Budget Impact Analysis of Metformin Sustained Release for the Treatment of Type 2 Diabetes in The Netherlands

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ORIGINAL RESEARCH ARTICLE

Budget Impact Analysis of Metformin Sustained Release for the Treatment of Type 2 Diabetes in The Netherlands

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Abstract

Background Adverse drug reactions and medication nonadherence are well-known causes of sub-optimal disease control and worsened disease outcomes in patients who are treated for type 2 diabetes. Metformin sustained release (SR) might reduce these adverse events and improve medication adherence via a simplified treatment regimen for metformin immediate release (IR)-intolerant patients.

Objectives The aim of this study is to estimate the budget impact of metformin SR for the treatment of type 2 diabetes in the Netherlands, compared to the current standard of care (SoC) with metformin IR.

Methods A budget impact model was built to represent the course of the disease and treatment pathway of type 2 diabetes patients eligible for metformin SR from a healthcare payer's perspective. Patients were considered eligible if they used less than 2000 mg metformin IR per day, but suffered from adverse events that might lead to therapy discontinuation, and if they were newly diagnosed with type 2 diabetes. The costs of type 2 diabetes treatment and related complications over a time horizon of 3 years were calculated. Univariate sensitivity analyses were conducted to show which parameters have the biggest influence on the budget impact.

Results The budget impact analysis showed cost-savings of − €1,962,335 over a period of 3 years through implementation of metformin SR as an alternative to SoC with metformin IR. Savings were mostly driven by the delay of other, more expensive type 2 diabetes treatments, such as insulin. In sensitivity analyses, medication adherence and persistence appeared to have the biggest influence on the budget impact.

Conclusion Metformin SR could potentially be a cost-saving alternative to metformin IR for the treatment of type 2 diabetes in the Netherlands, especially in patients experiencing adverse events with metformin IR. However, more research is needed to better predict the effect of using once-daily metformin, compared to multiple dosages, on medication adherence and persistence and to evaluate whether metformin SR really decreases the amount of adverse events.

Key Points for Decision Makers

Using metformin sustained release (SR) might be a cost-saving alternative to the standard of care with metformin immediate release, due to the delay of other, more expensive treatments.

Adherence and persistence to metformin SR have a high impact on the results of the budget impact analysis.

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1 Introduction

The population with type 2 diabetes mellitus is expanding rapidly due to ageing of the population and increased obesity. Estimations show an increase from 1.1 million in 2017 up to 1.3 million patients diagnosed with diabetes in 2025 in the Netherlands, out of which 91% will have type 2 diabetes [1, 2]. In 2015, the cost of diabetes care was approximately €1.6 billion, which was 1.8% of total healthcare expenditures.

Diabetes is characterized by a high blood glucose, or so called hemoglobin A1c (HbA1c), level of > 7% (> 53 mmol/mol). Lowering these levels is of great importance for controlling the disease. Type 2 diabetes is associated with severe macro- and microvascular complications, such as cardiovascular disease, foot amputations, renal disease and visual impairment, especially in patients with

poor metabolic control. Sufficient management of diabetes and, therefore, properly controlled HbA1c levels are essential for reducing the risk of these complications [3].

Good metabolic control by oral type 2 diabetes treatment could possibly delay other, more invasive treatments, like insulin. Treatment with metformin immediate release (IR) has proven to be effective in clinical trials; however, adverse events (AEs) are a common problem. A Dutch study showed that 34.5% of the patients on metformin IR experienced AEs, and 11.4–16.1% discontinued their treatment within the first year after initiation [4, 5]. Medication nonadherence, partially due to (gastrointestinal) AEs and difficult treatment regimens, is a well-known problem in type 2 diabetes patients [6]. A switch from metformin IR to metformin sustained release (SR) might offer an improvement in experienced gastrointestinal AEs when metformin IR is not tolerated [7–9]. Reducing the amount of AEs has the potential to improve medicine compliance and adherence, which subsequently might reduce the need for other, more expensive antidiabetic drugs and potentially promote better long-term health outcomes [10–12]. Also, once-daily dosing may simplify the treatment regimen for type 2 diabetes patients and contribute to better treatment adherence. Therefore, metformin SR might improve glycemic control, ultimately reducing the risk of severe diabetes complications and postponing the use of other, more expensive antidiabetic drugs.

