


ORIGINAL ARTICLE

The burden of poor glycaemic control in people with newly diagnosed type 2 diabetes in Sweden: A health economic modelling analysis based on nationwide data

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Abstract

Aim: To evaluate the economic and clinical burden associated with poor glycaemic control in Sweden, in people with type 2 diabetes (T2D) initiating first-line glucose-lowering therapy.

Materials and Methods: Population data were obtained from Swedish national registers. Immediate glycaemic control was compared with delays in achieving control of 1 and 3 years, with outcomes projected over 3, 10 and 50 years in the validated IQVIA CORE Diabetes Model. Glycaemic control was defined as glycated haemoglobin (HbA1c) targets of 52, 48 and 42 mmol/mol, as recommended in Swedish guidelines, according to age and disease duration. Costs (expressed in 2019 Swedish krona [SEK]) were accounted from a Swedish societal perspective.

Results: Immediate glycaemic control was associated with population-level cost savings of up to SEK 279 million and SEK 673 million versus delays of 1 and 3 years, respectively, as well as small population-level life expectancy benefits of up to 1305 and 2590 life years gained. Reduced levels of burden were a result of lower incidence and delayed time to onset of diabetes-related complications.

Conclusions: Even in people with T2D initiating first-line glucose-lowering therapy, the economic burden of poor glycaemic control in Sweden is substantial, but could be reduced by early and effective treatment to achieve glycaemic targets.

KEYWORDS

diabetes complications, glycaemic control, health economics, type 2 diabetes

1 | INTRODUCTION

Diabetes is associated with a substantial clinical and economic burden worldwide, with type 2 diabetes (T2D) accounting for more than 90% of cases.¹ In Sweden, diabetes was estimated to affect approximately 5% of the population in 2019, accounting for more than SEK 30 billion of

healthcare expenditure, and five to six people were estimated to die from diabetes-related complications every day.^{1,2} Approximately 70% of direct diabetes-related expenditure is associated with the treatment of diabetes-related complications, while indirect costs relating to lost workplace productivity also constitute a substantial burden.^{3–5} Reducing the incidence of complications as early as possible in individuals' lifetimes is

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therefore crucial in reducing the clinical and economic burden associated with the disease.

Achieving glycaemic control (measured via glycated haemoglobin [HbA1c]) represents a key target for people with T2D, as several landmark studies have indicated that maintaining lower HbA1c levels can reduce the incidence of long-term diabetes-related complications.^{6–10} Moreover, early and intensive multifactorial risk factor control has been shown to significantly lower the risk of cardiovascular and microvascular events, as well as reduce the risk of cardiovascular-related and all-cause mortality.^{11–13} Maintaining diabetes-related risk factors within target ranges has also been associated with little or no excess risk of death, myocardial infarction or stroke compared with the general population, while HbA1c values of 48 mmol/mol (6.5%) or higher and 53 mmol/mol (7.0%) or higher have been associated with increased risks of diabetes-related complications and mortality, respectively, even over the short term.^{14,15} Ensuring individuals are kept at glycaemic targets early in the treatment algorithm therefore represents one of the best strategies for reducing the incidence of costly diabetes-related complications.

Early and intensive glycaemic control is endorsed in Sweden, with an HbA1c target of 52 mmol/mol (6.9%) recommended for the general population with T2D, and lower targets of 42–48 mmol/mol (6.0%–6.5%) recommended for people with newly diagnosed T2D aged younger than 55 years at diagnosis.¹⁶ Despite this, recent evidence has suggested that poor glycaemic control is a problem in Sweden, with a substantial number of people not achieving glycaemic targets.^{17,18} Data from the Swedish National Diabetes Register (NDR) indicated that 45% of all Swedish people with T2D and 30% of recently diagnosed individuals were not achieving glycaemic control (HbA1c 52 mmol/mol or lower) in 2019.¹⁷ In addition, more than 40% of people with recently diagnosed T2D did not reach a glycaemic target of 48 mmol/mol or lower, a concerning statistic given the association between HbA1c values below this threshold and a lower risk of diabetes-related complications.^{15,17}

Considering the wide array of glucose-lowering therapies available for treating T2D, there is substantial scope for reducing the clinical and economic burden associated with poor glycaemic control by intensifying individuals to more efficacious therapies as early as possible, particularly in newly diagnosed populations.¹⁹ However, the decentralized market of Sweden represents a challenge, as regional healthcare payers often consider different time horizons when evaluating budgets. The current analysis, based on nationwide Swedish data, therefore aimed to evaluate the burden associated with poor glycaemic control in people with newly diagnosed T2D failing to reach glycaemic targets with their initial glucose-lowering medication over both short- and long-term time horizons, and to quantify the potential gains in life expectancy, quality-adjusted life expectancy and cost savings should glycaemic control be achieved.

