-1}) = \alpha(Y_{i,t-1} - Y_{i,t-2}) + \beta(X_{i,t} - X_{i,t-1}) + (\varepsilon_{i,t} - \varepsilon_{i,t-1}) \qquad (2)$$

However, there is an endogeneity problem in equation 2 because $Y_{i,t-1}$ is correlated with $\varepsilon_{i,t-1}$,which means that the OLS estimates of α are still inconsistent. Using two-stage least squares with instruments variables that are both correlated with $(Y_{i,t-1} - Y_{i,t-2})$ and uncorrelated with $(\varepsilon_{i,t} - \varepsilon_{i,t-1})$ is a way to obtain consistent estimates of α. For this, Anderson and Hsiao [76] suggested instrumenting $(Y_{i,t-1} - Y_{i,t-2})$ with either $(Y_{i,t-2} - Y_{i,t-3})$ or $Y_{i,t-2}$.

Holtz-Eakin et al. [77] noted that further lagged levels of $Y_{i,t}$ can be used as instruments. Arellano and Bond [78] used the generalized method of moments (GMM) developed by Hansen [79] to exploit all possible instruments. They obtained estimators using the moment conditions generated by lagged levels of the dependent variable $(Y_{i,t-1}, Y_{i,t-2}, \ldots)$. These estimators are called difference GMM estimators. There are two

cases in which difference GMM estimators do not work well: if model errors are heteroskedastic and if a given independent variable does not change over time. In response to this, Arellano and Bover [80] and Blundell and Bond [81] proposed using lagged differences of the dependent variable $(Y_{i,t-1} - Y_{i,t-2})$ as instruments for $Y_{i,t-1}$ in equation 1, in addition to lagged levels of $Y_{i,t-1}$ as instruments for $(Y_{i,t-1} - Y_{i,t-2})$ in equation 2. The estimators obtained in this way are called system GMM estimators. We used this system GMM for our dynamic panel data model, estimating it using the *xtabond2* command [75] in STATA (StataCorp LP, College Station, TX, USA).

After estimating the time-path equations, we applied them in the test sample and predicted the biomarkers for three years after diagnosis. The observed values were then regressed on the predicted values to test the one-sided hypothesis of positive correlation (H0: $\beta 1 \leq 0$) [82]. In additionally, we compared our predictions with predictions made with time-path equations in UKPDS Outcome Model 1 [64] using the root mean squared error.

Paper II

In this paper, times until the first and second T2DM-related complications (i.e., AMI, HF, NAIHD, and stroke) after diagnosis during the five years of follow up were modelled. For first-event equations, all patients were followed from 1 January 2004 until the first event or withdrawal (due to death or other reasons), or until the censoring date of 31 December 2008 was reached. The patients who experienced their first event after diagnosis earlier than 1 January 2004 were excluded. Time since diagnosis was used as the time scale in the first-event equations. For second-event equations, the patients were followed from the date of the first event until the second event or withdrawal (due to death or other reasons), or until the censoring date. The patients experiencing two events after diagnosis and before 1 January 2004 were excluded. The time since the first event was used as the time scale in the second-event equations.

There are several statistical methods for handling recurrent-event data when a subject experiences repeated occurrences of the same type of event [83]. Of these methods, we applied the Prentice, Williams, and Peterson gap time (PWP-GT) model [84] for our study as it was consistent with our research question and has been demonstrated to be a more useful model for analysing recurrent event data than other models [83].

In the PWP-GT model, the time since the prior event is considered as time at risk, meaning that the clock is set to zero after each event. In other words, the PWP-GT model is a conditional model in which a subject is at risk conditioned on previous events. In addition, the baseline hazard function is event specific in this model.

For both sets of risk equations (i.e., for the first and second events), the Weibull proportional hazard regression was used to estimate the risk of developing these events after the diagnosis of DM. The Weibull model is a parametric model in which it is assumed that the hazard functions follow a Weibull distribution. The Weibull distribution has a baseline hazard of the form $h_0(t) = pt^{p-1}exp(\beta_0)$, where p is the shape parameter estimated from the data and determining the shape of the hazard function. If $p > 1$, the hazard increases over time; if $p < 1$, the hazard decreases over time; and if $p = 1$, the hazard is constant. The scale parameter is $exp(\beta_0)$. Given a set of explanatory variables, x_j, the Weibull proportional hazard function is as follows [85]:

$$h(t|x_j) = h_0(t)\, exp(x_j\beta_x) = pt^{p-1}\, exp(\beta_0 + x_j\beta_x)$$

Parametric models are more suitable for CSMs as these specify the functional form of the hazard function (i.e., how the risk of an event changes over time) [86]. After the risk equations were estimated in the training sample, their predictive accuracy was evaluated in terms of discrimination ability and calibration in the test sample. The discrimination ability is the ability of a risk equation to correctly separate individuals into those who will and will not experience the event of interest. This ability was evaluated using Harrell's C statistics [87], whit a value closer to one indicating better discrimination. The calibration of a risk equation, i.e., the extent to which the risk predicted by an equation equals the risk observed in the data [88], was assessed using a modified Hosmer-Lemeshow X^2 test [89]. In this case, the observed and predicted numbers of events were grouped by 10 deciles of predicted risk scores. The predicted number of events for each subject was calculated by subtracting the martingale residuals for subject *i* from the observed number of events for subject *i* [90].

The method of last observation carried forward was used to impute the missing values. The linearity of the continuous variables was checked using design variables and residual plots [91]. The non-linear relationships

were fitted using linear splines [92]. The final equation for each event was selected by backward selection processes from the full model, including all covariates including plausible interactions. The maximum likelihood ratio test was used to test the significance of the covariates, with the 5% level used as the limit of significance.

Paper III

The health utility (HU) associated with a number of T2DM-related complications was estimated. HU is a quality weight used to calculate QALYs in economic evaluations [93]. It is related to HRQoL but incorporates preferences in measuring health status. In this paper, HU was derived using the Swedish version of the EQ-5D instrument. The EQ-5D is the generic multi-attribute questionnaire most used worldwide to elicit HU. The EQ-5D covers five attributes: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each attribute has three levels: no problems, some problems, and severe problems [94], resulting in 243 (3^5) possible health states. The responses to these attributes are weighted based on the preferences elicited from a general population/patients sample to calculate an HU score. We used the UK [95] and Swedish [96] sets of preferences to calculate the HU index. While the UK preferences were derived using hypothetical health states, the Swedish ones were based on experienced health (i.e., ratings of one's own health).