Various studies have shown therapeutic equivalency or even benefit of metformin SR when compared to metformin IR, with comparable glycemic control and sometimes a more favorable AE profile [7, 10, 11, 13–15]. The economic value, however, has not yet been determined. Therefore, the aim of this study was to perform a budget impact analysis (BIA) of the implementation of metformin SR compared to standard of care (SoC) with metformin IR for the treatment of type 2 diabetes in the Netherlands.

2 Methods

2.1 Model Design

Following the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) guidelines "Principles of Good Practice for Budget Impact Analysis," a BIA was conducted using a model built in Microsoft Excel 2016 [16, 17]. This model evaluated the impact of introducing metformin SR, as an alternative to metformin IR, for the treatment of type 2 diabetes against a background of other antidiabetics (Fig. 1). Several studies showed comparable efficacy and safety for metformin SR when compared to metformin IR. Most of these studies, however, are considered "switch-studies," meaning patients included in the metformin SR population have already experienced AEs from metformin IR. This leads to bias, which is why AEs were not included in this model [7, 10, 11, 13–15].

Figures 2 and 3 show the treatment pathway of patients who are treated following SoC, but are eligible for metformin SR, over a period of 3 years. Patients in Fig. 2 switched to metformin SR, and patients in Fig. 3 keep using metformin IR. Within these years, they could either keep using metformin or switch to other medications. Besides these metformin IR-intolerant patients, 67,249 newly diagnosed type 2 diabetes patients who initially started metformin SR treatment in year 1 were considered as well (Figs. 4, 5) [18, 19]. Guidelines from the Dutch College of General Practitioners (*Nederlands Huisartsen Genootschap* [NHG]) were used to outline the treatment pathway of type 2 diabetes patients [20]. Persistency was modeled based on a study that assessed the transition rates of patients with type 2 diabetes between different drugs (classes) (Figs. 2, 3, 4, 5) [21].

Following the ISPOR guidelines, we simulated the treatment pathway of each individual patient over a 3-year time horizon, based on annual persistence rates per type

Fig. 1 Flow through of the budget impact model. *HbA1c* hemoglobin A1c, *IR* immediate release, *OLGD* other glucose-lowering drugs, *SR* sustained release
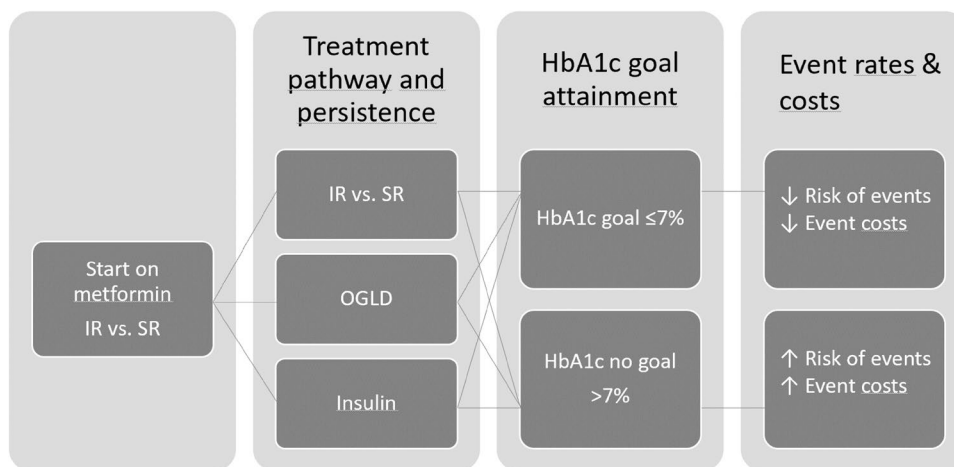
2 diabetes drug category. Drug categories taken into consideration were (1) metformin, (2) other glucose-lowering drugs (OGLDs: sulphonylurea derivatives, thiazolidinediones, alpha-glucosidase inhibitors, glinides, dipeptidyl peptidase-4 [DPP-4] inhibitors, glucagon-like peptide-1 [GLP-1] agonists, sodium-glucose co-transporter-2 [SGLT-2] inhibitors) and (3) insulin. Following the distribution of patients through the treatment pathway in the model, the possibility of medication (non)adherence was assessed and corresponding probabilities of HbA1c goal achievement were included [22–24]. Studies in patients using metformin SR showed adherence rates ranging

