Master's Degree Dissertation

Cost-effectiveness Analysis of Continuous subcutaneous insulin infusion compared with multiple daily injections in adult patients with type 1 and type 2 Diabetes mellitus: a systematic review

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"I declare that I have written the submitted piece of work independently, and I did not use any outside support except for the quoted literature and other sources mentioned in the paper."

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Abstract

Background: Insulin replacement therapy is the cornerstone for the treatment of type 1 and 2 diabetes mellitus. Two of the most used methods are continuous subcutaneous insulin infusion and multiple daily injections. This systematic review aims to find, can the continuous subcutaneous insulin infusion be considered cost-effective compared to the multiple daily injections?

Methods: A systematic search was conducted in August 2021 that focused on the published literature comparing the cost-effectiveness of continuous subcutaneous insulin infusion with multiple daily injections. Searched databases included Pubmed, Scopus, Cochrane, and UPF finder.

Results: A total of 621 publications were identified, of which 21 were analyzed. Results were significantly dependant on the study design and method used. Most of the studies based on Modelling reported that continuous subcutaneous insulin infusion is considered cost-effective compared to multiple daily injections with an average Incremental cost-effectiveness ratio of US $37,717/QALY gained, with an Adjusted Incremental cost-effectiveness ratio (to the year 2021) calculated as US $51,016/QALY gained. However, Randomized-controlled trials reported opposite results.

Conclusion: Continuous subcutaneous insulin infusion is proven cost-effective compared to Multiple daily injections, especially in patients with high mean HbA1C, and can thus be considered a valuable therapy option in adult patients with type 1 diabetes mellitus. More evidence is needed in patients with type 2 diabetes mellitus treatment, but it would most probably be cost-effective, especially in patients with difficulty reaching optimal HbA1C levels using Multiple daily injections.

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1. Introduction

Diabetes mellitus is a group of metabolic diseases characterized mainly by hyperglycemia resulting from insulin secretion or insulin action defects. The chronic hyperglycemia of diabetes is associated with long-term impairment, dysfunction, and failure of several organs, especially the kidneys, eyes, nerves, heart, and blood vessels. (1)

There are mainly two types of diabetes mellitus. Type 1 diabetes is an autoimmune disease that attacks insulin-producing cells in the pancreas; it is usually diagnosed in children and young adults but can develop at any age. Patients with Type 1 diabetes need to take insulin every day, and this is why it is also called insulin-dependent diabetes. In Type 2 diabetes, the insulin-producing cells in the pancreas do not produce enough insulin, and the insulin-target cells on which insulin acts develop resistance against insulin. (2)

Insulin-replacement therapy is the cornerstone of the management of diabetes mellitus. The most commonly used method is Multiple daily injections (MDI). The therapy involves injecting long-acting insulin once or twice daily as a basal dose and having further injections of rapid-acting insulin at each mealtime. During the last two decades, continuous subcutaneous insulin infusion (CSII) or known as (Insulin pumps) has become a recognized model of intensive diabetes treatment for many diabetes mellitus patients worldwide. (3)

An insulin pump is a machine connected to the body via a Cannula, which enables insulin to be delivered automatically or in response to instructions given by either pump wearer or his/her physician. (4)

The main objective of this study is to search for an answer to the question: are CSII cost-effective compared to MDI? Furthermore, if the answer is positive, in which situations exactly would it be cost-effective.

2. Methods

2.1. Eligibility Criteria

For the systematic review, all the published literature, including Randomized Controlled Trials, Observational studies, Non-Randomized case-control studies, studies based on Modelling as well as Systematic reviews about the cost-effectiveness analysis of comparing the Continuous subcutaneous insulin infusion (CSII) with Multiple daily injections (MDI) in adult patients with type 1 and type 2 diabetes mellitus were eligible to be included. For the Randomized Controlled Trails, the short-acting insulin had to be the same in both treatment groups, either regular insulin or an insulin analog. Studies that did not include Cost-effectiveness analysis, Budget impact analysis, or Economic analysis were not considered in the systematic review. Only studies with available full text were selected. The PRISMA Checklist was used.

2.2. Information Sources and Search Strategy

The search for the published literature was performed in Pubmed, Scopus, Cochrane, and UPF finder on 12.08.2021. The search was done using the following words: Cost-effectiveness (Benefit) Analysis of Continuous subcutaneous insulin infusion and multiple daily injections in adult patients with diabetes mellitus. The phrases and words used for the search in full Text, Abstracts, and Titles. Synonyms for continuous subcutaneous insulin, like insulin pump(s) and insulin infusion systems, were adapted accordingly in the search. No language or year filters were used.