We used OLS regression with robust standard errors to model the EQ-5D index score. Due to the skewed distribution of the EQ-5D data, several methods have been applied to these data in the literature [97, 98, 93], but OLS regression is the most common. Pullenayegum et al. [93] suggest that HU and HRQoL should be clearly distinguished. They argue that while HRQoL measurements are not bounded, HU are conceptually bounded above at 1 (i.e., one cannot do better than full health). Based on this argument, they recommend using OLS with robust standard errors as a valid approach to handling HU data.

In all analyses, T2DM-related complications were included in two forms. Model 1 included pooled events with AMI, HF, NAIHD, and stroke classed as macrovascular complications, and with kidney disorders, retinopathy, and amputation classed as microvascular complications. Model 2 treated each event as a separate event. To test whether the effects of T2DM-related complications differ between men and women, we estimated gender-specific equations and then compared coefficients using the *suest* command in STATA.

This command first combines the estimation results into one parameter vector and a simultaneous (co-) variance matrix of the sandwich/robust type; the test command is then used to implement the Wald test for equality of coefficients across models. The linearity of the continuous variables was checked using design variables and residual plots. In addition, the Wilcoxon matched-pairs signed-rank test was used to compare the median and distribution of the UK and Swedish tariffs, and Spearman's rank correlation was used to examine the consistency between these tariffs in their ranking of observed health states.

Paper IV

In this paper, we used data from our previous papers (papers II & III) to estimate the lifetime costs and benefits of three second-line treatment alternatives, i.e., GLP-1 agonists, DPP-4 inhibitors, or NPH insulin, as add-ons to metformin among T2DM patients in Sweden failing to reach Hba1c $\leq$ 7% with metformin alone. The GLP-1 receptor agonists were liraglutide (1.2mg daily) and exenatide (2mg once weekly), and the DPP-4 inhibitors were sitagliptin (100mg daily), saxagliptin (5mg daily) and vildagliptin (100mg daily). We conducted a cost–utility analysis using the Swedish Institute for Health Economics Cohort Model for T2DM (IHECM-T2DM), a cohort model consisting of two parallel Markov chains covering 120 microvascular health states and 100 macrovascular health states.

The microvascular health states comprise three complications: retinopathy (six stages, i.e., no retinopathy, background diabetic retinopathy, proliferative diabetic retinopathy, macular edema, proliferative diabetic retinopathy & macular edema, and severe vision loss), neuropathy (five stages, i.e., no neuropathy, symptomatic neuropathy, peripheral vascular disease, lower extremity amputation, and post lower extremity amputation) and nephropathy (four stages, i.e., no nephropathy, microalbuminuria, macroalbuminuria, and end-stage renal disease). The risks of these complications are estimated using equations from Bagust et al. [99], Brown et al. [100], and Eastman et al. [101].

The macrovascular health states comprise four complications: ischemic heart disease (IHD), myocardial infarction (MI), stroke, and heart failure (HF). IHD and HF contain two stages (i.e., no event and event) and MI and stroke contain five stages (i.e., no event, first event, post first event, subsequent event, and post subsequent event). To estimate the risk of these complications, the user is free to choose between three sets

of macrovascular risk equations: the NDR (paper II of the current thesis) [66], UKPDS Outcome Model 1 [64], and UKPDS Outcome Model 2 [102].

The IHECM-T2DM has a yearly cycle and time horizons of up to 40 years can be used. In addition, two sets of risk equations are available for estimating the mortality risk [64, 102]. The model also includes biomarkers evolution over time, treatment algorithm, and treatment-related side effects such as hypoglycaemia. Eight biomarkers are included in the model: HbA1c, systolic and diastolic BPs, total cholesterol, HDL, LDL, triglycerides and BMI. The evolution of these biomarkers over time is determined by the initial treatment effects and an annual drift. The treatment algorithm is used to define a sequence of glucose-lowering agents and treatment intensifications and depends on a user-defined switching threshold of HbA1c. The model starts by assigning the baseline clinical and demographic characteristics of the cohort, history of complications before diagnosis, and prevalence of diabetes-related complications. Moreover, the user should define the costs and HU associated with treatments and T2DM-related complications.

Three treatment strategies were evaluated in the study. In strategies 1 and 2, patients received the GLP-1 receptor agonists and the DPP-4 inhibitors, respectively, as add-ons to metformin. In both these strategies, patients progressed to NPH insulin 40 IU/day + metformin when HbA1c exceeded 7.5% and to intensified NPH insulin 60 IU/day + metformin when HbA1c $\geq$ 8%. In strategy 3, patients received NPH insulin 40 IU/day + metformin as the initial second-line treatment, and then progressed to NPH insulin 60 IU/day + metformin on reaching the HbA1c threshold of 8%.

For this study, we considered treatment effects as the absolute change from the baseline values (extracted from the literature) in HbA1c and weight. The rates of mild, moderate, and major hypoglycaemia were also included. These treatment effects were applied for the first year after treatment, after which constant annual drift was assumed for the various treatment strategies. The costs were accounted for from a societal perspective (2013 Swedish krona, SEK) and included health care costs, productivity losses, and net consumption losses. HU data were extracted from published sources, including the estimates in paper III [103] of the current thesis.

We conducted a series of one-way sensitivity analyses to assess the impact of variation in the model inputs and assumptions on the results of the base case analysis. A probabilistic sensitivity analysis (PSA) was

conducted to assess the joint uncertainty of the input parameters using a Monte Carlo simulation with 1000 iterations. Non-parametric bootstrapping with 1000 bootstrap samples was then used to calculate the mean and bootstrap bias-corrected (BBC) 95% CI of costs, QALYs, and incremental cost-effectiveness ratios (ICERs). ICER, a measure used to report the results of cost–effectiveness and cost–utility analyses, is a ratio of differences in costs and health effects between alternatives. The equation for the ICER for two hypothetical interventions is as follows:

$$\mathrm{ICER} = \frac{\mathrm{COST}_1 - \mathrm{COST}_2}{\mathrm{EFFECT}_1 - \mathrm{EFFECT}_2}$$

This shows the extra costs per extra health effects achieved by intervention 1 compared with intervention 2.

Results

Paper I

The time paths of five biomarkers in a sample of newly diagnosed T2DM patients were estimated. The median follow up was four years with 9,536 (LDL) to 25,447 (BMI) person-years of follow up data available for analysis. For all biomarkers, the one-year lag of the biomarker (i.e., the biomarker value in the prior year) was the main predictor of the current value and was <1, implying convergence over time. In other words, individuals with high biomarkers values at baseline would experience a decreasing trend, and vice versa. Moreover, the one-year lag of BMI was higher than that of the other biomarkers, implying that weight loss is less readily achieved among people with T2DM in Sweden (Table 2).