between 80 and 97.2% [14, 25–27]. In this model, we assumed adherence to metformin SR in year 1 as 90%, mostly related to the simplified dosing regimen, and adherence to metformin IR was approximately 72%. Although the effects of nonadherence on achieved HbA1c have been studied for many antidiabetic drugs, the relation is not quantified for all glucose-lowering drugs. Using pooled data on HbA1c target achievement, the drugs for which quantification was missing were graded under one common denominator: OLGD [24]. Based on the Dutch and international guidelines for type 2 diabetes treatment, the HbA1c target value was set to ≤ 7% (≤ 53 mmol/mol) [20,

Fig. 2 Treatment pathway of SR eligible type 2 diabetes patients currently on SoC who are switched to SR [21]. *INS* insulin, *OGLD* other glucose-lowering drug, *SoC* standard of care, *SR* sustained release
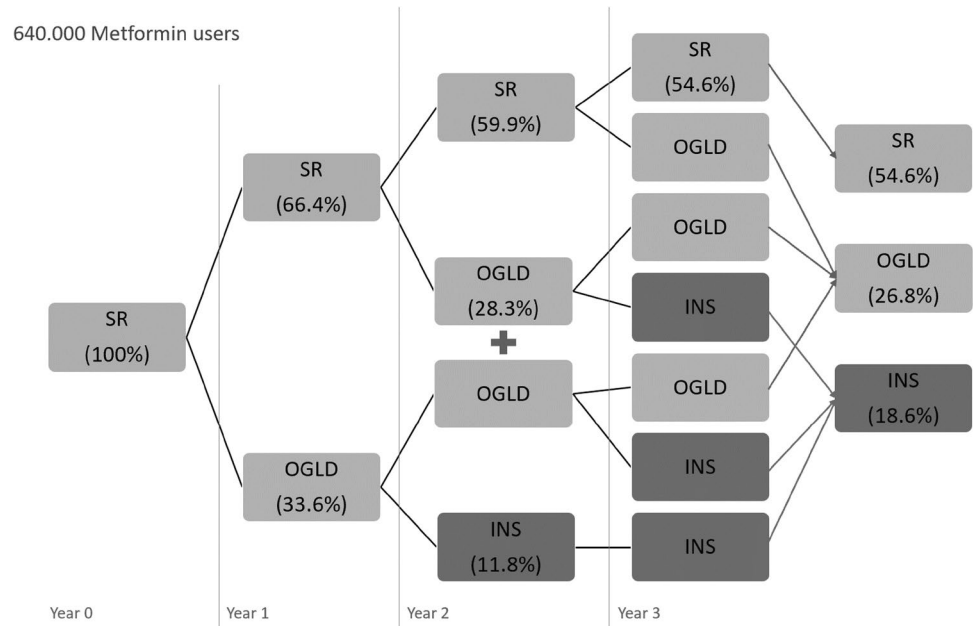