2 | MATERIALS AND METHODS

2.1 | Study design and population

The level of poor glycaemic control in Sweden was evaluated in people with T2D who were new users of glucose-lowering treatment

(Figure 1). Inclusion criteria were defined as filing of at least one prescription of any glucose-lowering medication from 1 January 2015 to 31 December 2016. The date of the first prescription during this time period was denoted ‘first prescription’, with the index date defined as 12 months after first prescription. Exclusion criteria were defined as filing of a prescription of any glucose-lowering drug within 12 months before first prescription (to ensure new users of glucose-lowering treatment were captured), or not fulfilling the definition for T2D at the index date. Data for relevant clinical variables, including HbA1c, were retrieved from 1 month before to 12 months after the index date. Therefore, data for relevant clinical variables, including HbA1c, were retrieved 11–24 months after first prescription of a glucose-lowering medication, giving the physician time to uptitrate and intensify treatment to reach the target. Where multiple measurements of clinical variables existed, values that were measured closest to the index date were used.

Data for these individuals were obtained from nationwide healthcare registers, including the NDR, the Swedish Prescribed Drug Register (PDR) and the National Patient Register (PAR). The NDR includes information on risk factors, diabetes-related complications and prescribed medications for people with diabetes aged 18 years or older, and captures virtually all people with diabetes in Sweden, with each individual providing consent for inclusion.^{20,21} Medication data were obtained from the PDR, which records all filed prescriptions from all pharmacies in Sweden.²² Data on co-morbidities were captured through the PAR, which records all admissions to hospitals and outpatient specialist visits.²³ Extracted data, which included age, duration of diabetes, proportion of males, HbA1c, blood pressure, serum lipid levels, body mass index (BMI) and proportion of smokers, were used to inform the baseline cohort characteristics in the model (Table 1). Racial characteristics were assumed to be 100% White, and heme levels (14.5 g/dL), white blood cell count ($6.8 \times 10^6/\text{mL}$), heart rate (72.0 beats per min) and waist to hip ratio (0.9) were set to IQVIA CORE Diabetes Model default values, in lieu of Sweden-specific data for these variables.

Three populations were simulated in the current study. Primary analyses were performed in individuals in poor control in the full population of people with T2D, capturing all individuals above the 52 mmol/mol glycaemic target in Sweden as well as those in even poorer control (those with HbA1c values ≥ 58 mmol/mol). Subgroup analyses were performed in the population with T2D aged 65 years or younger (Table 1).

2.2 | Modelling approach

The impact of poor glycaemic control was evaluated by comparing immediate glycaemic control (setting HbA1c to target values) with delays in achieving control of 1 and 3 years, over time horizons of 3, 10 and 50 years (Figure 2). It should be noted that individuals were not expected to live for 50 years; this time horizon was applied to capture all individual mortality. In the primary analyses of the full population, glycaemic control was defined as the general HbA1c target of

52 mmol/mol (6.9%) in Sweden.¹⁶ Two baseline HbA1c levels were tested, based on the mean HbA1c values of individuals with HbA1c levels of 53 mmol/mol or higher ($\geq 7.0\%$; $n = 19,477$; mean HbA1c of 64 mmol/mol [8.0%]) and 58 mmol/mol or higher ($\geq 7.5\%$; $n = 11,753$; mean HbA1c of 70 mmol/mol [8.6%]) in the full population. In the population aged 65 years or younger ($n = 30,693$ with measurable HbA1c), with a mean age of 54 years at baseline, glycaemic control was defined as the stricter targets of 42 and 48 mmol/mol (6.0% and 6.5%, respectively), with baseline HbA1c based on the mean value of the entire cohort (52 mmol/mol [6.9%]). Population-level burden was calculated as the product of the individual-level results from the model and the numbers of individuals in each dataset.¹⁶

The IQVIA CORE Diabetes Model (version 9.0) was used to project outcomes over the short and long term. The architecture, assumptions, features and capabilities of the model have been previously published.²⁴ The model is a widely used, non-product-specific, diabetes policy analysis tool that has been validated against real-life data, both upon original publication in 2004 and more recently in 2014.^{25,26} The model has also been used in numerous published cost-effectiveness analyses and submissions of novel diabetes

interventions worldwide.^{27–31} Relevant model outcomes include cumulative incidence and time to onset of complications, life expectancy, quality-adjusted life expectancy, direct costs arising from treatment of diabetes-related complications and indirect costs arising from lost workplace productivity.