Table 2. Person-years of follow up and estimated coefficient of the one-year lag of biomarkers.

Variable	HbA1c	Systolic BP	Total : HDL cholesterol ratio	LDL cholesterol	BMI
Person years of follow up	20,699	20,144	10,157	9,536	25,447
one-year lag of biomarker	0.53	0.47	0.54	0.35	0.81

Higher BMI was associated with higher values of all other biomarkers, while older age at diagnosis was generally associated with lower values of biomarkers. While women had lower HbA1c values, systolic BP, and total:HDL cholesterol ratio than did men, they had higher LDL cholesterol levels than did men. Smoking was positively associated with all biomarkers except BMI, but these positive associations were statistically significant only for systolic BP.

The results of validation indicated that, except for systolic BP, our time-path equations can accurately simulate the actual time path of biomarkers among T2DM patients not included in the equation development. In addition, these equations performed better than did those from the UKPDS Outcome Model 1.

Paper II

In total, 4,547 first and 2,418 second events were observed during the five years of follow up (Table 3). We found that experiencing a first event substantially elevated the risk of subsequent events.

Table 3. Number of events, person years of follow up, and annual incidence rates per 1000 T2DM patients during the study period.

Event	AMI		HF		NAIHD		Stroke	
	First	Second	First	Second	First	Second	First	Second
Number of events	1,084	411	1,366	947	1,104	746	993	314
Person years	80,010	5,969	82,378	2,715	76,174	4,089	82,232	4,127
Annual incidence rate per 1000	13.55	68.86	16.58	348.80	14.49	182.44	12.08	76.08

AMI = acute myocardial infarction; HF = heart failure; NAIHD = non-acute ischaemic heart disease

We found within- and between-event heterogeneities in associations between explanatory variables and the risk of experiencing an event. For example, while women had a lower risk of developing a first AMI/NAIHD event, they had a higher risk of developing a second event. On the other hand, while BMI elevated the risk of first HF and NAIHD, it was not a significant predictor of AMI or stroke. Older age at diagnosis was generally related to a higher risk of experiencing both first and second events during the follow up. Longer duration of diabetes at the time of the first event was generally associated with higher risk of a second event.

Although higher biomarker values were generally associated with a higher risk of first events, there were non-linear relationships between HbA1c and systolic BP and the risk of first HF and also between diastolic BP and the risk of first NAIHD. Microalbuminuria and macroalbuminuria were mostly associated with a higher risk of an event. The patients with a history of an event before diagnosis had a higher risk of developing the same event after diagnosis of T2DM.

For all complications, the shape parameter of the Weibull distribution was higher than 1, implying that the risk of experiencing a first event increased with the duration of diabetes. On the other hand, this parameter was less than 1 for second events, meaning that as more time elapsed after the first event, the risk of experiencing a second event decreased.

The results indicated that the equations had reasonable predictive accuracy in the test sample. We found satisfactory performance in terms of discrimination, with Harrell's C statistics of 0.75–0.85 for first events and 0.70–0.84 for second events in the test sample. In addition, calibration by comparing the predicted and observed number of events in ten deciles of risk score indicated acceptable performance in the test sample (Table 4).

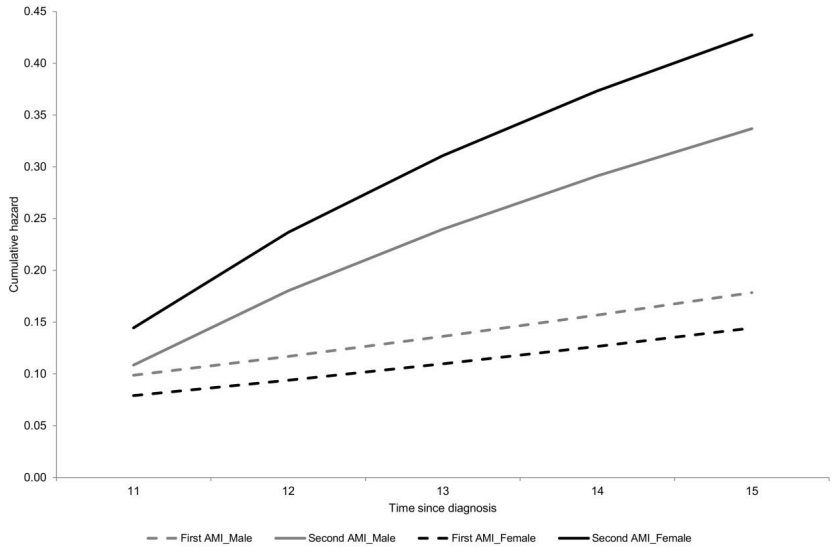
Table 4. Predictive accuracy of equations for the first and second events in the test sample.

Event		C statistics (95% CI)	HL X^2 (*P*-value) a
AMI	First event	0.79 (0.77–0.82)	16.33 (0.04)
	Second event	0.79 (0.74–0.84)	12.04 (0.15)
HF	First event	0.84 (0.82–0.86)	12.31 (0.14)
	Second event	0.84 (0.82–0.85)	22.67 (<0.01)
Stroke	First event	0.79 (0.76–0.82)	11.61 (0.17)
	Second event	0.70 (0.64–0.75)	9.99 (0.27)
NAIHD	First event	0.75 (0.72–0.78)	5.86 (0.66)
	Second event	0.77 (0.74–0.80)	14.07 (0.08)

AMI = acute myocardial infarction; HF = heart failure; NAIHD = non-acute ischaemic heart disease.
a. Hosmer-Lemeshow X^2 statistics

We illustrate the performance of our equations by estimating the risk of first and second AMI for a man and a woman using the following explanatory variables: age 65 years, diabetes duration 10 years, total cholesterol 4.3 mmol/l, HDL cholesterol 1.0 mmol/l, LDL cholesterol 2.0 mmol/l, HbA1c 8.0%, systolic BP 150 mmHg, macroalbuminuria, no smoking, no history of AMI before diagnosis, no HF during follow up, and no microalbuminuria. To estimate the risk of second AMI, we assumed that the patients had a first AMI in the 10th year after diagnosis. In addition, for simplicity, we assumed that the biomarker values were constant over the five years of follow up. Given these figures, the risks of first and second AMI during the five years of follow up (i.e., from the 11th to 15th years after diagnosis) were 10.51% and 33.68% for the man and 8.43% and 42.74% for the woman, respectively. Figure 2 shows the cumulative hazard of these events over the five years of follow up.