Fig. 3 Treatment pathway of SR eligible type 2 diabetes patients currently on metformin IR who stay on IR [21]. *INS* insulin, *IR* immediate release, *OGLD* other glucose-lowering drug, *SR* sustained release
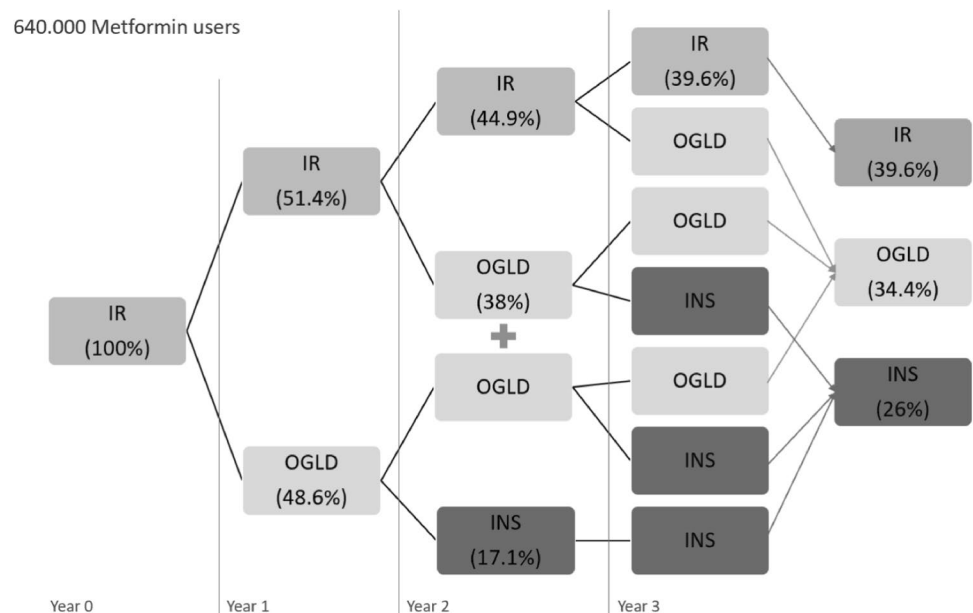
Fig. 4 Treatment pathway of newly diagnosed type 2 diabetes patients eligible for SR who start on SR [21]. *INS* insulin, *OGLD* oral glucose-lowering drug, *SR* sustained release
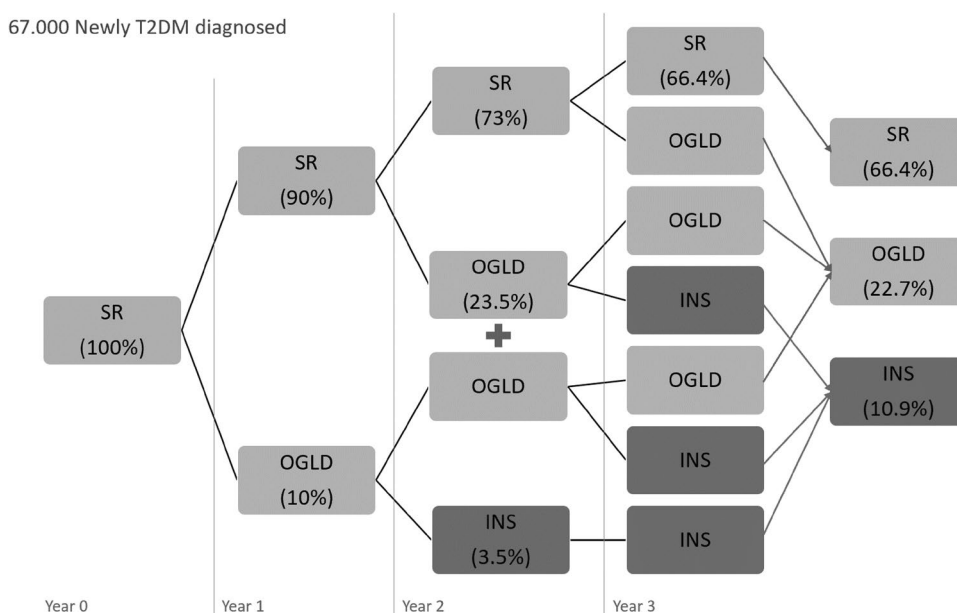

Fig. 5 Treatment pathway of newly diagnosed type 2 diabetes patients eligible for SR who start on IR [21]. *INS* insulin, *IR* immediate release, *OGLD* oral glucose-lowering drug, *SR* sustained release
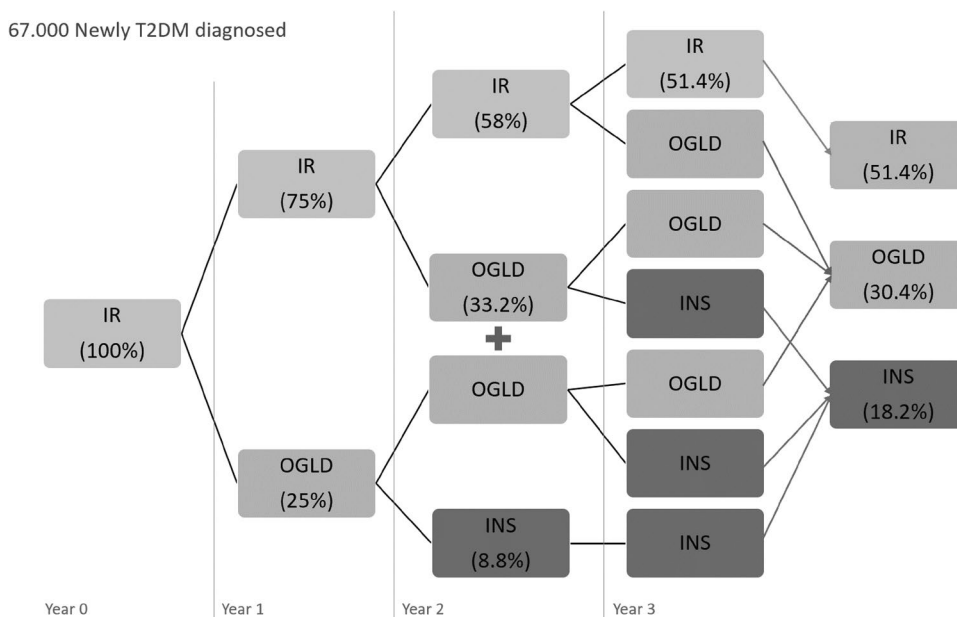
28, 29]. Consequently, categories representing "goal" or "no goal" were set to HbA1c ≤ 7% (≤ 53 mmol/mol) or HbA1c > 7% (> 53 mmol/mol), respectively. Probabilities of developing type 2 diabetes related macro- and microvascular complications were linked to the obtained HbA1c levels per treatment (Table 1) [30].

