

# Cost-effectiveness of sensor-augmented insulin pump therapy vs continuous subcutaneous insulin infusion in patients with type 1 diabetes in the Netherlands

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**Aim:** The aim of this study was to perform a cost-effectiveness analysis to establish the cost-effectiveness of sensor-augmented pump therapy (SAP) with automated insulin suspension vs continuous subcutaneous insulin infusion (CSII) alone in patients with type 1 diabetes in the Netherlands.

**Patients and methods:** The analysis was performed using the IQVIA CORE Diabetes Model (CDM) in two different patient cohorts: one with suboptimal glycemic control at baseline (mean age 27 years, mean baseline HbA1c 8.0% [64 mmol/mol]) and the other at increased risk of hypoglycemic events (mean age 18.6 years, mean baseline HbA1c 7.5% [58 mmol/mol]). Clinical input data were sourced from published literature, and the analysis was performed from the societal perspective.

**Results:** In patients with suboptimal baseline glycemic control, SAP improved quality-adjusted life expectancy by 1.77 quality-adjusted life years (QALYs) vs CSII (15.54 QALYs vs 13.77 QALYs) with higher lifetime costs (EUR 189,855 vs EUR 150,366), resulting in an incremental cost-effectiveness ratio (ICER) of EUR 22,325 per QALY gained. In this cohort, sensitivity analyses showed that the influence of SAP on fear of hypoglycemia (FoH) and baseline HbA1c were key drivers of results. In patients at increased risk of hypoglycemia, the gain in quality-adjusted life expectancy with SAP vs CSII was 2.16 QALYs (16.70 QALYs vs 14.53 QALYs) with higher lifetime costs (EUR 204,013 vs EUR 171,032) leading to an ICER of EUR 15,243 per QALY gained. In this patient group, findings were most sensitive to changes in assumptions relating to the incidence of severe hypoglycemic events in the CSII arm.

**Conclusion:** For type 1 diabetes patients in the Netherlands who do not achieve target HbA1c levels or who experience frequent severe hypoglycemic events on CSII, switching to SAP is likely to be cost-effective.

**Keywords:** cost, cost-effectiveness, type 1 diabetes, the Netherlands, sensor-augmented insulin pump therapy

## Introduction

The clinical and economic burden associated with type 1 and type 2 diabetes is substantial. In the Netherlands, there are currently an estimated 1.1 million people with diabetes, of whom approximately 9% (99,000 people) have type 1 diabetes.<sup>1</sup> In 2011, the total direct cost of managing diabetes patients (type 1 and type 2 diabetes combined) was estimated at EUR 1.7 billion, which constitutes approximately 2% of total health care spending in the Netherlands.<sup>2</sup> An analysis of temporal trends suggests

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that the incidence of type 1 diabetes in those aged  $\leq 19$  years is increasing; indeed, one study reported an annual increase in the age-adjusted incidence rate of type 1 diabetes of 3.7% per year over the period 1999–2011.<sup>3</sup> In the Netherlands, type 1 diabetes patients are mostly treated within clinics in secondary care settings and all pediatric type 1 diabetes patients are treated by hospital-based pediatricians.<sup>4</sup> The considerable clinical and economic burden as well as the humanistic burden of disease means that the evaluation of new technologies and interventions increasingly encompasses not only potential clinical benefits but also long-term cost-effectiveness and other aspects such as convenience and patient satisfaction, which may in turn influence patients' compliance with using new technologies.

One such example is sensor-augmented pump therapy (SAP), which combines continuous glucose monitoring (CGM) with continuous subcutaneous insulin infusion (CSII). Some of the most recently introduced SAP devices are also equipped with advanced features such as low glucose suspend (LGS) or even predictive low glucose suspension (SmartGuard™ technology). With the LGS feature, insulin delivery is temporarily suspended if glucose levels drop below a predefined threshold level. Predictive LGS is the most recently introduced feature and a more sophisticated feature, whereby insulin delivery can be suspended based on the prediction of low glucose levels within the next 30 minutes and insulin delivery is automatically resumed once blood glucose levels start to recover. In the Netherlands, in 2008, there were an estimated 13,000 diabetes patients using insulin pumps, 90% of whom were type 1 patients.<sup>5</sup> More recent data from Diabeter, a national diabetes center focusing on pediatric and adolescent diabetes, report that >50% patients aged 15–24 years and >60% patients aged  $\geq 25$  years treated within the Diabeter network were using insulin pumps.<sup>6</sup> However, it should be noted that these data are sourced from a single specialist center and may therefore not be nationally representative.