All analyses were performed using a first-order Monte Carlo approach, simulating 1000 cohorts, each consisting of 1000 individuals with identical risk factors (based on the mean estimates reported in Table 1), with the exceptions of sex and smoking status, with outcomes stable at this number of iterations. Future clinical and cost benefits were discounted at 3.0% per annum, in line with pharmacoeconomic guidance for the Swedish setting.³² Background mortality was captured through Sweden-specific life tables published by the World Health Organization, with remaining mortality captured from diabetes-related complications.³³

2.3 | Costs and other model settings

Costs were accounted from a Swedish societal perspective and expressed in 2019 Swedish krona (SEK). Direct costs captured the costs

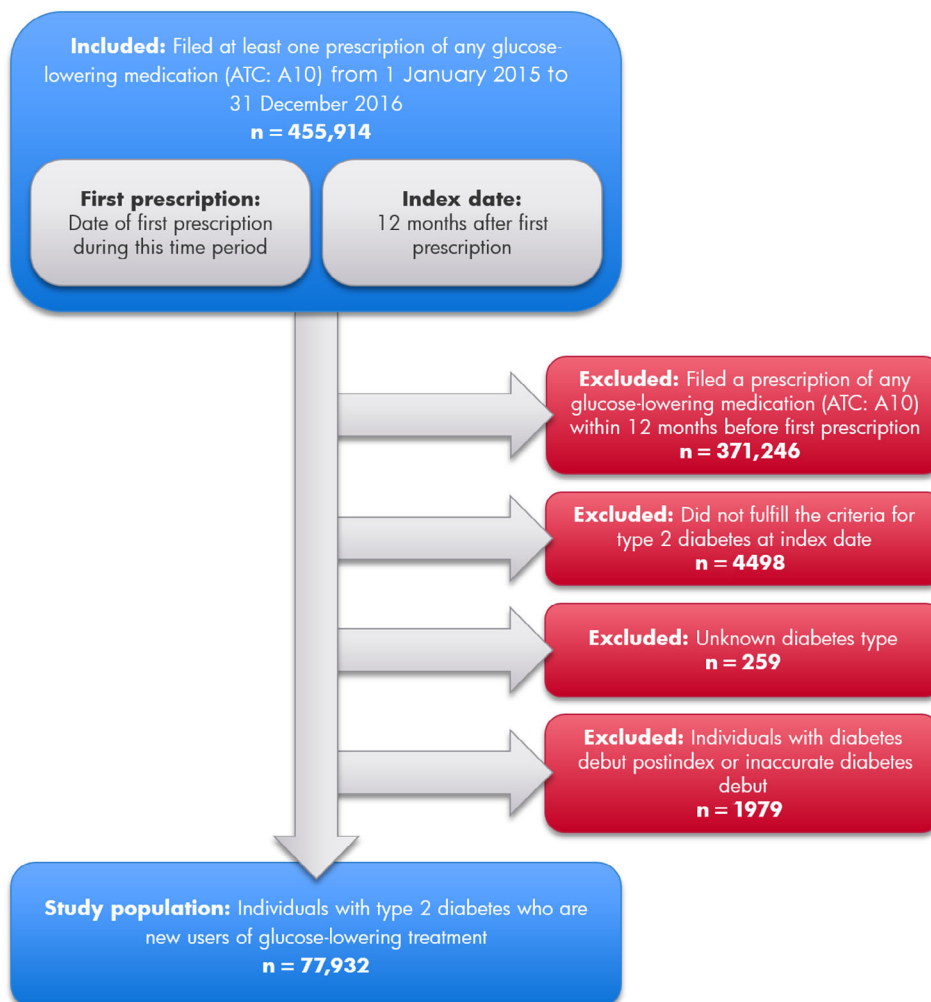


FIGURE 1 Selection of study population

TABLE 1 Baseline cohort characteristics applied in the analyses

Characteristic	Mean (standard deviation)	
	Full population (n = 77,932 ^a)	Population aged ≤65 years (n = 37,831 ^a)
Age (years)	64.9 (13.1)	54.1 (8.7)
Duration of diabetes (years)	4.2 (5.2) ^b	3.2 (3.9) ^b
Male (%)	58.6	61.8
HbA1c (mmol/mol)	Baselines of 64.0 (0.0) and 70.0 (0.0) tested	51.5 (13.9)
Systolic blood pressure (mmHg)	134.5 (16.0)	132.8 (15.6)
Diastolic blood pressure (mmHg)	78.7 (10.0)	81.1 (9.8)
Total cholesterol (mmol/L)	4.7 (1.2)	4.8 (1.2)
HDL cholesterol (mmol/L)	1.3 (0.4)	1.2 (0.4)
BMI (kg/m ²)	30.2 (5.7)	31.4 (6.0)
Smokers (%)	15.4	20.6

Abbreviations: BMI, body mass index; HDL, high-density lipoprotein.