The analysis was conducted from a healthcare payers' perspective. The influence of different parameters on the budget impact was assessed by univariate sensitivity analyses over a time horizon of 3 years, which was chosen to match the payers' budgeting process [17].

2.2 Study Population

The baseline study population included in the model was obtained from Dutch metformin user numbers, as reported in the Dutch drug information system of the National Health Care Institute (GIPdatabank), and was estimated at 640,000 [31]. Patients on metformin IR dosages higher than 2000 mg daily were excluded, since switching from metformin IR to SR is not recommended when the daily dosage of metformin IR is above 2000 mg. Also the maximum recommended dosage for patients starting metformin SR from the start of type 2 diabetes treatment is 2000 mg

Table 1 Event rates per 1000 person years for sufficient and non-sufficient HbA1c management [30]

Event	Goal (HbA1c ≤ 7%)	No goal (HbA1c > 7%)
All-cause mortality	0.0206	0.0324
(Non)fatal MI	0.0187	0.0317
(Non)fatal stroke	0.0056	0.0081
Amputation/death from peripheral vascular disease	0.0012	0.0049
(Non)fatal microvascular disease	0.0079	0.0238
Heart failure	0.0029	0.0053
Cataract extraction	0.0043	0.0065

HbA1c hemoglobin A1c, *MI* myocardial infarction

Table 2 Metformin IR use and breakdown of the daily dosage

Daily dosage (mg)	Breakdown				Number of prescriptions (%)
	Tablet (mg)	Number of tablets	Tablet (mg)	Number of tablets	
500	500	1			197 (23.26)
850	850	1			5 (0.59)
1000	1000	1			8 (0.94)
	500	2			288 (34.00)
1350	850	1	500	1	1 (0.12)
1500	500	3			103 (12.16)
	1000	1	500	1	3 (0.35)
1700	850	2			26 (3.07)
1850	850	1	500	2	1 (0.12)
2000	500	4			120 (14.17)
	1000	1	500	2	4 (0.47)
	1000	2			91 (10.47)
Total					847 (100)

IR immediate release

[32, 33]. As metformin SR is an alternative to metformin IR, we identified which patients would be able to switch from SoC to metformin SR and who would continue on metformin IR. Factors considered in this respect were (1) the discontinuation of metformin IR amongst newly diagnosed patients (16.1%), (2) the potential market share of metformin SR as calculated from medicine issue registries from the United Kingdom (22.53%), and (3) the percentage of patients currently on metformin IR who could be actively switched to metformin SR (0.1%) [5]. As this BIA covers multiple years, type 2 diabetes patient population growth was taken into account. This was calculated by the number of newly diagnosed patients minus the number of deaths, where the number of newly diagnosed patients was estimated to be 67,000 by the Dutch healthcare research institute NIVEL (2016) [19, 30, 34]. Transition probabilities are displayed in the electronic supplementary material (ESM).