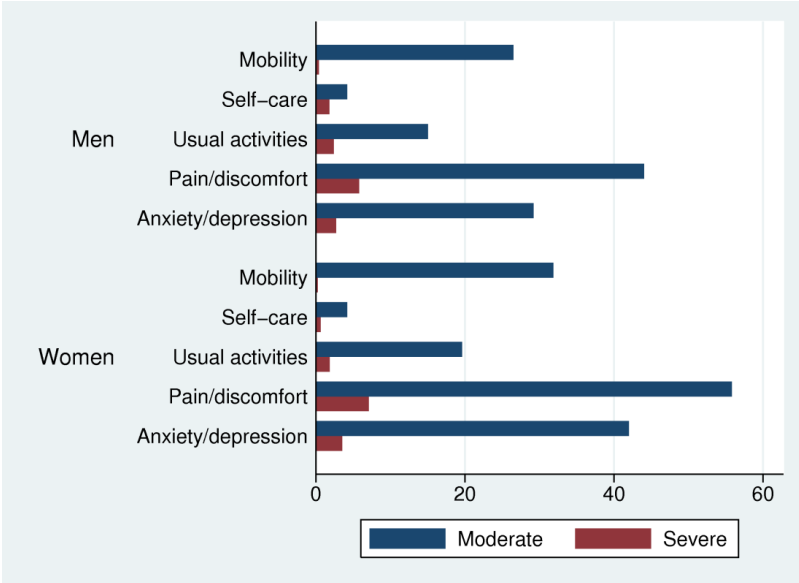
Figure 2. Predicted cumulative hazard of first and second acute myocardial infarction (AMI) for a hypothetical man and woman (see text).



Paper III

In total, 73 of 243 possible EQ-5D health states were observed in our study sample. Figure 3 shows the distribution of "moderate or severe problems" in the EQ-5D attributes. Note that the highest prevalence of "moderate or severe problems" was reported for the pain/discomfort (55.5%) and the lowest for the self-care (5.5%) attributes of EQ-5D. Women reported a higher incidence of "moderate or severe problems" for four of five attributes of the EQ-5D than did men ($p < 0.001$).

Figure 3. Percentage of respondents experiencing moderate/severe problems in the five EQ-5D dimensions.

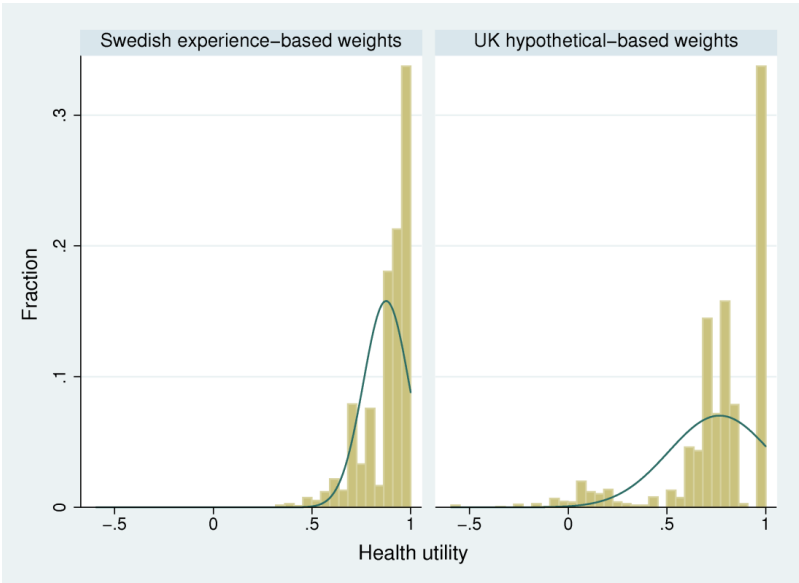


The UK EQ-5D index score was 0.74 (0.72–0.76) and 0.79 (0.77–0.80) among women and men, respectively ($p < 0.001$); the comparable figures were 0.86 (0.86–0.87) and 0.88 (0.88–0.89) using the Swedish experience-based utility weights, respectively ($p < 0.001$). Figure 4 shows the distribution of the UK and Swedish EQ-5D index scores. A significant difference ($p < 0.001$) was detected between these distributions using the Wilcoxon matched-pairs signed-ranks test. The Swedish EQ-5D index score had a narrower range than did the UK score. The Spearman's rank correlation between the UK and Swedish utility weights in ranking observed health states was high (p = 0.87; $p < 0.001$).

The results of OLS regression in the total sample indicated that being a woman, being older at diagnosis, and having a higher BMI were associated with lower HU in both the pooled and event-specific models. In the pooled model, the microvascular and macrovascular complications had the same negative effects on the UK EQ-5D index score (coefficients = –0.083); when we applied the Swedish EQ-5D index score, macrovascular complications had a slightly higher negative effect than did microvascular complications (–0.043 vs. –0.035). In the event-specific model, history of kidney disorders (–0.114) and of stroke (–0.111)

had the highest negative effects on the UK EQ-5D index score; with the Swedish tariffs, stroke (–0.059) and HF (–0.042) were associated with the lowest HU.

Figure 4. Distribution of the EQ-5D index score using the UK and Swedish health utility weights.



The results of pooled analysis of the samples stratified by sex indicated that while history of microvascular complications had the highest negative effect on HU among women, among men, history of macrovascular complications was associated with the greatest decline in HU (using either the UK or Swedish weights). In the event-specific model, history of kidney disorders (–0.248) was associated with the greatest deterioration in the UK EQ-5D index score among women, while none of the macrovascular complications had a statistically significant effect. On the other hand, among men, only macrovascular complications had statistically significant effects on the UK EQ-5D index score. When we applied the Swedish weights, the findings were similar except that stroke was also statistically significant among women.

In the pooled model, we did not find any significant heterogeneity in terms of multiple events or time since event, while in the event-specific model, we found that multiple strokes and NAIHD had greater negative effects on HU than did a single event and that an elapsed time of 2–5 years since an HF event had the greatest negative effect on HU. For all other complications, there was no change in their effects on HU in

terms of multiple events or time since event. In addition, when we focused on patients who experienced an event, we found that each year elapsed since micro- and macrovascular complications was associated with an increase in the UK EQ-5D index score of 0.013 and 0.007 units, respectively.

Paper IV

The results indicated that patients treated according to strategies 1 and 2 were expected to receive GLP-1 and DPP-4 for six and four years, respectively, before switching to insulin therapy. Patients on strategy 1 had a lower level of predicted HbA1c and BMI over their lifetime than did those on strategies 2 and 3. This translated into a lower incidence of macrovascular and microvascular events for patients on strategy 1.

