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ORIGINAL ARTICLE

Patient Values and Preferences Regarding Continuous Subcutaneous Insulin Infusion and Artificial Pancreas in Adults with Type 1 Diabetes: A Systematic Review of Quantitative and Qualitative Data

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Abstract

Objective: We produced, through a systematic review of quantitative and qualitative evidence, a synthesis of the issues of importance (values and preferences) to adult patients with type 1 diabetes regarding treatment with automated insulin delivery systems.

Methods: We searched MEDLINE, CINAHL, EMBASE, and PsycINFO from the inception of each database through September 2018. We included studies examining patient values and preferences for outcomes related to continuous subcutaneous insulin infusion or artificial pancreas treatment. We compiled structured summaries of the results and assessed the relative importance of each outcome. GRADE (Grading of Recommendations, Assessment Development, and Evaluation) and CERQual (Confidence in Evidence from Reviews of Qualitative research) approaches provided the structure for the evaluation of the quality of evidence and confidence in the findings. A mixed-methods result-based convergent design provided the structure for integration and presentation of results.

Results: We reviewed 1665 unique citations; 19 studies (8 quantitative and 11 qualitative) proved eligible. Glycemic control is the key attribute that drives patients' preference. Reduction of glycemic variability and decreased incidence of hypoglycemia and chronic complications proved of intermediate importance and were ranked similarly to components of treatment burden, including the size and appearance of devices, cost, ease of use, and the embarrassment of public use.

Conclusions: Clinician guidance may play a crucial role in determining patient values and preferences (for instance, patients' priority in glucose control rather than avoiding diabetic complications). Our results provide guidance for clinicians in discussing preferred insulin delivery systems with patients with type 1 diabetes.

Keywords: Continuous subcutaneous insulin infusion, Closed loop, Artificial pancreas, Values, Preferences, Mixed methods, Type 1 diabetes.

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Introduction

In adults with type 1 diabetes, continuous subcutaneous insulin infusion (CSII) alone or with real-time continuous glucose monitoring (CGM), compared with multiple daily injections of insulin (MDI), reduces the frequency of hypoglycemia and marginally improves metabolic control.[1–3] The development of a closed-loop system that combines CGM with computer-based algorithm to determine the amount of insulin delivered, also known as artificial pancreas (AP), may provide further improvements in both glycemic control and reduction in the risk of hypoglycemia.[4] Superior glucose control may delay the onset of macro- and microvascular complications of diabetes. For these reasons, the automated insulin delivery systems are now considered the gold standard for type 1 diabetes treatment.

To be optimally effective, these devices need to be well accepted by patients.[5] Some patients do not accept these technologically advanced alternatives and many studies report discontinuation or interrupted use.[6–8] Possible reasons for the discontinuation or disruption in use include differences in clinicians' versus patients' appraisal of benefits and harms. Moreover, values and preferences are likely to differ among patients with similar health states.[9] Understanding of patients' values and preferences may therefore guide clinicians in their discussions with patients, possibly resulting in helping patients make choices that are right for them and improving their subsequent compliance.

Such understanding will also be useful to guideline panels addressing insulin delivery systems moving from evidence to recommendations.[10] For instance, in the development of the Colombian clinical practice guidelines for prevention, early detection, diagnosis, management, and follow up of diabetes mellitus in adults,[11,12] the panel noted the absence of an available synthesis of evidence regarding patient values and preferences.

The aim of this study was to inform both individual clinicians and guideline panels, and to conduct a systematic review of the values and preferences evidenced from studies of adult patients with type 1 diabetes. The review addresses issues that arise in the treatment with CSII or AP, exploring patient experiences with these devices and their values and preferences concerning the outcomes associated with their use.

Methods

We developed a protocol to guide the conduct and analysis of our review (PROSPERO: CRD42018110457). We used a mixed-methods, result-based convergent approach,[13] including the synthesis of results from studies with diverse designs.[14] This approach provides a rich and highly practical understanding of the patient values and preferences on the outcomes associated with the treatment of CSII or AP.

Search strategy

With the assistance of a research librarian, we sought relevant studies through tailored searches of MEDLINE, EMBASE, CINAHL, and PsycINFO databases from the inception of each database through September 29, 2018. The search strategy included three blocks of search terms. The first block captured the concept of patient values and preferences using a validated filter[15]; the second block focused on adults with type 1 diabetes; and the third block on treatment with CSII with or without CGM, AP, or MDI. The search strategy in entirety is available (Supplementary Appendix SA1). There were no language or publication status restrictions. We did not find any non-English studies, and thus, translators were not needed.

Eligibility criteria

We included studies enrolling participants 18 years of age or older diagnosed with type 1 diabetes that elicited values and preferences on outcomes related to treatment with automated insulin delivery systems, including CSII with self-monitoring of blood glucose (SMBG), CSII with CGM or AP, compared with MDI, or comparisons between these treatments. In addition, we included studies reporting simultaneously the values and preferences of adults and adolescents if the proportion of adults was above 80%.