^aData for each characteristic were not available for all patients in each population.

^bRounded to 4.00 in the full population and 3.00 in the population aged ≤65 years, as the model only accepts integer values for duration of diabetes.

of treating diabetes-related complications and the costs of patient management, which were taken from published sources and inflated to 2019 SEK where appropriate using the most recently available inflation rate for health published by Statistics Sweden (Table S1).^{34–41} Quality of life was estimated using the ‘CORE Default Method’, which involves taking the lowest state utility associated with existing complications and adding event disutilities for any events that occur in that year to create annual utility scores for each simulated patient.²⁴ Utilities were taken from published sources (Table S2).^{42–48} No pharmacy or consumables costs were included in the analyses. Indirect costs arising from lost workplace productivity were based on the days off work estimates published by Sørensen and Ploug and the most recent annual salaries available in Sweden (Table S3).^{49,50} Indirect costs were only accrued while simulated individuals were below the set retirement age (65 years). Progression of physiological variables, including blood pressure, serum lipid levels and BMI, was assumed to remain constant over the duration of the analyses, to allow the impact of different levels of glycaemic control to be evaluated.

3 | RESULTS

3.1 | Primary analyses in the full population

The full population consisted of 77,932 people with T2D who were new users of glucose-lowering medication, with a mean age of

65 years, a mean diabetes duration of 4 years, a mean BMI of 30.2 kg/m², and 58.6% categorized as male (Table 1). A total of 19,477 and 11,753 people were estimated to be in poor glycaemic control (with HbA1c levels of ≥53 and ≥58 mmol/mol, respectively).

Modelled projections indicated that even short delays in achieving glycaemic control can have a substantial impact on costs, as well as small effects on life expectancy and quality-adjusted life expectancy, in people with T2D over both short- and long-term time horizons in Sweden (Tables 2, 3 and S5). Benefits were more pronounced over longer time horizons and versus longer delays in achieving glycaemic control, and were a result of reduced incidence and increased time to onset of diabetes-related complications with immediate glycaemic control.

For people with HbA1c levels of 53 mmol/mol and higher, with a mean baseline HbA1c of 64 mmol/mol, immediate glycaemic control (an HbA1c of 52 mmol/mol) was associated with population-level cost savings of SEK 39, 50 and 113 million over 3, 10 and lifetime time horizons, respectively, compared with a 1-year delay in achieving control (Table 3). Immediate glycaemic control was also projected to be associated with improvements in population-level life expectancy of 136, 467 and 1305 years over 3, 10 and lifetime time horizons, respectively, but individual-level improvements were small. Similar patterns were observed in quality-adjusted life expectancy (Table S5). Further cost savings of SEK 60, 219 and 303 million were observed over time horizons of 3, 10 and 50 years, respectively, when compared with a longer delay of 3 years in achieving glycaemic control. Population-level life expectancy benefits were also increased, to 117, 915 and 2590 years over time horizons of 3, 10 and 50 years, respectively, but individual-level benefits remained minor.

For people with HbA1c levels of 58 mmol/mol and higher, with a mean baseline HbA1c of 70 mmol/mol, immediate glycaemic control (an HbA1c of 52 mmol/mol) was associated with population-level cost savings of SEK 38, 77 and 107 million, over time horizons of 3, 10 and 50 years, respectively, versus a delay in achieving control of 1 year (Table 3). Population-level life expectancy was projected to be improved by 118, 470 and 928 years, although individual-level benefits were slight. Quality-adjusted life expectancy outcomes followed this pattern (Table S5). Over the same time horizons, immediate glycaemic control was associated with cost savings of SEK 69, 214 and 293 million versus a delay of 3 years, with projected benefits in population-level life expectancy of 129, 858 and 2257 years.