Evidence from clinical studies has shown that SAP provides significant improvements in HbA1c and hypoglycemic event rate vs multiple daily injections (MDIs) and also vs standard CSII in patients with suboptimal glycemic control.<sup>7,8</sup> Moreover, greater treatment satisfaction with SAP relative to CSII or MDI has also been reported in both pediatric patients and adults.<sup>9,10</sup> There is also accumulating evidence suggesting that SAP incorporating an automatic insulin suspension feature provides even further incremental clinical benefits relative to SAP alone. For example, in the ASPIRE study, which compared SAP + LGS with SAP alone, the LGS fea-

ture was associated with a reduction in both the rate and the severity of nocturnal hypoglycemic events compared with SAP without suspension.<sup>11–13</sup>

In response to advances in insulin pump technology and the high rate of uptake of insulin pump use in the Netherlands, a cost-effectiveness analysis of SAP with automated insulin suspension vs CSII alone in two different groups of patients with type 1 diabetes was performed. The analysis was performed in two separate cohorts: one with suboptimal glycemic control at baseline and the other with increased risk of hypoglycemic events.

## Patients and methods

### Model description and outcomes

Cost-effectiveness analysis was performed using the IQVIA CORE Diabetes Model (CDM; IQVIA, Basel, Switzerland). The CDM is a published and validated cost-effectiveness model that can be used in either type 1 or type 2 diabetes.<sup>14–16</sup> A comprehensive description of the CDM is provided by Palmer et al,<sup>14</sup> but briefly, the CDM is based on a series of interdependent sub-models that simulate the progression of diabetes and diabetes-related complications. The sub-models have a semi-Markov structure and use time, time-in-state, and diabetes type-dependent probabilities to simulate long-term disease progression. Monte Carlo simulation using tracker variables is used to overcome the memory-less properties of a standard Markov model and allows for interconnectivity and interaction between individual sub-models. Outcomes from the CDM include life expectancy, quality-adjusted life expectancy, time to onset of diabetes-related complications, direct and indirect costs, and incremental cost-effectiveness ratios (ICERs).

### Simulation cohorts and treatment effects

The cost-effectiveness of SAP vs CSII was investigated in two different patient cohorts. The first cohort was type 1 diabetes patients with suboptimal glycemic control at baseline (mean baseline HbA1c 8.0% [64 mmol/mol]), and the second one was type 1 diabetes patients at increased risk of hypoglycemic events. The rationale for this is that it permits independent assessment of the long-term outcomes with SAP in terms of improved glycemic control (in patients with poor glycemic control at baseline) and influence on hypoglycemic event rate (in patients at increased risk of hypoglycemic events).

Cohort characteristics of the patients with suboptimal glycemic control at baseline were sourced from an individual patient-level meta-analysis of randomized controlled trials by Pickup et al<sup>17</sup> and, where necessary, supplemented with data

from the Diabetes Control and Complications Trial (DCCT)<sup>18</sup> (Table 1). A treatment effect in terms of HbA1c reduction of  $-0.42\%$  was assumed for the SAP arm and  $-0.10\%$  for the CSII arm. Treatment effects were based on formulae published by Pickup et al<sup>17</sup> in an individual patient-level meta-analysis of the effects of CGM vs self-monitoring of blood glucose (SMBG) on glycemic control in patients with type 1 diabetes and accounted for age, baseline HbA1c, and sensor use. The treatment effect in the SAP arm was based on an assumed annual sensor usage of 43 sensors per year (each lasting for 6 days, ie, average sensor use of 4.95 days per week). Rates of severe hypoglycemic events were assumed to be the same in both treatment arms based on the findings of meta-analysis by Pickup et al<sup>17</sup> (event rate of 2.6 events per 100 patient-years).

Baseline cohort characteristics and treatment effects for the cohort at increased risk of hypoglycemic events were from a randomized controlled trial of SAP vs CSII in 95 type 1 diabetes patients at increased risk of hypoglycemic events owing to impaired awareness of hypoglycemia (Table 1). In the base case analysis rates of severe hypoglycemic events of 2.2 events per 100 patient-months in the CSII arm and 0 events per 100 patient-months in the SAP arm were applied.<sup>19</sup>

## Costs and utilities

For intervention costs, only the incremental cost of SAP relative to CSII was applied. The total incremental cost for SAP was EUR 2,713 and included 43 sensors per year (corresponding to 70% usage) and the sensor kit, which includes MiniLink™ transmitter, MiniLink™ charger, MiniLink™ tester, batteries, and Enlite™ sensor™. The analysis also captured the reduced rate of SMBG in the SAP arm, based on the findings from an observational study,<sup>20</sup> in which SAP was associated with an SMBG use of 4.35 strips per day compared with 7.11 strips per day in the CSII arm.