2.3 Data Collection

To represent the baseline use of metformin IR as accurately as possible, data were collected from three pharmacies representative of the Netherlands by pharmatech company Medstone [35]. These data were used to determine the average cost of metformin use in the Netherlands. The data were collected from one pharmacy situated in a city, one in a more rural area and one in a small village between August 1, 2017 and July 31, 2018 and using Anatomical Therapeutic Chemical (ATC) classification system code A10BA02. Further data handling is described in supplementary Fig. 7 (see the "Data handling metformin use" section in the ESM). Based on the summary of product characteristics (SmPC) recommendations, patients who used more than 2000 mg metformin IR were excluded from the model, leaving information on 847 prescriptions from unique patients. The obtained data

included information on the total daily dosage, tablet breakdown and the number of prescriptions (Table 2).

Research has shown the daily dosages of both metformin formulations are compatible [36]. To convert the use of metformin IR to metformin SR, we assumed that the distribution of patients using certain tablet regimens was similar between both formulations. However, because metformin IR is available as 500 mg, 850 mg and 1000 mg and metformin SR as 500 mg, 750 mg and 1000 mg, some assumptions had to be made regarding the daily dosage of metformin SR (Table 3).

2.4 Costs

Costs are shown in Table 4 and the ESM ("Drug cost overview" section). Annual drug costs per patient per daily dosage (or insulin unit) were calculated using the prescription standard for type 2 diabetes from the National Health Care Institute (*Zorginstituut Nederland* [ZIN]) [37, 38]. The annual costs of metformin SR are calculated based on the assumption of a once-daily treatment regimen. The BIA only includes costs as paid by the healthcare payer, therefore excluding the patient's own contribution to the total product price. Costs of insulin care and non-insulin care were based on information as provided by the Dutch Diabetes Foundation (*Diabetes Vereniging Nederland*) and was combined with treatment costs from health insurer declarations [39, 40]. Insulin care consisted of medication, testing strips, blood glucose measuring device, blood extraction equipment, insulin pens and syringes, remaining diabetes tools, an insulin pump and regular checkups/coaching at the ophthalmologist or with a diabetes nurse. Non-insulin care costs consisted of medication, regular checkups and

Table 3 Metformin IR versus metformin SR treatment regimens

Daily dosage metformin IR (mg)	Daily dosage metformin SR (mg)
500	500
850	750
1000	1000
1350	1250
1500	1500
1700	1500
1850	1750
2000	2000

IR immediate release, *SR* sustained release

Table 4 Costs included in the budget impact analysis, 2018 price levels

	Cost per patient per year	References
Treatment costs		
Metformin SR 500 mg	€21.41	[37]
Metformin SR 750 mg	€32.00	[37]
Metformin SR 1000 mg	€42.71	[37]
Metformin IR 500 mg	€5.23	[37]
Metformin IR 850 mg	€8.88	[37]
Metformin IR 1000 mg	€10.10	[37]
SGLT-2 inhibitor	€579.19	[37]
Sulphonylurea derivatives	€25.42	[37]
Thiazolidinediones	€13.63	[37]
Alpha-glucosidase inhibitor	€230.68	[37]
Glinide	€131.04	[37]
DPP-4 inhibitor	€493.32	[37]
GLP-1 agonist	€1210.03	[37]
Insulin (per unit, IU)	€0.03	[37]
Insulin care	€456.17	[37]
Non-insulin cost usual care	€645.00	[37]
Event costs		
(Non)fatal MI	€5309	[42]
(Non)fatal stroke	€14,280	[42]
Amputation/death from peripheral vascular disease	€61,084	[42]
(Non)fatal microvascular disease	€94,557	[42]
Heart failure	€2966	[42]
Cataract extraction	€3054	[42]

DPP-4 dipeptidyl peptidase-4, *GLP-1* glucagon-like peptide-1, *IR* immediate release, *MI* myocardial infarction, *SGLT-2* sodium-glucose co-transporter-2, *SR* sustained release

coaching by a professional [39, 40]. All costs were inflated to the year 2018, using Dutch inflation rates [41]. For the BIA, discounting was not applied, as it was our goal to show

financial streams at each selected budget period and not the net present value at the moment of decision-making [17].

3 Results

3.1 Budget Impact Analysis

Over 3 years, the total economic burden of type 2 diabetes controlled with metformin IR was €45,723,744. This, compared to the burden of using metformin SR for treatment of type 2 diabetes over 3 years, which was €43,761,409, leads to cost savings of €1,962,335. No acquisition cost savings were seen in year 1, but during the next 2 years, cost savings substantially increased. Also type 2 diabetes event cost savings increased over the years; however, not as strongly (Table 5).