3.2 | Subgroup analyses in the population aged 65 years or younger

The population aged 65 years or younger comprised 37,831 people with T2D who were new users of glucose-lowering medication, with a mean age of 54 years, a mean duration of diabetes of 3 years, mean baseline HbA1c of 52 mmol/mol, mean BMI of 31.4 kg/m², and 61.8% categorized as male (Table 1). Within this cohort, data on HbA1c levels were available for 30,693 individuals. In this population,

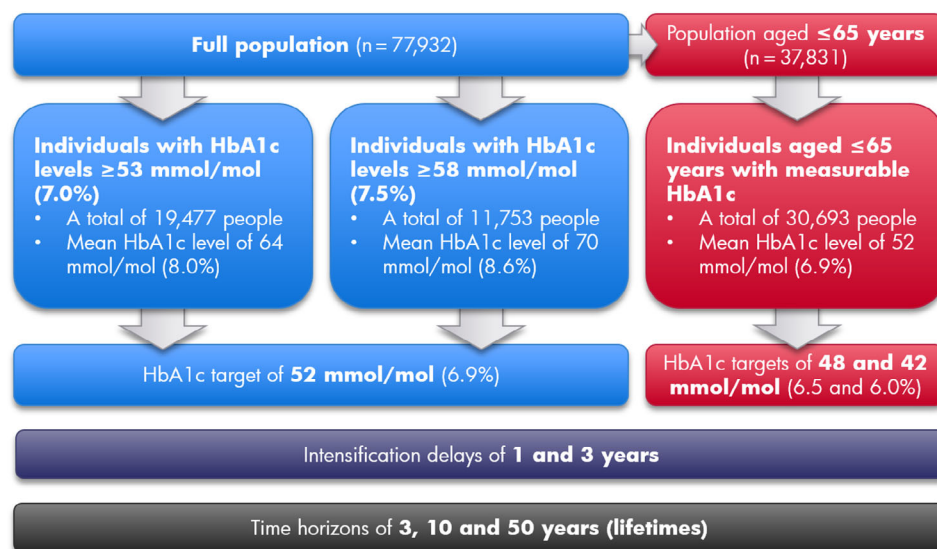


FIGURE 2 Overview of modelled scenarios

immediate glycaemic control (an HbA1c of 48 mmol/mol) was associated with population-level cost savings of SEK 46, 63 and 279 million versus a delay in achieving control of 1 year, over time horizons of 3, 10 and 50 years, respectively (Table 3). Population-level life expectancy was comparable over 3- and 10-year time horizons, with small benefits of 982 years observed over individuals' lifetimes. Compared with a 3-year delay in achieving glycaemic control, immediate control was associated with combined direct and indirect cost savings of SEK 67, 248 and 527 million over 3-, 10- and 50-year time horizons, respectively, while population-level life expectancy was comparable over a 3-year time horizon and slightly improved by 184 and 921 years over 10- and 50-year time horizons, respectively. Improvements in individual-level life expectancy and quality-adjusted life expectancy remained small throughout.

When lowering the HbA1c target to 42 mmol/mol, immediate glycaemic control was associated with combined cost savings of SEK 79, 192 and 100 million versus a delay of 1 year over 3-year, 10-year and lifetime time horizons, respectively. Life expectancy was comparable over 3- and 50-year time horizons, with small population-level gains of 215 life years over a 10-year time horizon (Table 3). Compared with a delay in achieving glycaemic control of 3 years, immediate control was associated with lower combined costs of SEK 156, 617 and 673 million, while population-level life expectancy was projected to be comparable over a 3-year time horizon and slightly improved by 614 and 2118 years over 10- and 50-year time horizons, respectively. Similar outcomes were observed for quality-adjusted life expectancy (Table S5).

4 | DISCUSSION

This large cohort study showed that delays in achieving glycaemic control in people with newly diagnosed T2D were projected to constitute a considerable economic burden in Sweden over both the short and long term. Projected cost savings with immediate glycaemic control were shown to increase over longer delays and time horizons in

all but one analysis: bringing people aged 65 years or younger to a target HbA1c of 42 mmol/mol, versus a delay of 1 year over a 50-year time horizon, was associated with reduced cost savings compared with the same analysis over a 10-year time horizon. These results were most likely a result of increased survival in the poor control arm because of inherent variation in the model, but cost savings were still achieved through early glycaemic control. All other analyses led to substantial cost savings with immediate glycaemic control versus remaining in poor control.