2.3. Selection Process

The reviewer analyzed the results in two phases. The first phase is screening the titles and the abstracts of the results for relevance and duplicate studies. Studies that met the eligibility criteria were selected for the second phase analysis. The second phase was proofreading the Abstracts and Full Text when available to choose the final list of the studies. No Automation tools used

2.4. Data Items Collected

The primary outcome collected from the studies is the Incremental Cost-effectiveness Ratio (ICER) between the two comparators. Other outcomes included the type of the study, year of publishing, diabetes mellitus type, country, currency, discount rate, and the year currency if available; The data collected manually without automation tools from the Studies

The studies included are divided into groups according to their type into Systematic Reviews, Randomized Controlled Trials, Observational Studies, Non-Randomized Case-Control studies, and Finally, studies based on Modelling. The results are presented and summarized in Tables, showing which studies conclude that one comparator is more cost-effective than the other one. The studies based on Modelling, Average ICER, and adjusted ICER for the US $ (the year 2021) with a 3% discount rate are presented in a table along with the main characteristics of the studies.

2.5. Missing data

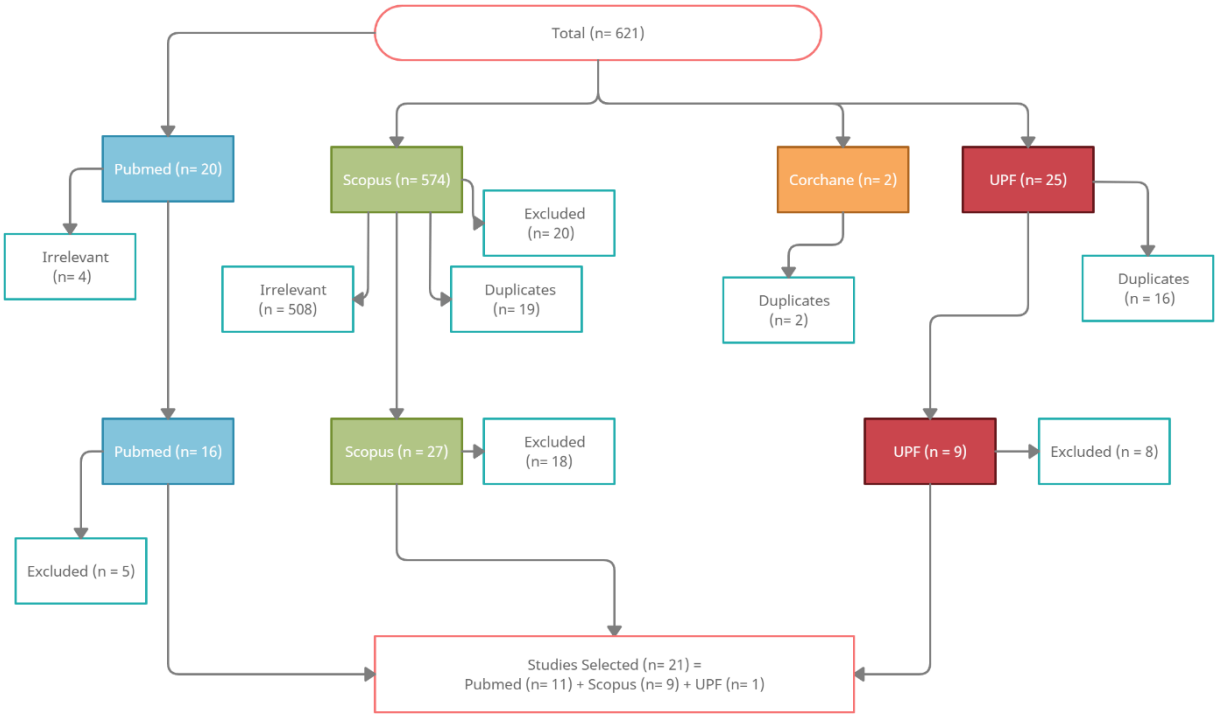
Missing information about funding sources in the studies selected was considered not to have received funding.

2.6. Data Synthesis

In the present systematic review, no meta-analysis has been performed. However, Adjusted ICER for the year 2021 values were calculated with a 3% discount rate using the following formula: Future Value = Present Value * (1 + r) ^n using Excel.

3. Results

3.1 Study selection



The number of Studies selected were 21 (n= 21); the studies were from the following countries: the US, Netherland, UK, Spain, Canada, Australia, Mexico, Finland, Sweden, and Germany. Most of the studies were about Type 1 diabetes mellitus only (17/21 – 82%), and four studies included Type 2 diabetes mellitus.