3.2 Sensitivity Analysis

In the univariate sensitivity analysis, parameters were varied over a range from 75% to 125%. Out of the 53 variables included in the analysis, 15 parameters with the biggest influence on the outcome are shown in Fig. 6. The tornado diagram shows that not achieving HbA1c targets resulting from medication adherence or persistence was most influential. Low adherence or persistence might make the use of metformin SR more costly than metformin IR.

4 Discussion

Several studies have assessed the therapeutic differences between metformin IR and metformin SR in an attempt to demonstrate metformin SR's added value [7, 10, 11]. However, the economic impact of using metformin SR in routine clinical practice for the treatment of type 2 diabetes in the Netherlands has not yet been quantified.

The results of this BIA show that metformin SR could be a cost-saving alternative to metformin IR in the treatment of type 2 diabetes. The resulting differences in costs between the two formulations are mostly caused by differences in acquisition costs. This can be explained by a wide variety in metformin treatment regimens amongst the type 2 diabetes patient population and the corresponding treatment costs. Drug costs included in the model are chosen conservatively, always choosing the cheapest treatment option when more than one was possible. Furthermore, the metformin SR prices included in the model are the upper reimbursement limits, as set by the government. To properly reflect the payers' perspective, it is necessary to include the drug prices as paid by the healthcare payer.

Table 5 Results budget impact analysis

	Metformin IR			Metformin SR		
	Year 1	Year 2	Year 3	Year 1	Year 2	Year 3
Acquisition cost	**€2,061,721**	**€4,096,323**	**€6,309,202**	**€2,128,603**	**€3,997,456**	**€6,007,782**
MI	€415,665	€743,836	€1,066,591	€404,490	€723,412	€1,037,354
Stroke	€300,786	€537,283	€769,386	€295,099	€526,889	€754,507
Amputation	€602,622	€1,086,865	€1,567,360	€565,633	€1,019,258	€1,470,580
Microvascular disease	€4,766,415	€8,576,388	€12,346,956	€4,523,268	€8,131,975	€11,710,778
Heart failure	€38,104	€68,239	€97,903	€36,952	€66,133	€94,889
Cataract extraction	€50,890	€90,941	€130,268	€49,834	€89,011	€127,505
Type 2 diabetes event cost	**€6,174,482**	**€11,103,553**	**€15,978,464**	**€5,875,277**	**€10,556,678**	**€15,195,613**
Total cost	**€8,236,203**	**€15,199,876**	**€22,287,666**	**€8,003,880**	**€14,554,134**	**€21,203,395**
Budget impact				− €232,323	− €645,741	− €1,804,271
Total budget impact						**− €1,962,335**

IR immediate release, *MI* myocardial infarction, *SR* sustained release
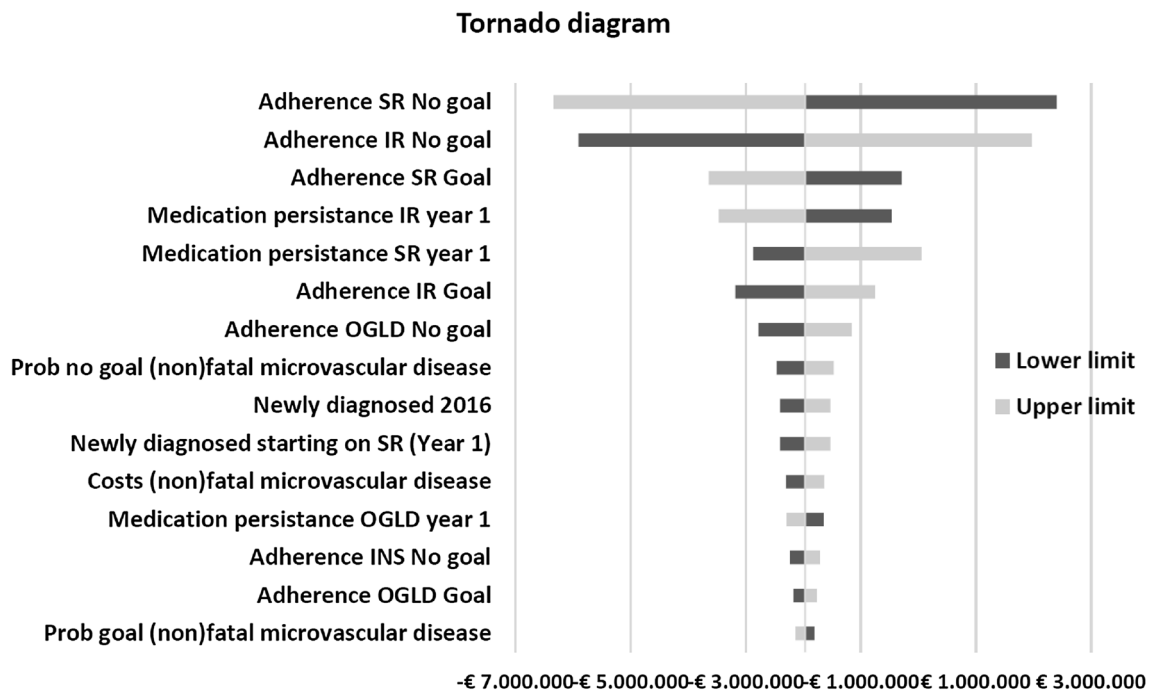
Tornado diagram