**Table 1** Baseline cohort characteristics

	Mean (SD)
<b>Cohort with suboptimal glycemic control at baseline<sup>17,18</sup></b>	
Age, years	27 (15.6)
Male, %	48.5
Duration of diabetes, years	13.2 (10.8)
HbA1c, % (mmol/mol)	8.0 (64)
<b>Cohort with increased risk of hypoglycemic events<sup>19</sup></b>	
Age, years	18.6 (11.8)
Male, %	49.5
Duration of diabetes, years	11 (8.9)
HbA1c, % (mmol/mol)	7.5 (58)

Direct costs for diabetes-related complications were sourced from published literature<sup>21–28</sup> and inflated to 2014 EUR using the consumer price index published by the Centraal Bureau voor de Statistiek (Statistics Netherlands) (Table 2). Indirect costs due to lost productivity associated with diabetes-related complications were based on the human capital approach using findings from a study conducted in Denmark by Sørensen and Ploug.<sup>29</sup> For indirect cost calculations, the mean age at first income was 25.2 years, the age at retirement was 65 years, and the number of working days was 228 days per year. Average salaries for males and females were sourced from the Centraal Bureau voor de Statistiek.

For the cohort with suboptimal glycemic control at baseline, a utility benefit associated with reduced fear of hypoglycemia (FoH) was applied to the SAP arm. Findings from the INTERPET study showed that the SAP was associated with a 6.9 U decrease in the Hypoglycemia Fear Survey (HFS).<sup>30,31</sup> Previous

**Table 2** Costs of diabetes-related complications

Complication	Cost, EUR	References
Myocardial infarction, year of event	5,138	21
Myocardial infarction, subsequent years	1,932	21
Angina, first year	11,119	22
Angina, subsequent years	154	23, 24
Congestive heart failure, first year	2,870	25
Congestive heart failure, subsequent years	325	23, 24, 25
Stroke, year of event	13,819	21
Stroke, subsequent years	1,932	21
Stroke death within 30 days	8,603	21, 25
Hemodialysis, annual	89,447	26
Peritoneal dialysis, annual	66,434	26
Renal transplant, first year	91,503	25
Renal transplant, subsequent years	3,680	25
Severe hypoglycemic event	2,567	25
Minor hypoglycemic event	0	Assumed
Ketoacidosis event	4,468	25
Lactic acidosis event	4,468	25
Edema onset	5,651	25
Edema follow-up	711	25
Laser photocoagulation	543	25
Cataract operation	2,955	25
Cataract operation follow-up	204	25
Blindness, year of onset	919	25
Blindness, subsequent years	441	25
Neuropathy, year of onset	10,335	25
Neuropathy, subsequent years	528	25
Amputation event	59,111	25
Amputation prosthesis	4,000	27
Gangrene treatment	1,250	28
After healed ulcer	154	28
Infected ulcer	1,690	28
Standard uninfected ulcer	2,678	28
Healed ulcer, history of amputation	1,608	28

**Note:** All costs are presented in 2014 EUR.

findings from another study reported that a 1 U increase in HFS score corresponds to a 0.008 U decrease in EQ-5D<sub>index</sub> score.<sup>32</sup> Consequently, the 6.9 U decrease in HFS score associated with SAP was assumed to correspond to a utility benefit of 0.0552.

A quality-of-life (QoL) adjustment was also made for the cohort at increased risk of hypoglycemic events that considered the combined effect of the reduction in severe hypoglycemic event rate and reduced FoH with SAP based on the findings of a previous study by McBride et al.<sup>33</sup> A utility benefit of 0.038 was applied to the SAP arm and a decrement of -0.035 was applied to the CSII arm.

## Other model settings

The time horizon of the analysis was that of patient lifetimes. A discount rate of 4% per annum was applied to future costs, and a discount rate of 1.5% per annum was applied to clinical outcomes, in line with recommendations for the Netherlands.<sup>34</sup> The base case analyses were performed from a societal perspective and therefore included both direct and indirect costs.

## Sensitivity analyses

A series of one-way sensitivity analyses were performed for each patient group to determine the key drivers of outcomes in both patient groups. For both patient cohorts, sensitivity analyses were performed around time horizon and discount rate as well as perspective. The base case analysis was performed from the societal perspective (ie, incorporating both direct and indirect costs); therefore, a sensitivity analysis was performed in which only direct medical costs were included.