According to the definition proposed by the GRADE (Grading of Recommendations, Assessment Development, and Evaluation) working group,[16] we considered patient values and preferences to be ''the relative importance patients placed on the outcomes'' for the decision that they are considering. The quantitative component considered any design reporting values and preferences regarding decisions of treatment, including health state value, multiattribute utility instruments, direct choice or forced choice, or studies providing nonutility measurement of health states (e.g., surveys on treatment burden). The qualitative component included studies aimed to explain the relative importance that patients place on those outcomes, through exploration of patient views, experiences, attitudes, or perceptions, and, in some cases, identify additional outcomes important to patients.

We excluded nonprimary studies (e.g., clinical practice guidelines, reviews, commentaries, communications, letters, or viewpoints), case reports, or case series and studies reporting health-related quality of life or satisfaction of participants with type 1 diabetes that did not elicit patients' values and preferences. We also excluded studies of health care professionals or proxy decision makers.

Study selection and data abstraction

Pairs of reviewers (O.M.-V., D.H., T.D., P.E.A., Y.Z., A.M.-G., A.R.-M.) working independently and in duplicate determined the eligibility status of all identified citations first by screening the titles and abstracts, then by reviewing the full texts of all potential eligible articles. Reviewers participated in calibration exercises to ensure consistency/standardization of screening for eligibility. Reviewers' discrepancies were resolved first by discussion and then, if necessary, through consultation with a third reviewer (G.G.).

Two reviewers abstracted the information from all eligible studies, independently and in duplicate, using pilot-tested, standardized forms developed specifically for studies of values and preferences (available from the authors on request), and modified to fit the context of automated insulin delivery systems in patients with type 1 diabetes.

Data abstracted included study population (demographics), clinical characteristics (duration of diabetes), study characteristics (design and sampling strategy), methods used

to elicit values and preferences, outcomes assessed, and quantitative and qualitative findings. Reviewers resolved disagreements by discussion, or with the help of a third reviewer.

Quality assessment

We assessed quantitative study limitations using a novel instrument, proposed by the GRADE working group,[16] that evaluates the following four domains: selection of participants into the study (appropriate sample); completeness of data (response rate and attrition); measurement instrument (validity, reliability, administration of the methodology, understanding the methodology); and data analysis. For the evaluation of limitations of qualitative studies, we used the Critical Appraisal Skills Programme (CASP) checklist.[17]

Evidence summary

We planned to carry out three subgroup analysis if data permitted: analysis by age groups considering the possible differences between adults younger than 25,[2] patients who decided to interrupt the treatment, and participants who were reportedly pregnant. Although we planned to conduct meta-analyses if the outcomes considered across eligible quantitative studies were similar, the variability in methods and the manner in which outcomes were measured and presented precluded statistical pooling. We therefore grouped outcomes into main themes and presented them in narrative and tabular form. We classified the relative importance of the outcome in four categories (very important, intermediate importance, limited importance, or unimportant). The GRADE framework provided the structure for assessing quality of evidence and included the following domains: risk of bias, indirectness, inconsistency, and imprecision.[16,18] The GRADE assessment for quality of evidence is presented.

Our description of the qualitative findings utilized a content analysis methodology, seeking feedback from respondents without deeper interpretation. The CERQual (Confidence in Evidence from Reviews of Qualitative research) approach provided the structure for assessment of quality of evidence from qualitative studies,[19] including four components: the methodological limitations,[20] coherence,[21] adequacy of data,[22] and relevance.[23] Results include presentation of the CERQual and Summary of Qualitative Findings (SoQF).

GRADE uses three synonymous terms to address the trustworthiness of the evidence: quality, certainty, and confidence. Because of the fundamental differences in making inferences from quantitative and qualitative studies, we use the term ''quality of evidence'' for quantitative studies and ''confidence in evidence'' for qualitative studies.

Following our result-based convergent design, we addressed quantitative and qualitative studies separately using different but congruent and complementary synthesis methods (GRADE and CERQual approaches), with final integration of results.[13]

Results

Study characteristics

Our search yielded 1665 unique citations; 19 studies[24–42] proved eligible (Fig. 1). Eight studies providing quantitative