Treatment strategy 1 was associated with improvements of 0.10 and 0.25 discounted QALYs compared with strategies 2 and 3, respectively. On the other hand, from a societal perspective, treatment strategy 1 was associated with SEK 34,865 and SEK 40,802 higher discounted costs than were strategies 2 and 3, respectively. This resulted in an ICER of SEK 353,172 for strategy 1 versus strategy 2 and an ICER of SEK 160,618 versus strategy 3. These findings mean that assuming a willingness to pay (WTP) of SEK 500,000 per QALY gained in Sweden, strategy 1 can be considered more cost-effective than either strategy 2 or 3.

The results of univariate sensitivity analyses indicated that our base case analyses were robust to variation in the inputs and assumptions applied in the model. Several key drivers of the results for all comparisons are shown in Table 5. When we excluded the disutility associated with every unit of BMI over 25 (0.006 in the base case) in comparing strategies 1 and 2, then the ICER was over SEK 500,000 per QALY gained. In all other sensitivity analyses, ICERs remained below SEK 500,000 per QALY gained, so the conclusion from the base case analysis did not change.

Table 5. Percentage changes in ICERs from the base case analysis.

Driver	Strategy 1 vs. 2	Strategy 1 vs. 3	Strategy 2 vs. 3
Including insulin disutility of –0.049 in the model	–42.1	–46.7	–48.3
Excluding net consumption loss	–11.1	–31.3	Strategy 2 dominant
Upper limit of 95%CI for initial HbA1c change	–16.6	–18.5	–17.2
Excluding the disutility of BMI > 25	+87.4	+51.9	+34.2
Excluding the disutility due to mild/moderate hypoglycaemia	+40.3	+59.9	+79.8
Excluding incidents of moderate and major hypoglycaemia	+30.4	+46.0	+94.1

The PSA results confirmed the findings of the base case analyses. In comparing of strategies 1 and 2, the estimated ICER was SEK 319,217 (BBC 95% CI: SEK 309,849–330,212). Assuming a WTP of SEK 500,000 per QALY gained, strategy 1 had a 74.7% likelihood of being considered cost-effective in comparison to strategy 3. In comparing strategies 1 and 3, the ICER was SEK 153,277 (BBC 95% CI: SEK 150,788–155,766). Assuming a WTP of SEK 500,000 per QALY gained, strategy 1 was expected to have a 100% probability of being cost-effective in comparison to strategy 3. Finally in comparing strategies 2 and 3, the ICER from the PSA was SEK 40,277 (BBC 95% CI: SEK 37,436–43,119). Assuming a WTP of SEK 500,000 per QALY gained, strategy 2 was expected to have a 98.1% probability of being cost-effective in comparison to strategy 3.

Discussion

General message

Economic evaluations are widely used as a tool to aid informed decision making in health care systems around the world. For example, in Sweden, there has been growing interest in applying economic evaluations in health care decision making since the introduction of the Dental and Pharmaceutical Benefits Agency (TLV)[1] in 2002. The TLV, the main health technology assessment body regarding pharmaceuticals, assesses the cost-effectiveness of both prescription and hospital drugs and decides whether a drug should be subsidized and included in the National Drug Benefit Scheme [104]. Regarding new products, pharmaceutical companies must submit economic evaluations as part of their applications to the TLV for reimbursement [105].

One of the main applications of economic evaluations is related to resource allocation decisions about chronic diseases which impose a raising enormous financial burden on societies. T2DM is one of these chronic diseases that due to its high prevalence and related costs is considered as a major health care concern for health care planners worldwide. In response to this concern, economic evaluations (especially based on CSMs) are increasingly used to model T2DM progression and to quantify the lifetime costs and outcomes associated with various disease management strategies [64, 65].

However, to aid informed decision making, the structure of these models and their input data must be representative and relevant to the local context [106, 107]. For example, pharmacoeconomic guidelines generally request that structure of CSMs should reflect the clinical patterns and the underlying nature of disease in the local context [107]. Available CSMs in the T2DM context rely mainly on findings of the Framingham observational cohort study [67], and of two RCTs: the UKPDS [68] and DCCT [69]. There are several reasons why these data might not be generalizable to routine clinical practice of T2DM management today and in Sweden. In addition, we believe that the results of these studies have influenced T2DM management and that these effects should be incorporated in updating existing or developing new CSMs. To

1. The Agency was called the Pharmaceutical Benefits Board (LFN) until 2008.

our best knowledge, there is a lack of the Swedish-specific data to be used in a CSM of T2DM. Therefore, we aimed to partly fill this gap using register based data from the routine clinical practice in Sweden.

The results of the current thesis highlighted the importance of estimating and incorporating the jurisdiction-specific data in CSMs whenever new data is available. In addition, these results reflect the T2DM clinical pattern in Sweden and might be more accurate source to aid informed decision making in Sweden than using data from other countries. Therefore, it is suggested that the results of this thesis should be used in developing/updating CSMs of T2DM or in economic evaluations alongside clinical trials in the Swedish setting.

Biomarker' changes over time

We found that the value of a biomarker in the preceding year was a significant predictor of the current value of that biomarker. As in time-path equations from the UKPDS Outcome Model [64], the coefficients on these lagged variables were less than 1 for all biomarkers, implying that biomarkers converge to a certain level over time. In other words, the difference between two people with high and low biomarker level at diagnosis decreases over time. Difference in treatment intensity between these people might explain this observation. In line with our finding, a recent cohort study in three European countries found that T2DM patients with the highest biomarker levels at baseline experienced the largest reduction in biomarker levels over the five years of follow up [108].

Generally, men diagnosed at a younger age had a worse biomarker profile than did other patients, possibly due to differences in genetic factors, behavioural factors (e.g., life style and treatment compliance), knowledge, risk aversion, and treatment modality (e.g., choice and intensity of treatment). This finding suggests that these patients potentially constitute a target group for receiving more intensive treatments, including life style and educational interventions.

The results of validation indicated that, except for systolic BP, our time-path equations can accurately simulate the actual time path of biomarkers for people with T2DM in Sweden. In addition, compared with the equations from the UKPDS Outcome Model, our equations made more accurate predictions. This

highlights the usefulness of developing new equations whenever new data is available, as these might more accurately reflect the circumstances specific to a time and place.

Risk of developing macrovascular complications

There is limited evidence of the risks of developing first and subsequent events in representative samples of patients with T2DM in routine clinical practice. In this thesis, we estimated separate risk equations for the first and second occurrences of four major T2DM-related complications using a large high-quality nationwide population-based database from Sweden. As expected, experiencing a first event substantially elevated the risk of a second event. This finding implies that excluding the risk of subsequent events or assuming constant risk for the first and subsequent events in a CSM might lead to biased results, especially when an intervention is effective at preventing recurrent events.