In the 2nd phase of studies selection, Nineteen Studies (n= 19) were excluded as they do not compare CSII vs. MDI. Three Studies (n= 3) were excluded as they do not include an Adult population; Furthermore, another three studies (n= 3) were excluded because the full text is not available online. More detailed information can be found in Table 5 in the Appendix section.

For the risk of bias, a total of six studies (n= 6) were excluded as they compared sensor-augmented CSII vs. MDI. More information about these studies can be found in Table 6 in the Appendix section.

Most of the studies received funding (n= 17), with about eight studies based on Modelling (n= 8) out of eleven studies received funding from Insulin-pumps manufacturing companies.

3.2. Systematic Reviews (n=5)

The systematic review published by A. Pease et al. in the Year 2020 comparing the Cost-effectiveness of different health technologies in adults with type 1 diabetes concluded that CSII appeared to be cost-effective, predominantly in populations with higher HbA1c levels and rates of hypoglycemia. (5)

In 2015, S. Roze et al. published a systematic review, which highlighted that CSII is cost-effective vs. MDI in Type 1 diabetes across the 8 Countries with a mean incremental cost-effectiveness ratio of €30 862 (17 997 – 43 727), US $40 143 (23 409 – 56 876) per QALY gained. Furthermore, CSII was associated with improved life expectancy and quality-adjusted life expectancy (0,4 – 1,10 QALYs in adults) driven by lower HbA1C and lower frequency of hypoglycemic events vs. MDI. However, CSII was associated with higher lifetime direct costs but cost-savings from reduced diabetes-related complications partially offset this. (6)

The systematic review about the Cost-effectiveness of Advanced Technologies in the Management of Patients with Diabetes Mellitus published in 2015 by R. Vigersky concluded that most currently available technologies improve HbA1c with a better rate of hypoglycemia. The advanced technologies appear to be cost-effective in diabetes mellitus management, especially when including the cost of hypoglycemia. However, there have been a few cost-effectiveness studies of CSII. In cost-effectiveness studies, an appropriate value is considered an ICER of $50 000/QALY, although it may extend up to $300 000/QALY in the United States. (7)

E. Cummins et al. concluded in the systematic review published in 2010 that: based on the totality of the evidence, using observational studies to supplement the limited data from randomized trials against MDI, CSII offers some advantages over MDI in Type 1 diabetes for children and adults. There was no evidence that CSII is better than analog-based MDI in Type 2 diabetes or pregnancy. The authors highlighted that one of the most critical weaknesses of the evidence was the minimal number of randomized trials of CSII against the most modern forms of MDI, using analog insulins. The systemic review is based on studies conducted between 2002 and 2007, with most of the studies being Observational studies and few Randomized controlled trials. It is essential to mention that, meanwhile, there are considerable improvements in CSII technology. (8) (9)

Colquitt et al. summarized in their systematic review published in 2004 that CSII results in a modest but worthwhile improvement in glycated hemoglobin in adults with Type 1 diabetes compared with optimized MDI. It has not been possible to establish the long-term benefits of such a difference in glycated hemoglobin, although there is an expectation that it would be reflected in a reduction in long-term complications. However, there is inadequate evidence, and material presented to offer context on quality-of-life are based on patients' testimonies from those who have had a positive experience of CSII. (10)

Table 1 Summary results of systematic reviews:

Author	Year Published	DM Type	Result
A. Pease	2020	1	CSII is cost-effective
S. Roze et al.	2015	1	CSII is cost-effective
R. Vigersky	2015	1 and 2	CSII is cost-effective
E. Cummins et al.	2010	1 and 2	CSII provides some advantages, limited evidence
Colquitt et al.	2004	1	CSII results in a modest improvement, with limited evidence.

3.3. Randomized Controlled Trials (n=2)

The Randomized control trial done by Wan W. et al. concluded that initiating an insulin pump in adults with Type 1 Diabetes already using Continuous Glucose Monitoring was associated with higher costs and reduced quality of life. However, they highlighted that Additional Evidence regarding the clinical effects of adopting combinations of new technologies from trials and real-world populations is needed to confirm these findings. The main limitation of the trial is that standardized methods for pump training did not accompany the introduction of CSII. Secondly, the study was not designed and powered to detect an effect for clinical outcomes (such as HbA1C) other than time-in-range. (11)