In the cohort with suboptimal glycemic control at baseline, sensitivity analyses were performed around the costs of the sensors and sensor kit as well as the number of sensors used annually. In the base case, it was assumed that 43 sensors per year were used; sensitivity analyses were performed in which the number of sensors used was increased to 48 and 61 per year. In this patient cohort, sensitivity analyses were also performed around baseline HbA1c, SMBG use, and FoH. In a series of sensitivity analyses, the effect of changing mean baseline to 7.5% (58 mmol/mol), 8.5% (69 mmol/mol), and 9.0% (75 mmol/mol) was investigated (compared with 8.0% [64 mmol/mol] in the base case). Similarly, the effect of reducing and negating the QoL benefit in terms of FoH was examined by performing simulations where, in the SAP arm, no FoH utility benefit was included and where the utility benefit was reduced to 0.0184 (compared with 0.0552 in the base case). The value of 0.0184 for the FoH utility benefit was based on the previously published findings by the Juvenile Diabetes Research Foundation Continuous Glucose Monitoring Study Group.<sup>35</sup> Sensitivity analyses were also performed in which SMBG use in the SAP

arm was changed to 7.11, 6.11, and 2.11 per day, compared with 4.35 per day in the base case.

In the cohort at increased risk of hypoglycemic events, sensitivity analyses were performed around the severe hypoglycemic event rate in the CSII arm, which was decreased to one event per 100 patient-months in one analysis and increased to eight events per 100 patient-months in a second analysis (compared with 2.2 events per 100 patient-months in the CSII arm in the base case).<sup>19</sup>

## Results

### Cohort with suboptimal glycemic control at baseline

In the patient cohort with suboptimal baseline glycemic control (mean baseline HbA1c 8.0% [64 mmol/mol]), the long-term use of SAP was associated with a gain in quality-adjusted life expectancy by 1.77 quality-adjusted life years (QALYs) relative to CSII (15.54 QALYs vs 13.77 QALYs; Table 3). Total lifetime costs (direct and indirect) for SAP

**Table 3** Summary of base case analyses

	SAP	CSII	Δ SAP–CSII
<b>Hyperglycemia at baseline cohort</b>			
Quality-adjusted life expectancy, QALYs	15.54	13.77	1.77
Total costs, EUR	189,855	150,366	39,489
Total direct costs, EUR	119,799	75,301	44,498
Treatment costs	61,927	14,989	46,938
Management costs	19,461	19,150	311
Cardiovascular complication costs	4,355	4,332	23
Renal complication costs	11,665	13,351	-1,686
Ulcer/amputation/neuropathy costs	16,912	18,008	-1,096
Ophthalmic complication costs	3,211	3,212	-1
ICER, EUR per QALY gained	22,325		
<b>Increased risk for hypoglycemia cohort</b>			
Quality-adjusted life expectancy, QALYs	16.70	14.53	2.16
Total costs, EUR	204,013	171,032	32,981
Total direct costs, EUR	125,021	86,676	38,345
Treatment costs	66,246	16,144	50,102
Management costs	20,829	20,658	171
Cardiovascular complication costs	3,495	3,432	63
Renal complication costs	11,104	10,963	141
Ulcer/amputation/neuropathy costs	18,419	18,187	232
Ophthalmic complication costs	3,689	3,638	51
ICER, EUR per QALY gained	15,243		

**Abbreviations:** CSII, continuous subcutaneous insulin infusion; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; SAP, sensor-augmented pump therapy.



were EUR 39,489 higher than those for CSII (EUR 189,855 vs EUR 150,366) resulting in an ICER of EUR 22,325 per QALY gained. SAP was also associated with a delay in the mean time to the onset of all diabetes-related complications included in the CDM. In particular, the onset of several complications including proliferative retinopathy, proteinuria, ulcer, and neuropathy was delayed by over 1 year.

If only direct costs were considered, the ICER was marginally higher at EUR 25,168 per QALY gained, which would still fall below the commonly cited willingness-to-pay threshold of EUR 30,000 per QALY gained. Indeed, in the base case analysis, at a willingness-to-pay threshold of EUR 30,000 per QALY gained, the likelihood of SAP being considered cost-effective vs CSII was 88.5% (Figure 1).