The inclusion of indirect costs in the analysis was aligned with health economic guidance for the Swedish setting, and represents a strength of the current study.³² However, the full population evaluated in the primary analyses did not accrue indirect costs, as the average age was beyond the set retirement age for Sweden (65 years) at baseline. In the population aged 65 years or younger, indirect costs were accrued for the first 10 years of the analyses, and represent a substantial portion of the combined cost savings observed with immediate glycaemic control; these results show the importance of identifying younger individuals with newly diagnosed T2D and ensuring that glycaemic control is achieved and maintained, to reduce both the short- and long-term economic burden associated with lost workplace productivity and early retirement.

The use of the stricter HbA1c targets of 42 and 48 mmol/mol in the population aged 65 years or younger was based on the mean age at baseline (54 years) and guidance in Sweden, which indicates a lower glycaemic target for individuals with newly diagnosed T2D aged younger than 55 years.¹⁶ These subgroup analyses show that further reductions in HbA1c beyond the general target of 52 mmol/mol can be beneficial to people with T2D. However, it should be noted that these analyses did not account for treatment-related adverse events, such as hypoglycaemia, which can occur with certain glucose-lowering medications when aiming for lower HbA1c levels, and these effects should be considered when assessing individualized therapies.¹⁹ That acknowledged, the impact of hypoglycaemia on the estimates of burden was most likely negligible given the HbA1c values applied in the current analysis; Lipska et al. reported a comparable risk of

TABLE 2 Patient-level health economic outcomes for all analyses

Analysis	Life expectancy, years			Combined costs, SEK		
	Immediate control	Poor control	Difference	Immediate control	Poor control	Difference
Full population, baseline HbA1c 64 mmol/mol (8.0%), HbA1c target 52 mmol/mol (6.9%)						
1-year delay, 3-year time horizon	2.60	2.59	+0.01	67,069	69,066	-1997
1-year delay, 10-year time horizon	7.09	7.07	+0.02	201,641	204,203	-2561
1-year delay, 50-year time horizon	11.52	11.46	+0.07	390,498	396,295	-5797
3-year delay, 3-year time horizon	2.60	2.59	+0.01	67,069	70,162	-3093
3-year delay, 10-year time horizon	7.09	7.05	+0.05	201,641	212,895	-11,253
3-year delay, 50-year time horizon	11.52	11.39	+0.13	390,498	406,035	-15,538
Full population, baseline HbA1c 70 mmol/mol (8.6%), HbA1c target 52 mmol/mol (6.9%)						
1-year delay, 3-year time horizon	2.60	2.59	+0.01	67,069	70,314	-3245
1-year delay, 10-year time horizon	7.09	7.06	+0.04	201,641	208,167	-6526
1-year delay, 50-year time horizon	11.52	11.45	+0.08	390,498	399,611	-9113
3-year delay, 3-year time horizon	2.60	2.59	+0.01	67,069	72,899	-5830
3-year delay, 10-year time horizon	7.09	7.02	+0.07	201,641	219,868	-18,227
3-year delay, 50-year time horizon	11.52	11.33	+0.19	390,498	415,437	-24,939
Population aged ≤65 years, baseline HbA1c 52 mmol/mol (6.9%), HbA1c target 48 mmol/mol (6.5%)						
1-year delay, 3-year time horizon	2.74	2.74	0.00	105,606	107,091	-1484
1-year delay, 10-year time horizon	7.92	7.92	0.00	506,163	508,230	-2068
1-year delay, 50-year time horizon	15.98	15.94	+0.03	722,579	731,664	-9085
3-year delay, 3-year time horizon	2.74	2.74	0.00	105,606	107,804	-2198
3-year delay, 10-year time horizon	7.92	7.91	+0.01	506,163	514,243	-8080
3-year delay, 50-year time horizon	15.98	15.95	+0.03	722,579	739,738	-17,159
Population aged ≤65 years, baseline HbA1c 52 mmol/mol (6.9%), HbA1c target 42 mmol/mol (6.0%)						
1-year delay, 3-year time horizon	2.75	2.74	0.00	102,716	105,274	-2558
1-year delay, 10-year time horizon	7.94	7.93	+0.01	481,285	487,553	-6268
1-year delay, 50-year time horizon	16.18	16.18	0.00	681,659	684,917	-3258
3-year delay, 3-year time horizon	2.75	2.74	0.00	102,716	107,804	-5088
3-year delay, 10-year time horizon	7.94	7.92	+0.02	481,285	501,372	-20,087
3-year delay, 50-year time horizon	16.18	16.11	+0.07	681,659	703,585	-21,925

Abbreviation: SEK, 2019 Swedish krona.