Fig. 6 Univariate sensitivity analysis. *INS* insulin, *IR* immediate release, *OGLD* other glucose-lowering drug, *SR* sustained release

As do all economic analyses, this BIA has its limitations. In order to quantify the added economic value of metformin SR over metformin IR, several assumptions had to be made. Since there was a lack of data on the long-term patient treatment pathways, we simulated the flow of the estimated eligible patient population over all possible drug treatments as prescribed following the Dutch treatment guidelines for type 2 diabetes, while taking into account the treatment's market share [20, 43]. Future research, where type 2 diabetes patients are followed over a longer period of time, could provide viable data on treatment pathway utilization and the effects of metformin SR on changes in medication adherence and persistence. These data could validate assumptions, decrease uncertainty and increase the models predictive strength. Another drawback of the 3-year time horizon is that diabetes-related complications often occur within 5–10 years or even longer. Because a longer time horizon will require a considerable amount of assumptions and will therefore increase uncertainty, a long time horizon is not recommended [16, 17].

To calculate the cost of metformin SR use, we assumed a treatment regimen of one dose per day. This is also

recommended by the manufacturer; however, if glycemic control is not satisfying, patients can switch to a dose regimen of metformin SR twice daily [32]. We expect this to be the case for a small amount of patients, and since it might only slightly change the price of the daily dosage, it will have a small effect on the outcome as well.

Although several studies have shown therapeutic equivalency between metformin SR and IR, there is also some evidence that shows metformin SR to be better tolerated, especially when it comes to gastrointestinal side effects [8, 44]. The savings that can be generated by implementing metformin SR could potentially be higher than are presented in this model.

The cut-off value for HbA1c is set to 7% (53 mmol/mol) to divide the patient population into two groups: proper glycemic control with lowered type 2 diabetes event risks and improper glycemic control with an increased risk of type 2 diabetes events. However, it should be mentioned that this cut-off is not applicable to all patient populations, as it cannot always be a realistic target. Doctors can deviate from this value based on a patients age, disease duration and life expectancy [20]. Because we calculated the event rates using patients with different HbA1c targets, we predict the effect on the outcome to be negligible. Also, the predictive value of HbA1c for reduction of mortality and complications is still up for debate, as it has not been inconclusively proven that a reduction of HbA1c results in a reduction of mortality or severe macro- and microvascular complications [45, 46].

As diabetes treatments are often added upon one another, it might be that the BIA underestimates the potential cost savings that could be achieved by the delay of other type 2 diabetes drugs. Not one drug, but multiple at the same time will be postponed. The accumulation of treatments, however, does not always result in improved disease outcomes. Therefore the need for suitable treatments from the start of the disease are needed as diabetes is a progressive disease which ultimately leads to deteriorating health [47].

5 Conclusion

Our budget impact model shows potential cost savings for metformin SR when compared to SoC with metformin IR for the treatment of type 2 diabetes in the Netherlands. However, to strengthen the model and its outcomes, more research on the therapeutic effects and patient-related outcomes of metformin SR is needed.

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