Our results indicated that the risks of first events increased as diabetes duration increased, but that the risks of second events decreased with increasing time since the first event. These findings suggest that, among patients not experiencing a macrovascular event after diagnosis, more attention should be paid to those with longer-standing diabetes. In addition, for people experiencing a macrovascular event after diagnosis, the period immediately after a first event is the most hazardous time to experience a subsequent event, so more intensive care should be given at this early time. Similar findings were reported for MI among general population in Sweden and UK [109, 110].

We found non-linear relationships between HbA1c, systolic and diastolic BPs, and risks of first macrovascular events. This finding is in line with recent evidence from both randomized and non-randomized studies [111-116]. For example, the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial found that reducing systolic BP below 130 mm Hg was not associated with reduced risk of CVDs in people with DM [116]. Moreover, our threshold values for systolic and diastolic BPs are in agreement with the ADA- recommended BP target of 140/80 mm Hg [32] and the new Swedish guideline target of 140/85 mm Hg for T2DM patients [117]. These non-linear relationships call into question the additional benefits of very tight control of BP and HbA1c and hence have important implications for CSMs, as ignoring these might bias their results.

We found empirical inter-dependency between macrovascular events, i.e., experiencing one event increases the risk of experiencing others. In addition, patients with history of an event before diagnosis are more likely to experience the same type of event after diagnosis. These findings have important implications for CSMs in T2DM, as highlighted by the ADA [11]. The results of the model validation indicated that our risk equations performed well in both training and test samples, which implies that they might be useful not only for CSM applications, but also in evaluating macrovascular complication risks in clinical practice and in identifying high-risk T2DM patients.

T2DM-related complications and health utility

There is limited evidence regarding HU scores for a range of common diabetes-related complications among patients with T2DM in Sweden. Previous Swedish studies have either reported results regarding the impact of a specific complication on HU [118], have included mainly type 1 diabetes patients [119], or have evaluated the association between complications and HRQoL rather than HU [120], which limits their application in economic analyses. We tried to fill this gap by estimating the effect of a number of T2DM-related complications on HU using data from the NDR. Our results indicated that, as expected, history of T2DM-related complications was associated with lower HU scores after controlling for clinical and demographic covariates.

The mean UK EQ-5D index for patients with no complications (0.79) was similar to the values reported in previous studies [121, 122]. In addition, a recent systematic review [123] recommended using this value in economic modelling of T2DM. This facilitates the comparability of previous studies and economic analyses using our estimates, and implies that our results might be transferable to other settings. The range of HU decrement for complications in the total sample extended from 0.012 for retinopathy to 0.114 for kidney disorders using the UK tariff. As found in previous studies [121, 124], across macrovascular complications, stroke had the highest negative impact on HU. Despite these similarities, the estimated HU scores we determined for specific complications differed from those found in previous studies. Differences in sample characteristics, clinical setting, range of complications studied, and statistical analysis methods might partly explain these disparities in HU scores.

In line with results from the UKPDS 62 study [121], we did not find significant changes in the effect of complications on HU with time since event in the total sample; however when we included only patients with a history of complications, we found that the HU decrement associated with micro- and macrovascular complications diminished over time. Although this finding was expected, as these events are believed to have a large detrimental effect on HRQoL in the time immediately following the event [125], this should be interpreted with caution due to the small sample sizes, especially for microvascular complications (*n*=87).

Application of the Swedish tariff was associated with higher mean HU and smaller absolute coefficients in the regression analyses. These discrepancies have important implications for cost–utility analyses, as these might lead to smaller effect differences and in turn larger incremental cost–utility ratios, implying less cost-effective interventions [126]. These differences in estimates were likely due to the narrower range of the Swedish tariff. While the UK tariff ranges from negative values to 1, the Swedish tariff has a narrower range from 0.34 to 0.97. Applying different rating approaches (i.e., experienced health in the Swedish tariff vs. hypothetical health in the UK tariff) might be one reason for the difference in the observed range of scores. It has been reported that the experienced health approach generally results in higher values than does the hypothetical health approach [127, 128]. Several reasons have been suggested for these discrepancies, including failure to rate the same health state, having different measuring rods, and patient adaptation to particular health states [129].

GLP-1 agents are cost-effective options as add-ons to metformin

The results of our modelling study indicated that, assuming a WTP value of 500,000 SEK, the treatment strategy using GLP-1 agents are cost-effective in comparison to treatment strategies using either DPP-4 inhibitors or NPH insulin from both the societal and health care payer's perspective. These results imply that later transition to NPH insulin (i.e., as third-line therapy after providing incretin-based therapies) is cost-effective compared with earlier transition (i.e., as second-line without providing incretin-based therapies) with ICERs of less than 200,000 SEK.

While GLP-1 agents are more expensive than DPP-4 inhibitors, they are associated with a greater reduction in HbA1c and greater weight loss, which makes them a cost-effective option. These effects influence health outcomes in two ways: first, by resulting in lower cumulative incidence of T2DM-related complications and

second, because higher reduction in HbA1c delays switching to NPH insulin, resulting in fewer expected episodes of hypoglycaemia from a lifetime perspective. This finding was most sensitive to the disutility due to BMI > 25, when assuming no disutility resulted in an ICER higher than SEK 500,000 per QALY gained. This suggests that there should be a sub-group of patients with BMI > 25 for whom GLP-1 is even more cost effective in comparison to DPP-4 [130].

While NPH insulin was associated with a greater HbA1c reduction, it also resulted in weight gain and more hypoglycaemic episodes than did incretin-based therapies. Our results suggest that initiating NPH insulin as third-line therapy after providing incretin-based therapies is a cost-effective option compared with initiating NPH insulin as second-line treatment. However, it should be noted that the cost-effectiveness of incretin-based therapies decreased as the HbA1c threshold for switching to NPH insulin increased. This implies that as the number of years on these treatments increases, the marginal costs of the treatments come to outweigh the marginal benefits, and the ICER rises. While these results were most sensitive to the assumptions related to the incidence of hypoglycaemia and the disutility of hypoglycaemia and insulin, the main conclusion was robust to all these variations.

The ICERs reported in our study is higher than that reported in a previous study in Sweden which applied the same model [131]. Differences in utility decrement, baseline characteristics, and treatment effects might partly contribute to this discrepancy. Moreover, the ICERs reported in our study are higher than those reported in studies in other countries [130, 132, 133]. Alongside above mentioned differences, there are differences in perspective (societal vs. healthcare payer), costs of medications/complications, and applied model that limits comparability of our study with previous ones. All these studies applied the CORE diabetes model [134], which uses the different risk equations for macrovascular complications than does the model we applied.