hypoglycaemia in people with T2D with HbA1c levels of 42–52 mmol/mol (6.0%–6.9%), 53–63 mmol/mol (7.0%–7.9%) and 64–74 mmol/mol (8.0%–8.9%).⁵¹

While the current study is hypothetical in nature, the use of data from the NDR represents a key strength. The NDR is a highly respected and accurate source and allows monitoring of the degree to which guidelines and recommendations are being followed, and no high-quality alternatives capturing a similar number of individuals with T2D in Sweden currently exist. Transparency is also high with aggregated data accessible to the general public since 2014.^{52,53} Data extraction allowed the exact numbers of individuals at each level of HbA1c to be identified, which allowed calculation of a highly accurate estimate of the burden relating to poor glycaemic control in individuals with T2D currently living in Sweden. This is in contrast to using a percentage estimate of individuals in poor glycaemic control and applying this to an estimate of the overall number of people with diabetes. However, it

should be noted that any incident cases of T2D (individuals diagnosed in subsequent years) were not captured in the current study, and the calculated levels of burden are therefore probably underestimates.

A potential criticism of the analysis was the possible inclusion of individuals who had previously received glucose-lowering therapy in the study population. New users were defined as having no record of filing a prescription of any glucose-lowering medication within 12 months before first prescription; it was therefore possible that some study participants had been pharmacologically treated before this time. However, the impact of these data was expected to be negligible, as, due to the progressive nature of T2D, the need for glucose-lowering medications following first-line therapy often remains, and individuals discontinuing pharmacological therapy after initiation were expected to be rare.

A challenge of reimbursing medical interventions in Sweden is the decentralized market, with budgetary decisions made by regionalized

TABLE 3 Population-level health economic outcomes for all analyses

Analysis	Life expectancy, years			Combined costs, million SEK		
	Immediate control	Poor control	Difference	Immediate control	Poor control	Difference
Full population, baseline HbA1c 64 mmol/mol (8.0%), HbA1c target 52 mmol/mol (6.9%)						
1-year delay, 3-year time horizon	50,621	50,484	+136	1306	1345	-39
1-year delay, 10-year time horizon	138,170	137,702	+467	3927	3977	-50
1-year delay, 50-year time horizon	224,453	223,148	+1305	7606	7719	-113
3-year delay, 3-year time horizon	50,621	50,504	+117	1306	1367	-60
3-year delay, 10-year time horizon	138,170	137,274	+915	3927	4147	-219
3-year delay, 50-year time horizon	224,453	221,863	+2590	7606	7908	-303
Full population, baseline HbA1c 70 mmol/mol (8.6%), HbA1c target 52 mmol/mol (6.9%)						
1-year delay, 3-year time horizon	30,546	30,429	+118	788	826	-38
1-year delay, 10-year time horizon	83,376	82,917	+470	2370	2447	-77
1-year delay, 50-year time horizon	135,442	134,513	+928	4590	4697	-107
3-year delay, 3-year time horizon	30,546	30,417	+129	788	857	-69
3-year delay, 10-year time horizon	83,376	82,518	+858	2370	2584	-214
3-year delay, 50-year time horizon	135,442	133,185	+2257	4590	4883	-293
Population aged ≤65 years, baseline HbA1c 52 mmol/mol (6.9%), HbA1c target 48 mmol/mol (6.5%)						
1-year delay, 3-year time horizon	84,222	84,160	+61	3241	3287	-46
1-year delay, 10-year time horizon	242,966	242,966	0	15,536	15,599	-63
1-year delay, 50-year time horizon	490,321	489,338	+982	22,178	22,457	-279
3-year delay, 3-year time horizon	84,222	84,191	+31	3241	3309	-67
3-year delay, 10-year time horizon	242,966	242,782	+184	15,536	15,784	-248
3-year delay, 50-year time horizon	490,321	489,400	+921	22,178	22,705	-527
Population aged ≤65 years, baseline HbA1c 52 mmol/mol (6.9%), HbA1c target 42 mmol/mol (6.0%)						
1-year delay, 3-year time horizon	84,252	84,191	+61	3153	3231	-79
1-year delay, 10-year time horizon	243,580	243,365	+215	14,772	14,964	-192
1-year delay, 50-year time horizon	496,613	496,705	-92	20,922	21,022	-100
3-year delay, 3-year time horizon	84,252	84,191	+61	3153	3309	-156
3-year delay, 10-year time horizon	243,580	242,966	+614	14,772	15,389	-617
3-year delay, 50-year time horizon	496,613	494,495	+2118	20,922	21,595	-673

Abbreviation: SEK, 2019 Swedish krona.

payers considering different time horizons, often over the short term. This is particularly challenging for medications for T2D, where certain benefits are only observed over the long term. Indeed, health economic analyses for diabetes therapies are recommended to be performed over individuals' lifetimes.⁵⁴ However, the current study has shown that reductions in the clinical and economic burden associated with immediate glycaemic control were observable even at shorter time horizons of 3 and 10 years, with further benefits observed over 50 years. This shows that investment in and prescription of efficacious glucose-lowering medications can lead to substantial cost savings, even over the short time periods often considered by Swedish healthcare payers.