S. Heller et al. published 2017 their cluster-randomized trial. They concluded that adding CSII therapy to structured training in flexible insulin therapy did not significantly enhance glycemic control

or psychosocial outcomes in adults with DM type 1. The study design is a multicenter, open-label, parallel-group cluster randomized controlled trial, including economic and psychosocial evaluations with a follow-up period of 24 months. one of the limitations in the study is the short follow up 24 months, as a reflection of the true costs saved would require a much longer follow up, which is challenging to implement in an RCT. It is worth noting that the study reported the mean difference (MD) in HbA1c change at two years, at which the baseline HbA1c was ≥ 7.5%, was –0.24% [95% confidence interval (CI) –0.53% to 0.05%] in favor of the CSII (p = 0.098). (12)

Table 2 Summary results of Randomized Controlled Trials:

Author	Year Published	DM Type	Result
Wan W. et al.	2018	1	MDI is dominant
S. Heller et al.	2017	1	CSII did not significantly enhance glycemic control or psychosocial outcomes.

3.4. Observational Studies (n=2)

The observational study published in Sweden by Emilie Toresson Grip et al. highlighted that Nine years of real-world data on all measurable diabetes-related resource use show robust results for additional costs of insulin pump therapy in adults. The study calculated insulin pump therapy and MDI costs in individuals with type 1 diabetes using real-world data with nine years of follow-up. However, the time frame may need to be even longer to detect differences in treatment effects that have consequences for total costs exceeding those in this study. (13)

Marga Giménez et al. highlighted in their observational study that the higher costs associated with CSII therapy might be offset by the severe hypoglycemic events prevented. It is worth noting that this study is limited to only possible complications of diabetes, which is hypoglycemia. Prevention of other complications like Retinopathy, nephropathy, and polyneuropathy will impact the costs saved and the patient's quality of life. (14)

Table 3 Summary of Observational Studies:

Author	Published Year	Diabetes Type	Result

Emilie Toresson Grip et al.	2019	1	Inconclusive results
Marga Giménez et al.	2017	1	the higher costs associated with CSII therapy might be offset by the severe hypoglycemic events prevented

3.5. Non-Randomized Case-Control Studies (n=1)

The non-randomized, case-control study published by A. Nicolucci et al. in 2008 suggests Quality of life gains deriving from greater lifestyle flexibility, less fear of hypoglycemia, and higher treatment satisfaction when CSII is compared with either glargine-based or NPH-based MDI regimens. (15)

3.6. Studies based on Modelling (n= 11)

Most of the studies used IQVIA CORE Diabetes Model (CDM) (n= 8), one study used (n= 1) used the Sheffield Type 1 Diabetes Policy Model, and two studies (n= 2) used Author's created model.

In Mexico, Svetlana V Doubova et al. published in the year 2019 a study with cost-effectiveness analysis performed using IQVIA CORE Diabetes Model (CDM) based on data obtained from Mexican DM Type 1 adult patients (≥ 18 years) that received care at two national IMSS medical centers in 2016. The study concluded that CSII could be considered cost-effective in the context of IMSS (The Mexican Institute of Social Security) when considering a threshold of three GDPs per capita with 43,9 probability. Results would improve substantially when patients have an HbA1C above 9%. (16)

The study published by S. Roze et al. in Finland concluded that CSII is likely to represent a cost-effective treatment substitute for patients with type 2 diabetes with poor glycemic control despite optimization of MDI. The study is based on long-term projections of clinical and economic outcomes associated with CSII use in Diabetes Mellitus Type 2 using the IQVIA CORE Diabetes Model (CDM). Data in the Model are based on the OpT2mise trial, which highlighted that CSII is associated with a 1.1% HbA1C decrease in patients with poor glycemic control at baseline. (17)

Daniel John Pollard et al. in 2018 concluded that the routine use of CSII in adults without an immediate clinical need for a CSII, as identified by National Institute for Health and Care Excellence

(NICE), would not be cost-effective. The authors in this study undertook two approaches to assess the cost-effectiveness of CSII: an economic evaluation alongside the clinical trial (EEACT) and a long-term economic model to determine the lifetime outcomes. Data on the costs and quality-adjusted life-years (QALY) and the biomedical outcomes were obtained from the REPOSE trial. The model used in this study is The Sheffield Type 1 Diabetes Policy Model version 1.3.2. is an individual-level simulation model used to estimate the lifetime costs and QALYs associated with pump + DAFNE (Dose Adjustment for Normal Eating) and MDI + DAFNE. The key strengths of the study are that it is based on a thoroughly conducted cluster RCT with the economic data directly collected during the study. The study has limitations in terms of the evidence used to enlighten the long-term variations in HbA1c, which were based on five observational studies with follow-up ranging from 3.7 to 10 years, rather than trials with long follow-up periods. (18)