Heterogeneities in the effects of explanatory variables

An important finding of this thesis that might have substantial implications for risk equations and CSMs was heterogeneity in the effects of a number of explanatory variables on outcomes in papers II and III. Failure to account for these heterogeneities might lead to biased results of CSMs.

In paper II, we found heterogeneities in the effects of covariates within the same event (i.e., first or second events) as well as between events. An example of within-event heterogeneity is the association between gender and the risk of first and second AMI. While the risk of a first AMI was lower for women, women were more vulnerable to a second AMI event. Similar heterogeneity has been reported in general population, i.e., while the risk of first MI is higher among men, women are more susceptible for a recurrent event [135]. In MONICA Iceland Study [136], the male/female rate ratio of the first MI was 3.0 and for the second MI this figure declined to 1.2. This heterogeneity implies that if a CSM considers only the risk of first AMI, then treating women would appear to be less cost-effective, while if the higher risk of a second event is considered, the previous conclusion might be incorrect. The varying effects of a number of biomarkers on the risk of first and second events constituted another example of within-event heterogeneity, as some biomarkers were significant predictors of the first, but not the second, events. The similar finding was reported in the UKPDS outcome model 2 [102].

As an example of between-event heterogeneity, consider the effects of BMI. While BMI was not associated with the risk of AMI or stroke events, it was an independent predictor of first HF and NAIHD. This illustrates how specific-event equations may lead to more accurate results than does estimating one equation for all events pooled as "CVD events", which is a common practice in developing risk equations [137, 138].

In paper III, we found evidence suggesting the presence of heterogeneities in associations between a number of diabetes-related complications and HU scores in terms of gender, multiple events, and time since event. The results indicated that women were more negatively influenced by microvascular complications, while men were more sensitive to macrovascular complications. This gender heterogeneity in response to health measures is in line with the results of previous studies [139, 140], implying that men and women respond differently to factors related to their health.

The HU deterioration due to multiple stroke and NAIHD episodes was more profound than that due to a single event. This means that separating the first and subsequent events instead of pooling them as a history of events might lead to more accurate CSMs. For example, if intervention A is more effective than intervention B at preventing the occurrence of multiple stroke events, then failure to distinguish between

multiple and single events will lead to the underestimation of QALYs gains due to intervention A and biased results favouring intervention B, all else being equal.

The presence of these heterogeneities is in line with growing interest in personalized medicine in clinical practice [141, 142] and economic evaluations [143, 144]. It is believed that capturing the patient heterogeneity would support a more efficient allocation of limited health resources and increase population health gains [145]. For example, if an intervention which is cost effective for females and not for males is not reimbursed, then there would be forgone health benefits as a subgroup of patients does not receive the optimal treatment [146]. Due to its importance, capturing patient heterogeneity is considered as a quality criterion for good practice in economic evaluations [147].

Despite the importance of capturing these heterogeneities, these are frequently neglected in current economic evaluations and subsequent policy decisions. It is suggested that a number of reasons might contribute to this neglect including a lack of guidance how to acknowledge patient heterogeneity, the large demand of data, increasing model complexity, and ethical or equity concerns when excluding patient subgroups [148, 144]. For example, a recent systematic review showed that while most pharmacoeconomic guidelines suggested general methodological advice to acknowledge patient heterogeneity, there is no specific guidance on exploring and reflecting heterogeneity in cost-effectiveness analyses [148]. Our results suggest that acknowledging patient heterogeneity and effort to incorporating them in economic evaluations of T2DM treatments might improve the efficiency of health care in Sweden.

Obesity as a major concern

The results of our thesis indicate that prevention and treatment of obesity should be considered as a main priority in management of T2DM in Sweden. In paper I, we found that BMI was positively associated with higher levels of other biomarkers. Moreover, the coefficient on the lagged variable of BMI was higher than for other biomarkers, implying that weight was less readily lost by T2DM patients in Sweden. Failure to achieve favourable changes in BMI among T2DM patients was reported in a previous study by the NDR [149]. Weight gain related to glucose-lowering drugs, especially insulin, might partly explain weight loss difficulties among T2DM patients [150].

In paper II, we found that BMI was an independent predictor of the risk of first HF and NAIHD after controlling for other biomarkers. There is inconsistent evidence of association between BMI and CVD outcomes in people with T2DM. The results of the PROactive study indicated that in patients with T2DM and CVD co-morbidity, all-cause mortality and hospitalization were lower in overweight and mildly obese patients than in patients with BMI < 25 kg/m^2 [151]. On the other hand, findings of large observational studies have indicated increased CVD risk with increasing BMI in T2DM patients [152-155].

In paper III, we found that every unit increase in BMI was associated with a 0.006-unit reduction in the UK EQ-5D index score after controlling for T2DM-related complications and modality of treatment. This estimate is similar to the estimates from previous studies for BMI ≥ 25 kg/m^2 [122, 156]. In paper IV, we found that while therapies had similar effects on HbA1c, treatment strategy producing the greatest weight reduction (i.e., GLP-1) was a cost-effective option compared with other treatment strategies.

Taken together, our findings suggest that, besides its indirect effect through biomarkers and T2DM-related complications, BMI has an important direct impact on health outcomes among patients with T2DM. Moreover, the weight gain associated with T2DM therapies and the fact that patients with T2DM are generally overweight before starting any type of anti-diabetic therapy highlight the importance of weight loss in T2DM management through lifestyle interventions and anti-diabetic treatments that are weight-neutral or associated with weight loss. These facts imply that weight management has important clinical and economic benefits for patients and societies. A recent study showed that a moderate weight loss (≥ 5% of initial body weight) over four years of follow up was associated with 13% reduction in costs of diabetes medications [157]. In Sweden, the results of the Swedish Obese Subjects (SOS) study indicated significant clinical and economic benefits resulting from bariatric surgery for patients with T2DM [158-162] . From a computer modeler point of view, these findings imply that including BMI in CSMs is crucial in order to evaluate therapeutic interventions for T2DM.

Strengths and limitations

A major strength of our study was the availability of longitudinal data on biomarkers and complications for a large number of T2DM patients obtained from reliable and validated national registers of diabetes,

morbidity, and mortality in Sweden. These data were collected from the NDR database, with high coverage of diabetes patients in Sweden, suggesting that they are highly representative. In addition, these data represent clinical patterns in the post-UKPDS era reflecting more updated data on situation of T2DM management compared to the data from the UKPDS including patients since 1971. These data were obtained during routine clinical practice and no exclusion criteria regarding risk factors or complication history were applied, which may increase the generalizability of our results. Using registry data on T2DM-related complications is a major advantage compared with studies that use self-reported data, which are prone to recall bias.