A limitation of the analysis, inherent to all health economic modelling analyses, was the uncertainty associated with the projections of outcomes. Only point estimates were reported for all outcomes (mean values from analyses performed with a first-order

Monte Carlo approach), as analyses applying a second-order Monte Carlo approach were not performed. Moreover, there was uncertainty around the predicted influence of HbA1c on macrovascular outcomes over the shorter time horizons of 3 and 10 years. While the IQVIA CORE Diabetes Model is based on the UK Prospective Diabetes Study (UKPDS) Outcomes Model, and uses data from the UKPDS study to project outcomes, it should be noted that significant benefits in cardiovascular outcomes were not observed after 10 years in the UKPDS study arm with intensively controlled HbA1c, but were first seen in the 10-year follow-up study.^{6,9} The UKPDS also indicated that HbA1c alone was not the driving factor in reducing the incidence of complications, with reductions in blood pressure shown to provide significant benefits; treatment for T2D should therefore consider a more holistic treatment approach, rather than a sole focus on reducing HbA1c.^{6,11-13,19} While the current analysis did not capture changes in physiological variables other than HbA1c, the design of the study was theoretical in nature,

aiming to estimate the economic and clinical burden attributable to poor glycaemic control. Assuming no differences in modelling variables other than HbA1c levels, combined with use of a widely used, published and validated health economic model of T2D, also meant that long-term modelling uncertainty was minimized.^{25,26} Nonetheless, given the findings of the UKPDS, reductions in additional variables as well as HbA1c would be expected to yield even greater cost savings and health benefits.^{6,11–13,19} Even further benefits would be elucidated should greater delays in achieving control be considered, for example, in populations with more advanced T2D, where long delays in treatment intensification to insulin therapy have been observed.⁵⁵

No pharmacy or consumable costs were included in the current analysis, as the aim was to quantify the economic burden associated with diabetes-related complications arising from poor glycaemic control. Providing an accurate estimate of the costs individuals would accrue is challenging, given the wide range of diabetes therapies available and the recommended individualized approach to treatment decisions.¹⁹ Additional factors that can cause poor glycaemic control must also be considered when evaluating the results of the current analysis, as poor self-management and compliance can impact individuals' HbA1c levels. However, additional healthcare spending on glucose-lowering therapies is arguably justified by the current analysis, given the population-level cost savings observed when glycaemic control is achieved. Further cost-effectiveness analyses of novel interventions are required to elucidate which specific medications offer value for money for individuals with T2D and healthcare payers in Sweden.

In conclusion, based on data from the NDR, the economic burden of poor glycaemic control in individuals with T2D in Sweden was projected to be substantial, but could be considerably reduced by early and effective treatment to achieve and maintain glycaemic targets. These projections should help inform healthcare payers when considering medications for reimbursement, and healthcare professionals and people with T2D when implementing individualized therapies.

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CONFLICT OF INTEREST

A-MS, SF and RB have no relevant financial or conflicts of interest to declare. MH has received personal fees (lectures fees) from AstraZeneca, Boehringer Ingelheim, Eli Lilly, Novo Nordisk and Sanofi, outside of the submitted work. SG has received personal fees (lectures fees and research grants) from AstraZeneca, Boehringer Ingelheim, Eli Lilly, Merck Sharp & Dohme, Novo Nordisk and Sanofi, outside of the submitted work. ÅE and NE are employees of Novo Nordisk Scandinavia AB and own Novo Nordisk stocks. WV and SM are employees of Ossian Health Economics and Communications, which received consulting fees from Novo Nordisk Scandinavia AB to support preparation of the analysis.

AUTHOR CONTRIBUTIONS

All the named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article,

take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published. All the authors had full access to all of the data in this study and take complete responsibility for the integrity of the data and accuracy of the data analysis.

DATA AVAILABILITY STATEMENT

All data generated or analyzed during this study are included in this published article.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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