William H. Herman et al. concluded that in the DCCT (The Diabetes Control and Complications Trial) scenarios, MDI therapy was cost-saving, and pump therapy was cost-effective, costing ~$82,000 per QALY-gained (<$100,000/QALY-gained). Furthermore, the study modeled the costs over 30 years of three different scenarios: Modern MDI, Modern Pump Therapy, and Modern Pump with Continuous Glucose Monitoring compared to Modern Basic Therapy. The calculated ICER (compared to Modern Basic Therapy) was $3,835 for the Modern MDI and $52,654 for the Modern Pump Therapy. It is worth noting that there was no direct comparison between MDI and Pump Therapy. (19)

The study published in 2016 in Germany by Y. F. Zöllner et al. based on a decision-analytic budget impact model concluded that the use of CSII resulted in fewer severe hypoglycemic events requiring hospitalization (SHEH) and complication-borne diabetic events (CDEs) compared to MDI. The incurred CSII implantation costs are hence offset to a substantial degree by cost savings in complication treatment. The budget impact model was developed in Microsoft® Excel® 2010 to consider the impact of switching 20% of patients with DM type 1 from MDI to CSII. The effects of HbA1c used in the model were obtained from the Diabetes Control and Complications Trial and a long-term study on the impact of intensive treatment on mortality. The costs of CSII treatment were sourced from the German reimbursement schedule for the Year 2014, and the costs of SHEH and CDE were obtained from published sources and inflated from the reported costs year to 2014 cost. One of the study's limitations is that the model uses only a 4-year time horizon; however, diabetes mellitus management has a lifetime duration. HbA1c is known to be linked to the rate of many diabetic complications, and it is possible that the true improved glycemic control impact would become apparent over a longer time scale only. (20)

In 2016, S. Roze et al. published a study based on the results of the OpT2mise randomized control trial and Long-term projection using the IQVIA CORE Diabetes Model (CDM). They concluded that: In the Netherlands, the CSII represents a cost-effective option in patients with type 2 diabetes who have poorly-controlled HbA1c despite optimization of MDI. Since the ICER is below the willingness-to-pay threshold of EUR 80,000 per QALY gained, CSII is likely to represent a good value for money in treating poorly-controlled type 2 diabetes patients compared with MDI. The results show that, for patients who cannot achieve reasonable glycemic control with MDI, the use of CSII is associated with substantial clinical benefits and notably delays the onset of all major diabetes-related complications considered in this analysis. The use of CSII for people with type 2 diabetes who cannot achieve reasonable glycemic control with MDI thus results in improved clinical outcomes and long-term cost savings due to reduced incidence of complications and represents good value for money. (21)

The study published by Meaghan E St Charles et al. used IQVIA CORE Diabetes Model (CDM) to determine the ICER of CSII compared with MDI from the perspective of a Canadian provincial government. Based on this analysis, the study concluded that CSII might be a cost-effective treatment option than MDI in Canada's adult patients with type 1 diabetes. The study used the change in glycosylated Hemoglobin HbA1C as a primary input variable. The study did not provide an ICER of CSII compared with MDI from a societal perspective, which would reflect more authentic results. (22)

The authors Meaghan St Charles and Peter Lynch et al. also published in the year (2009) a similar study using IQVIA CORE Diabetes Model; however, this study is from the US payer perspective. The results show that by setting the willingness to pay at $50,000/QALY, the analysis showed that CSII is a cost-effective option for patients with T1DM in the United States. The study is limited to the US Payer perspective; a societal perspective would have been more appropriate. (23)

The study done by Neale Cohen et al. in 2007, using the IQVIA CORE Diabetes Model (CDM), concluded that CSII is associated with ICERs in the range of $A 53,022 – 259,646 per QALY gained, with most ICERs representing good value for money in Australia. (24)

Ignacio Conget Donlo et al. published in 2006 in Spain a study using IQVIA CORE Diabetes Model (CDM) to simulate the long-term clinical and economic consequences for DM Type 1 patients. The study highlighted that the improvement in the glucose control among those patients using CSII was related to an overall lower cost in the management of DM Type 1 patients, which was found to have a favorable cost-utility ratio compared to conventional MDI treatment. (25)

The study published by S Roze et al. in 2005 concluded that in the UK, CSII was associated with an ICER of pounds 25,648 per QALY gained vs. MDI, representing good value for money. The study used the IQVIA CORE Diabetes Model (CDM) to stimulate disease progression in a cohort of patients with baseline characteristics taken from published UK studies. (26)

The average ICER is US $37,717, with Adjusted ICER (to the year 2021) calculated as US $51,016/QALY gained. Most of the values are between $20,660/QALY and $86,712/QALY, which is still a good value with a willingness to pay up to $100,000/QALY.