Sensitivity analyses showed that, in this cohort, the results were sensitive to changes in the assumptions around the QoL benefit associated with SAP use and also baseline HbA1c (Table 4). In the base case analysis, the use of SAP was assumed to be associated with an annual utility benefit of 0.0552 owing to a reduction in FoH. However, if this utility benefit was reduced to 0.0184, the gain in quality-adjusted life expectancy was reduced to 0.86 QALYs and the ICER was increased to EUR 46,147 per QALY gained. Similarly, if this utility benefit was negated entirely, the ICER was further increased to EUR 98,820 per QALY gained for SAP vs CSII. Sensitivity analyses also showed that SAP is likely to be most cost-effective in those patients with the poorest glycemic control. If the mean baseline HbA1c was increased to 8.5% (69 mmol/mol), the ICER was reduced to EUR 19,595 per QALY gained. Moreover, at a mean baseline HbA1c of 9.0% (75 mmol/mol), the ICER for SAP vs CSII was further reduced to EUR 17,894 per QALY gained. These two sensitivity analyses may be the most relevant to the analyses as 8.0% (64 mmol/mol) is the threshold for the reimbursement of SAP in adults in the Netherlands.

## Cohort at increased risk of hypoglycemic events

In the cohort at increased risk of hypoglycemic events, the incremental gain in quality-adjusted life expectancy associated with SAP use was 2.16 QALYs (16.70 QALYs with SAP vs 14.53 QALYs with CSII; Table 3). However, total lifetime costs (direct and indirect) were EUR 32,981 higher for SAP than for CSII (EUR 204,013 vs EUR 171,032). The combination of higher quality-adjusted life expectancy, but higher lifetime costs, resulted in an ICER of EUR 15,243 per QALY gained for SAP vs CSII. The analysis of the cost-effectiveness acceptability curve showed that, in this patient group, at a

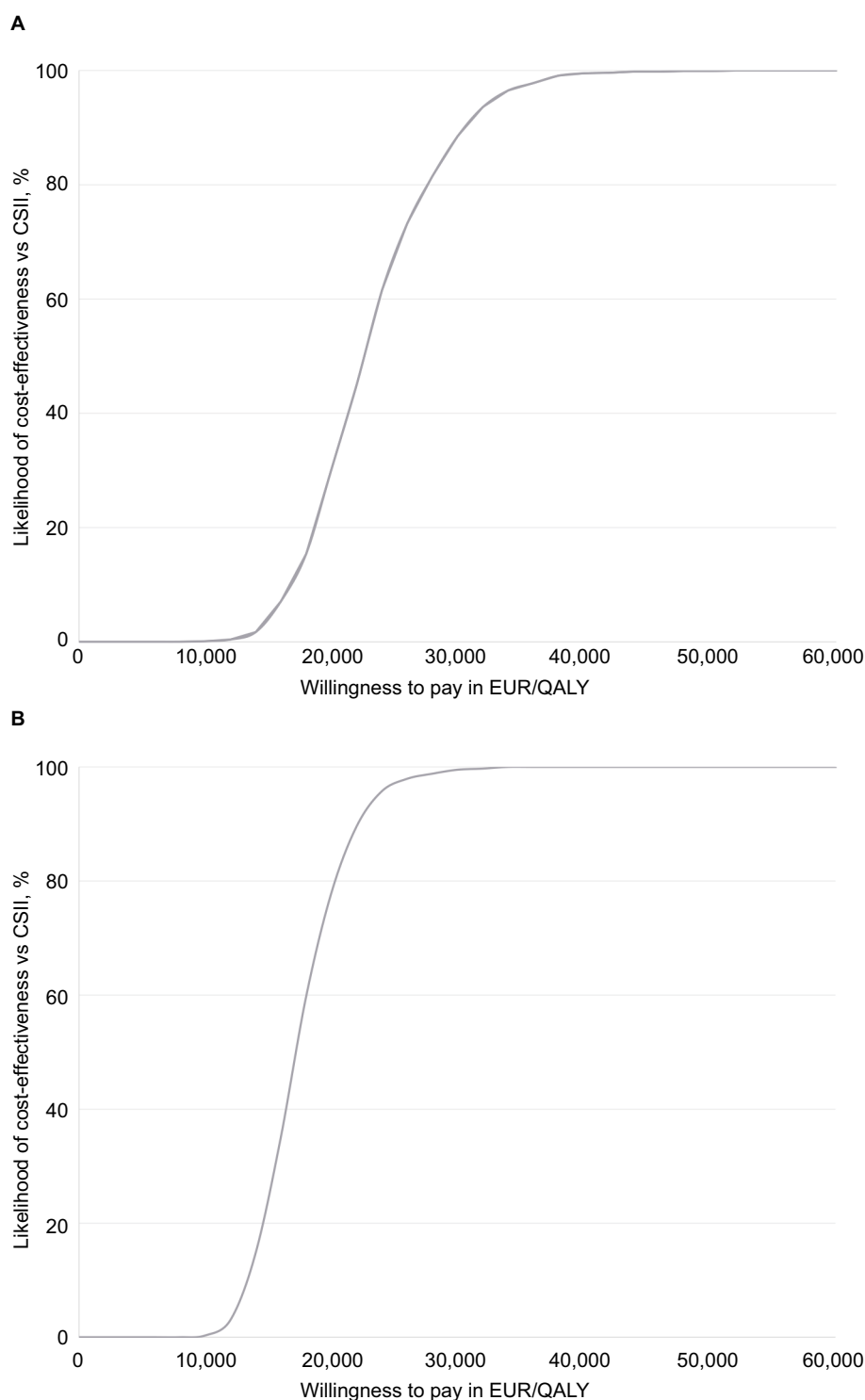
willingness-to-pay threshold of EUR 30,000, the likelihood of SAP being considered cost-effective compared with CSII was 99.5% (Figure 1). The use of SAP was also associated with a reduced cumulative incidence and delay to the onset of diabetes-related complications. The most pronounced delay was for neuropathy, the mean onset of which was delayed by 1.17 years with SAP compared with CSII alone.