In paper I, we applied an econometric model that produces less biased estimates than does the OLS method applied in the UKPDS Outcome Model [64]. Furthermore, the dynamic specification of the model enabled us to distinguish between the short- and long-term effects of changes in covariates on biomarkers. The time-path equations for LDL cholesterol and BMI had not previously been estimated among patients with T2DM. Applying the Swedish tariff to estimate HU decrement in paper III is among the first applications of this tariff in Sweden. Providing estimates based on both the UK and Swedish tariffs facilitates the conducting of sensitivity analysis in future cost–utility analyses, as recommended by the TLV in Sweden. In paper IV, we applied utility decrements for a number of complications from a Swedish sample with T2DM, and used Swedish-specific risk equations for macrovascular complications, which allowed us to estimate the risk of first and second events, and extracted treatment effects on the main biomarkers (i.e., HbA1c and weight) from a meta-analysis instead of a single clinical trial. We also used the HbA1c threshold to determine the treatment pathway, reflecting clinical practice and national guidelines. These improve the external validity and relevance of our results to policy-making in the Swedish setting.

The results of our study should be interpreted in light of certain limitations. The main limitation of our study is its observational design, which is prone to three main types of biases, i.e., selection bias, information bias, and confounding bias [163], possibly resulting in biased estimates. As we used register-based data, the possibility of error in the recording of data, including biomarkers and ICD-10 codes, may be a source of information bias. For example, data on smoking may have been biased due to underreporting by participants and under-recording by health care staff.

Due to lack of data on some explanatory variables, confounding bias is possible in our study. In particular, socioeconomic variables and the presence of comorbidities (e.g., neuropathy) are potential confounders in our studies that we did not control for due to lack of data. While selection bias might not be a concern in papers I, II, and IV, in paper III the EQ-5D data were collected using a mail survey with a 65% response rate, which raises the possibility of selection bias. However, characteristics of the sample used in paper III were similar to those of the samples used in other papers (Table 1). In paper III, we measured HU scores using the EQ-5D, which might be unable to discriminate across complications or treatment modality in the diabetes context [164, 165]. In addition, not controlling for the severity of diabetes-related complications due to lack of data might limit both the internal and external validity of our findings in paper III. Paper III used a cross-sectional design, implying that no causal inference should be drawn from the results.

In paper IV, we included only hypoglycaemia as a treatment-related adverse event in the model. The incretin-based therapies are associated with more episodes of non-hypoglycaemia-related adverse events, such as nausea, than is insulin glargine [166, 167]. If insulin glargine and NPH insulin are comparable with respect to adverse events, then our reported ICERs in comparing GLP-1/DPP-4 with NPH insulin are somewhat underestimated. However, we do not expect this to have influenced the final conclusion, as these ICERs are far from our assumed SEK 500,000 WTP value. Due to lack of data, we did not take into account the possibility of treatment discontinuation by patients, which might limit the generalizability of our findings. Moreover, our conclusions are based on a baseline HbA1c of 7.7%, so generalizability to patients with higher HbA1c values is limited.

Future research

The present thesis provides part of the data required in conduction economic evaluation studies using CSMs or alongside clinical trials in the T2DM context in Sweden. However, there are a number of issues that can be dealt with in future studies. In paper I, we estimated time-path equations for five biomarkers over a maximum of seven years of follow up among newly diagnosed T2DM patients. Considering the availability of data covering a longer period, we suggest updating these equations with data on a larger sample (including previously diagnosed patients) over a longer period.

In paper II, we estimated the risk of four major macrovascular complications among patients with T2DM. As risk equations for microvascular complications are also required in CSMs, estimating the risk of first and subsequent microvascular events using the NDR data is a subject for future research. While the performance of equations in papers I and II was validated among Swedish patients, future research should validate them in other populations to evaluate the feasibility of transferring them to other settings.

In paper III, the HU scores were estimated using a generic measure (i.e., EQ-5D) at a single point of time, which limits the validity of the findings. Using diabetes-specific measures alongside the EQ-5D and evaluating HU at multiple points in time might largely mitigate these limitations. In conducting these studies in the future, collecting data on socioeconomic variables should be considered to limit the possibility of confounding bias. In paper IV, a cohort simulation model was applied to evaluate the cost-utility of three treatment strategies for T2DM. Using microsimulation models to conduct the same analysis and using the same model to compare the costs and outcomes of other treatment strategies would be other suitable subjects for future studies.

Conclusion

CSMs are widely used to conduct economic evaluations to support informed decision-making concerning resource allocation in health care. There is a lack of such models based on country-specific data for T2DM in Sweden. The current thesis aimed to fill this gap by producing equations required to develop/update a CSM of T2DM using data from routine clinical practice in Sweden. The results indicated the importance of developing and refining the equations as new data become available. A current cohort simulation model was updated using these equations and was applied to evaluate the lifetime costs and outcomes of three T2DM treatment strategies in routine clinical practice in the country. The main conclusions related to the thesis are as follows:

- The time-path equations for five major biomarkers were estimated for a large sample of newly diagnosed T2DM patients in the post-UKPDS era. The results highlight the necessity of updating the time-path equations for CSMs as new data become available. Life style interventions for weight control should be considered integral to any disease management strategy in the T2DM context.

- There are significant heterogeneities in the effects of covariates on the risk of first and second T2DM-related macrovascular events. Taking these heterogeneities into account by including separate risk equations for first and second events might improve the accuracy of CSMs.
- The HU scores associated with a number of T2DM-related complications were estimated and can be used in cost–utility analyses in Sweden. Among women, HU was more sensitive to microvascular complications, while among men macrovascular complications had a more negative impact on HU. Due to the narrower range of the Swedish tariff, the conclusions based on it might differ from those based on the UK tariff, and this should be considered when interpreting the findings of economic evaluations using the Swedish tariff.
- Assuming a WTP of SEK 500,000 per QALY, treatment strategies with incretin-based therapies (i.e., GLP-1 and DPP-4) are cost-effective options compared to NPH insulin as an add-on to metformin among T2DM patients who fail to achieve HbA1c $\leq$ 7% in Sweden. In addition, given current treatment costs and evidence regarding treatment efficacy (i.e., in terms of HbA1c and weight), GLP-1 agonists could be considered cost-effective relative to DPP-4 inhibitors in a Swedish setting.

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