Table 4 Summary of Studies based on Modelling:

Author(s)	Year of Publication	DM Type	Country	Currency	Year reported	Model Used	ICER/ QALY	ICER in US$ 2021	Adjusted ICER
Svetlana V Doubova	2019	1	Mexico	MXN$	2016	CORE	MXN$369,593	$ 17,822	$20,660
S. Roze et al.	2019	2	Finland	Euro	2017	CORE	EUR 47,834	$54,143	$60,938
D. J. Pollard et al.	2018	1	UK	GBP	-	The Sheffield Type 1 Diabetes Policy Model	A*		
William H. Herman et al.	2018	1	US	US$	2014	-	US$52,654	$52,654	$64,457
Y. F. Zöllner et al.	2016	1	Germany	Euro	2014	-	B*		
Roze S. et al.	2016	2	Netherlands	Euro	2013	CORE	EUR 60,474	$68,452	$86,712
Meaghan E St Charles et al.	2009	1	Canada	Can$	2006	CORE	Can$23,797	$18,944	$23,997
Meaghan St Charles, Peter Lynch et al.	2009	1	US	US$	2007	CORE	$16,992	$16,992	$26,472
Neale Cohen	2007	1	Australia		2006	CORE	$A74,147	$54,141	$81,893
Ignacio Conget Donlo	2006	1	Spain	Euro	2005	CORE	EUR 29,947	$21,867	$35,090
Roze S. et al	2005	1	UK	GBP	2003	CORE	GBP 25,648	$34,434	$58,621

A No ICER calculated as CSII is proven to be not cost-effective*

B Budget impact analysis: total cost offsets of €183 085 281 within the 4-year time horizon*

4. Discussion

The clinical effectiveness of CSII is proven in many published literature; however, its cost-effectiveness has been a matter of debate. Various results are obtained based on their study designs. For example, randomized controlled trials mostly show that MDI is more cost-effective, which is a logical interpretation in the context of the study, which usually lasts a few months and does not have enough time to reflect the total costs that might be saved in the future, by avoiding the possible complications of diabetes mellitus. Observational studies are a good option to reflect the total costs; however, there is a limited number of observational studies comparing both the MDI and CSII; Furthermore, due to the long-time of the study, which may last many years, it does not seem to be the preferable option for researchers. Studies based on Modelling are by far the most used study design comparing MDI and CSII. Modeling in general, and specifically, Markov Models, are an excellent option to reflect the future costs of Diabetes Mellitus complications.

The IQIVIA CORE is the most widely used model. The Phil McEwand et al. study demonstrated that the IQIVIA CORE Model is a validated tool for predicting significant diabetes outcomes and consequently is potentially suitable for supporting policy decisions relating to disease management in Type 1 Diabetes Mellitus and Type 2 Diabetes Mellitus. (27) Data input in the model plays a significant role in the results calculated by the model. Data based on RCTs should be used cautiously, as sometimes, they reflect only the efficacy of the comparators, but not the efficiency, which represents a more realistic result. Real-World data obtained from retrospective observational studies could be a better option.

Most of the published studies used the intermediate outcome of mean HbA1C (Hemoglobin A1C), a test that measures the average amount of glucose attached to hemoglobin over the past three months. (28) Significant HbA1c variability is associated with increased risk of all diabetic complications as well as cardiovascular mortality. The association between hypoglycemic occurrence, HbA1c variability, and mortality suggests that intermittent hypoglycemia results in poorer outcomes in diabetic patients. (29)

Almost all of the studies included in this systematic review agree that CSII is associated with better-controlled diabetes mellitus and lower HbA1C Levels; this would be reflected in studies that project the long-term complication avoided using CSII. One of the main reasons CSII is not proven cost-effective in some studies is the relatively short duration of these studies lasting from a few months

to a maximum of nine or ten years, which is still not long enough to include the costs saved in preventing complications.

The use of CSII is also associated with generally better life quality and higher satisfaction for the patients. This aspect is not considered in many studies and sometimes even inappropriately applied, for example, in the RCT of Wan W. et al. (11), as the candidates in the trial were not well trained to use the Pumps effectively.

Regarding the limitations in the studies, there are relatively few published studies about diabetes mellitus type 2. It is worth mentioning that Insulin-Pumps manufacturing companies funded a significant number of the studies based on Modelling. One of the limitations of this systematic review is the heterogeneity of the studies selected and the relatively few databases searched. A focused search on one type of study on more databases could have shown more outstanding results.