In this patient cohort, sensitivity analyses showed that the cost-effectiveness of SAP vs CSII was strongly influenced by the rate of severe hypoglycemic events in the CSII arm (Table 4). In the base case analysis, an event rate of 2.2 events per 100 patient-months was assumed for the CSII arm; in a sensitivity analysis where this was decreased to one event per 100 patient-months, the ICER was increased to EUR 18,288 per QALY gained. Conversely, in a sensitivity analysis in which an event rate of eight events per 100 patient-months was assumed in the CSII arm, the ICER for SAP vs CSII was considerably lower at EUR 5,470 per QALY gained. The high direct costs and potentially severe clinical consequences associated with severe hypoglycemic events suggest that for patients who continue to experience severe hypoglycemic events on CSII, switching to SAP is likely to be cost-effective.

## Discussion

The findings from cost-effectiveness analysis show that, for type 1 diabetes patients in the Netherlands, SAP with automated insulin suspension is likely to be cost-effective compared with CSII in patients with suboptimal glycemic control and patients who are at increased risk of hypoglycemic events. The findings presented in this study concur with those for type 1 diabetes in other Western European countries including the UK, France, Denmark, and Sweden.<sup>36–39</sup>

The uptake of insulin pump therapy in the Netherlands is considerably higher than many other European countries.<sup>6</sup> Establishing the patient groups who are likely to benefit most from switching to more sophisticated technologies such as SAP, as well as the patient groups in which this switch is cost-effective, provides useful information for payers, policy makers, and clinicians in the Dutch setting. In the Dutch Diabeter clinic network, in which 93% patients have type 1 diabetes, at the end of 2014, 57% were on CSII and 8% patients were on SAP.<sup>40</sup> Moreover, 87% of SAP patients, compared with 58% of CSII patients, had HbA1c < 7.5%, suggesting that in routine clinical practice in the Netherlands, there is potentially a substantial proportion of CSII-treated patients who may derive clinical benefit from switching to SAP.<sup>40</sup>



**Figure 1** Cost-effectiveness acceptability curve for SAP vs CSII.

**Notes:** (A) Patients with suboptimal glycemic control at baseline. (B) Patients at increased risk of hypoglycemic events.

**Abbreviations:** CSII, continuous subcutaneous insulin infusion; QALY, quality-adjusted life year; SAP, sensor-augmented pump therapy.

In the cohort with hyperglycemia at baseline, the influence of SAP on FoH was a key driver of outcomes. In the sensitivity analysis in which the utility benefit associated with reduced FoH was negated the ICER increased to over EUR 98,000 per

QALY gained, which would no longer be considered cost-effective using commonly cited willingness-to-pay thresholds. The Diabetes MILES, the Netherlands study,<sup>41</sup> investigated FoH in type 1 diabetes patients in the Netherlands. Notably,