Based on the results, CSII could be implemented in the clinical practice guidelines and recommended for patients with significantly high mean HbA1C values or patients who have difficulty complying with the MDI after receiving appropriate training on using the CSII. Future research would also focus more on combining the continuous glucose monitoring devices with the CSII; with the vast advancements in this technology, a complete replacement of the human pancreas with an artificial pancreas is possible. These advances, along with other methods of insulin presentation, would significantly improve the life quality of many patients.

5. Conclusion

CSII is proven cost-effective compared to MDI, especially in patients with high mean HbA1C; furthermore, it leads to better glycaemic control without a rise in hypoglycaemic events along with lower insulin requirements and higher quality of life. CSII can thus be considered a valuable therapy option in adult patients with type 1 diabetes mellitus. More evidence is needed in patients with type 2 diabetes mellitus treatment, but it would most probably be cost-effective, especially in patients with difficulty reaching optimal HbA1C levels using MDI.

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Appendix:

Table 5 Studies excluded in 2nd phase:

Ref. Number	Database	Authors	Title	Reason for exclusion
(30)	Pubmed	Nuboer R., Bruining GJ.	*Cost-effectiveness of continuous subcutaneous insulin infusion (CSII) in children: illusion or delusion?*	Included only Children, no adult population
(31)	Pubmed	Nargaard K. Sohlberg	*Cost-effectiveness of continuous subcutaneous insulin infusion therapy for type 1 diabetes*	Full text not available
(32)	Pubmed	Rose S., Smith-Palmer, Valetine WJ	*Long-term health economic benefits of sensor-augmented pump therapy vs continuous subcutaneous insulin infusion alone in type 1 diabetes: a UK perspective.*	No comparison of CSII vs. MDI
(33)	Scopus	Petkova, E., Petkova V.,	*Economic evaluation of continuous subcutaneous insulin infusion for children with diabetes - a pilot study: CSII application for children - economic evaluation*	Included only Children, no adult population

(34)	Scopus	Kwa, T., Zhang G., Shepard K. Wherry, K.	*The improved survival rate and cost-effectiveness of a 7-day continuous subcutaneous insulin infusion set*	No comparison of CSII vs. MDI
(35)	Scopus	Jendle, J., Smith-Palmer, Delbaere A. , Rose S.	*Cost-Effectiveness Analysis of Sensor-Augmented Insulin Pump Therapy with Automated Insulin Suspension Versus Standard Insulin Pump Therapy in Patients with Type 1 Diabetes in Sweden*	No comparison of CSII vs. MDI
(36)	Scopus	Rose S., de Portu S., Smith-Palmer	*Cost-effectiveness of sensor-augmented pump therapy versus standard insulin pump therapy in patients with type 1 diabetes in Denmark*	No comparison of CSII vs. MDI
(37)	Scopus	Ly, T.T., Brnabic A.J.M., Eggleston A.	*A cost-effectiveness analysis of sensor-augmented insulin pump therapy and automated insulin suspension versus standard pump therapy for hypoglycemic unaware patients with type 1 diabetes*	No comparison of CSII vs. MDI
(38)	Scopus	Roze S., Smith-Palmer, J., De Portu S., Delbaere A.	*Cost-effectiveness of sensor-augmented insulin pump therapy vs continuous subcutaneous insulin infusion in patients with type 1 diabetes in the Netherlands*	No comparison of CSII vs. MDI
(39)	Scopus	Palmer A.J., Rose S., Valetine W.J.	*Cost-effectiveness of detemir-based basal/bolus therapy versus NPH-based basal/bolus therapy for type 1 diabetes in a UK setting: An economic analysis based on meta-analysis results of four clinical trials*	No comparison of CSII vs. MDI
(40)	Scopus	Jendle, J., Pöhlmann, J.m De Portu, Roze S.	*Cost-effectiveness analysis of the MiniMed 670G hybrid closed-loop system versus continuous subcutaneous insulin infusion for treatment of type 1 diabetes*	No comparison of CSII vs. MDI
(41)	Scopus	Nicolucci A., Rossi M.C., Roze. S.	*Cost-effectiveness of sensor-augmented pump therapy in two different patient populations with type 1 diabetes in Italy*	No comparison of CSII vs. MDI