**Table 4** Summary of sensitivity analyses

	Quality-adjusted life expectancy, QALYs			Costs, EUR			ICER, EUR per QALY
	SAP	CSII	Δ	SAP	CSII	Δ	
Hyperglycemia at baseline cohort							
Base case	15.54	13.77	1.77	189,855	150,366	39,489	22,335
Direct costs only	15.54	13.77	1.77	119,799	75,301	44,498	25,168
Sensor + kit cost, −20%	15.54	13.77	1.77	179,622	150,366	29,256	16,548
Sensor + kit cost, −10%	15.54	13.77	1.77	184,739	150,366	34,373	19,441
Sensor + kit cost, +10%	15.54	13.77	1.77	194,971	150,366	44,635	25,229
Baseline HbA1c, 7.5% (58 mmol/mol)	15.97	14.25	1.72	183,368	141,704	41,664	24,182
Baseline HbA1c, 8.5% (69 mmol/mol)	15.12	13.27	1.85	196,300	160,027	36,273	19,595
Baseline HbA1c, 9.0% (75 mmol/mol)	14.67	12.79	1.88	203,650	169,980	33,670	17,894
Complication costs, +20%	15.54	13.77	1.77	201,402	162,402	39,000	22,059
Complication costs, −20%	15.54	13.77	1.77	178,286	138,310	39,976	22,611
FoH utility =0	14.17	13.77	0.40	189,855	150,366	39,489	98,820
FoH utility =0.0184	14.63	13.77	0.86	189,855	150,366	39,489	46,147
SAP SMBG use =7.11/day	15.54	13.77	1.77	195,757	150,366	45,391	25,673
SAP SMBG use =6.11/day	15.54	13.77	1.77	193,618	150,366	43,252	24,464
SAP SMBG use =2.11/day	15.54	13.77	1.77	185,064	150,366	34,698	19,626
Time horizon, 5 years	3.47	3.20	0.27	25,623	14,029	11,594	42,987
Time horizon, 10 years	6.34	5.81	0.53	51,052	30,713	20,339	38,369
Time horizon, 20 years	10.72	9.72	1.0	101,787	70,575	31,212	31,194
Time horizon, 40 years	14.85	13.24	1.61	173,282	135,259	38,023	23,561
0% discount rate	20.05	17.62	2.43	492,418	418,435	73,893	30,444
1.5% discount rate	15.54	13.77	1.77	331,250	274,672	56,578	32,001
4% discount rate	10.95	9.81	1.14	189,855	150,366	39,489	34,539
Sensor use =48 per year	15.66	13.77	1.89	193,080	150,366	42,714	22,594
Sensor use =61 per year	15.97	13.77	2.26	201,502	150,366	51,136	23,305
Increased risk for hypoglycemic event cohort							
Base case	16.79	14.53	2.16	204,013	171,032	32,981	15,243
Direct costs	16.70	14.53	2.16	125,021	86,676	38,345	17,722
0% discount rate	22.03	19.07	2.96	598,386	529,777	68,609	23,186
1.5% discount rate	16.70	14.53	2.16	382,297	332,202	50,095	23,152
4% discount rate	11.45	10.04	1.42	204,013	171,032	32,981	23,298
Time horizon, 10 years	6.28	5.59	0.69	47,493	32,490	15,003	21,756
Time horizon, 20 years	10.84	9.57	2.27	94,631	70,719	23,912	18,870
CSII SHE rate =1 per 100 patient-months	16.70	14.53	2.16	204,013	164,490	39,523	18,288
CSII SHE rate =8 per 100 patient-months	16.70	14.54	2.16	204,013	192,202	11,811	5,470

**Abbreviations:** CSII, continuous subcutaneous insulin infusion; FoH, fear of hypoglycemia; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; SAP, sensor-augmented pump therapy; SHE, severe hypoglycemic event; SMBG, self-monitoring of blood glucose.

mean FoH scores were lower than in other countries, which interestingly the authors partly attributed to the high uptake of insulin pump therapy in the Netherlands (54% of patients in the study used insulin pumps). It was also noted that high FoH owing to a history of severe hypoglycemic events may in instances lead to behavior modifications such as deliberately reducing insulin dose, resulting in suboptimal glycemic control, which can ultimately increase the risk of long-term complications. It is also important to note that the QoL impact of FoH in terms of utility values was derived from a single study (INTERPRET),<sup>30,31</sup> where the main indications for SAP initiation were glycemic instability, persistently high HbA1c,

recurrent hypoglycemia, hypoglycemia unawareness, and flexibility/lifestyle choice. The extent of FoH may vary between different patient populations and individuals, and conclusions relating to the impact of FoH may also be influenced by the accuracy with which its impact can be measured as different methods of eliciting utilities can result in different values, and for children and adolescents, patient-reported outcomes are sometimes determined using parents as proxies rather than the patients themselves. In terms of different individuals' experiences of FoH, in the recently published multinational IO HAT study, FoH was assessed on a scale of 0–10, where 0= no FoH and 10= absolutely terrified. In this study, while

the mean (SD) FoH score for patients with type 1 diabetes was 5.5 (3.3), 12.7% of patients reported a score of 0% and 17.1% reported a score of 10, illustrating that FoH may vary substantially from patient to patient.<sup>42</sup>

Baseline HbA1c was also a key determinant of cost-effectiveness in the cohort with suboptimal glycemic control at baseline. Sensitivity analysis around baseline HbA1c showed that SAP was most cost-effective in those with poorest glycemic control at baseline. In the base case analysis, the mean baseline HbA1c was 8.0% (64 mmol/mol). At a mean baseline HbA1c of 7.5% (58 mmol/mol), the ICER for SAP vs CSII was EUR 24,182 per QALY gained. However, in analyses where baseline HbA1c was 8.5% (69 mmol/mol) and 9.0% (75 mmol/mol), the ICER decreased to EUR 19,595 and EUR 17,894 per QALY gained, respectively. These sensitivity analyses are likely the most relevant to clinical practice in the Netherlands as the reimbursement of SAP in adults is limited to those with HbA1c > 8.0% (64 mmol/mol). In addition, one study recently reported that >20% of type 1 diabetes patients aged 15–24 years and >5% of those aged ≥25 years had a HbA1c level ≥9.0% (75 mmol/mol).<sup>6</sup>

In the cohort at increased risk of hypoglycemic events, a major driver of the cost-effectiveness of SAP was the higher rate of severe hypoglycemic events in the CSII arm. Clinical input data for this patient cohort were based on a randomized controlled trial performed in type 1 diabetes patients with impaired awareness of hypoglycemia.<sup>19</sup> Up to 30% of adults with type 1 diabetes have impaired awareness of hypoglycemia, which in turn increases the risk of severe hypoglycemic events.<sup>43</sup> The automated insulin suspension functionality of some SAP may therefore be particularly beneficial for patients with impaired hypoglycemia and/or a history of frequent severe hypoglycemic events. In addition, there is evidence to suggest that in type 1 diabetes patients, the distribution of severe hypoglycemic events is highly skewed, indeed in one multinational study of hypoglycemia, 5% of patients accounted for 54% of all severe hypoglycemic events.<sup>44</sup> As such, on an individual patient level, the use of SAP is likely to be highly cost-effective for the small proportion of patients who experience frequent severe hypoglycemic events. Notably, in the current analysis, only severe hypoglycemic events were accounted for, the QoL implications as well as the direct and indirect costs associated with minor hypoglycemic events were not included. While for many patients, minor events may be easily addressed and may not cause distress, for some patients, minor events may have a detrimental impact on everyday life. For example, hypoglycemia is known to lead to cognitive dysfunction in many patients, which may negatively influence the ability to

perform everyday activities such as driving.<sup>45</sup> In addition, even minor hypoglycemic events can have a considerable impact in terms of lost productivity. Indeed, in one multinational study, productivity loss due to non-severe hypoglycemic events was estimated at 8.3–15.9 hours (USD 15–93) per incident.<sup>46</sup>

The analysis performed in this study is associated with limitations. A limitation inherent to any health economic modeling analysis is the use of short-term clinical trial data to project outcomes over patient lifetimes. In the analysis presented for the cohort with the increase of hypoglycemic events, clinical input data were sourced from a clinical trial of 6-month duration. Similarly, input data for the cohort with suboptimal glycemic control at baseline were sourced from a meta-analysis of randomized controlled trials. However, large-scale long-term (>5 years) clinical and cost studies of SAP are currently lacking; therefore, health economic modeling represents a pragmatic alternative for the projection of long-term outcomes. The analysis did not account for the potential effect of adherence to SAP declining over time. In the base case analysis, an annual sensor use of 43 sensors was assumed (corresponding to mean sensor use of 71%). The findings of the SWITCH study showed that glycemic control was worse in patients with sensor use <70%;<sup>47</sup> therefore, any waning of adherence over time may negatively influence the long-term efficacy of SAP. In addition, although the analysis was performed from a societal perspective and therefore captured indirect costs, costs associated with informal caregivers such as parents and partners, which may be substantial, were not captured in the analysis. Indeed, in a recent study in pediatric patients from Spain, the cost of informal care was estimated to account for 83% of total annual direct and indirect costs. As such, total costs in the current study, in both treatment arms, may be underestimated.<sup>48</sup> A further limitation is that while the analysis was performed from a societal perspective, it did not capture the potential resource use costs associated with medical personnel training patients how to use SAP devices.

## Conclusion

Overall, the findings from the current analysis suggest that for CSII-treated type 1 diabetes patients in the Netherlands, who have either suboptimal glycemic control or are at increased risk of hypoglycemia, switching to SAP with automated insulin suspension is likely to confer long-term clinical benefits and is likely to be good value for money. Further, SAP is likely to be most cost-effective in patients with the poorest glycemic control at baseline and in patients who experience frequent severe hypoglycemic events.



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