(42)	Scopus	Li, R., Zhang P., Barker L.E.	*Cost-effectiveness of interventions to prevent and control diabetes mellitus: A systematic review*	No comparison of CSII vs. MDI
(43)	Scopus	Roze S., Smith-Palmer, Valentine, De Portu	*Cost-effectiveness of sensor-augmented pump therapy with low glucose suspend versus standard insulin pump therapy in two different patient populations with type 1 diabetes in France*	No comparison of CSII vs. MDI
(44)	Scopus	Siegel, K.R., Ali M.K.	*Cost-effectiveness of interventions to manage Diabetes: Has the Evidence changed since 2008?*	No comparison of CSII vs. MDI
(45)	UPF Finder	Evans, Marc, Mehta, Roopa	*Cost-Effectiveness of Insulin Degludec vs. Insulin Glargine U100 in Type 1 and Type 2 Diabetes Mellitus in a UK Setting*	No comparison of CSII vs. MDI
(46)	UPF Finder	Gilmer, Todd ,Roze	*Cost-Effectiveness of Diabetes Case Management for Low-Income Populations*	No comparison of CSII vs. MDI
(47)	UPF Finder	Jendle, Johan,Ericsson	*Achieving Good Glycemic Control Early After Onset of Diabetes: A Cost-Effectiveness Analysis in Patients with Type 1 Diabetes in Sweden*	No comparison of CSII vs. MDI
(48)	UPF Finder	Mora, Pablo	*Efficacy, safety and cost-effectiveness comparison between U-100 human regular insulin and rapid acting insulin when delivered by V-Go wearable insulin delivery device in type 2 diabetes*	No comparison of CSII vs. MDI
(49)	UPF Finder	Palmer, Andrew J.; Roze, Stephane	*The CORE Diabetes Model: Projecting Long-term Clinical Outcomes, Costs and Cost-effectiveness of Interventions in Diabetes Mellitus (Types 1 and 2) to Support Clinical and Reimbursement Decision-making*	No comparison of CSII vs. MDI
(50)	UPF Finder	Valentine, William J., Palmer, Andrew J.	*Long-term clinical and cost outcomes of treatment with biphasic insulin aspart 30/70 versus insulin glargine in insulin naive type 2 diabetes patients:*	No comparison of CSII vs. MDI

			cost-effectiveness analysis in the UK setting	
(51)	UPF Finder	Valentine, William J., VanBrunt, Kate.	*Treating Type 1 Diabetes Mellitus with a Rapid-Acting Analog Insulin Regimen vs. Regular Human Insulin in Germany: A Long-Term Cost-Effectiveness Evaluation*	No comparison of CSII vs. MDI
(52)	Scopus	DeVries JH.	*Health-economic comparison of continuous subcutaneous insulin infusion with multiple daily injection for the treatment of Type 1 diabetes in the UK: Response to Roze et al.*	Full text not available
(53)	Scopus	Valov V., Manova M., Savova Al.	*Modeling the cost and consequences of diabetes therapy*	Full text not available
(54)	Scopus	Hu S. Yang,H., Chen, Z.	*Clinical Outcome and Cost-Effectiveness Analysis of CSII Versus MDI in Children and Adolescent With Type 1 Diabetes Mellitus in a Public Health Care System of China*	Only Children and adolescent (< 18) are included

Table 6 Studies excluded due to comparison of Sensor-augment CSII vs MDI:

(55)	Pubmed	Gomez AM, Alfonso-Cristancho	*Clinical and economic benefits of integrated pump/CGM technology therapy in patients with type 1 diabetes in Colombia.*
(56)	Pubmed	Riemsma R., Corro Ramos, Birnie R	*Integrated sensor-augmented pump therapy system [the MiniMed® Paradigm™ Veo system and the Vibe™ and G4® PLATINUM CGM (continuous glucose monitoring) system] for managing blood glucose levels in type 1 diabetes: a systematic review and economic evaluation*
(57)	Scopus	Kamble S., Schulman, K.A, Reed	*Cost-effectiveness of sensor-augmented pump therapy in adults with type 1 diabetes in the United States*
(58)	Scopus	Pease, A., Zomer E. Liew, D., Earnest	*Cost-Effectiveness Analysis of a Hybrid Closed-Loop System Versus Multiple Daily Injections and Capillary Glucose Testing for Adults with Type 1 Diabetes*

(59)	Scopus	Kamble S., Weinfurt K.P., Schulman, K.A.	*Patient time costs associated with sensor-augmented insulin pump therapy for type 1 diabetes: Results from the STAR 3 randomized trial*
(60)	UPF finder	Cognet, ignacio	*Cost-effectiveness analysis of sensor-augmented pump therapy with low glucose-suspend in patients with type 1 diabetes mellitus and high risk of Hypoglycemia in Spain*