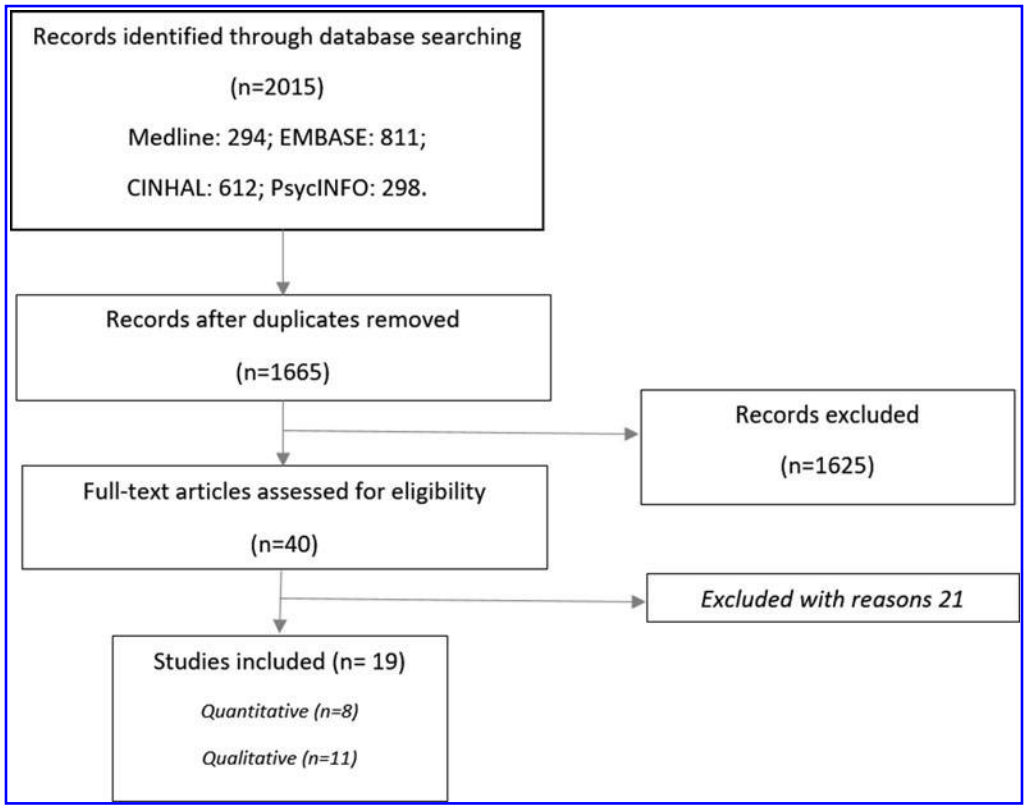

FIG. 1. PRISMA flow diagram.

information using cross-sectional surveys[24–31] varied in their approaches in eliciting patient values and preferences. Two studies used the insulin delivery system rating questionnaire,[25,27] an instrument that assesses the overall preference for the insulin delivery system. Other methodologies included multiple-choice and closed-ended questions or endorsement via Likert scales (Table 1 and Supplementary Table S1). Four of eight studies were industry funded.[25–27,30]

Eleven studies used a qualitative methodology design,[32–42] in seven of which the investigators used semistructured individual interviews to elicit values and preferences.[33,35,37–42] Three studies conducted focus groups, and one used both methods.[39] Six studies recruited patients participating in clinical trials.[35–38,40,42] Four studies addressed CSII[32–34,41] and seven the AP or hybrid closed-loop system, an AP that automates insulin delivery but requires user inputs (Table 2).

Quality of studies

Regarding risk of bias in quantitative studies (Supplementary Table S2), two studies included self-selected populations,[24,29] and one study recruited only patients who did not accept or discontinued treatment.[30] Three studies did not present a response rate.[24,25,29] One study reported a response rate of 10%.[30] In four studies, the instruments used to obtain the relative importance were developed only for the study; the measurement properties were not evaluated.[24,29–31] The researchers did not formally test the understanding of the tool in any study, but the instruments were simple enough that we inferred that the understanding of the patients was adequate. One study failed to distinguish between responses from adult patients and those from parents of children who used CSII.[24]

Methodological limitations of qualitative studies (Supplementary Table S3) included purposive sampling[32,41] and small sample sizes that prevented data saturation.[40,41] One study recruited participants from the helpline of a supply provider and did not gather demographic information.[33]

Synthesis of quantitative and qualitative studies

The analysis of quantitative studies identified two main themes: clinical efficacy (including glycemic control, hypoglycemia, glycemic variability, and complications) and treatment burden (including size and appearance of the devices, financial aspects, ease of use, confidence in technology, pain or discomfort, and embarrassment on public use).

Three quantitative studies reported regression models[25–27] to define the important factors to predict the preference for CSII[25,27] or the adoption of AP devices.[26] Other studies reported why the patients would stop using the devices,[24] the outcomes that patients perceived as barriers for using the CSII,[29] the factors that contributed to the decision to discontinue the CSII,[30] as well as the most important goals of treatment defined by the patients[28] (Table 3). Table 4 presents the synthesis of the evidence provided by quantitative studies, including the GRADE assessment for the quality of evidence for each outcome that varied from low to high.

Qualitative studies provided consistent and complementary information on all the themes identified in surveys and identified additional issues important to patients, including the flexibility to eat and exercise, the presence of unexpected tasks for patients while using AP (such as the need for user information about meals and exercise instead of using only the values from the sensors to calculate insulin doses), difficulty exercising when patients are using AP, advantages and disadvantages related to sleep, intimacy problems, and the feeling of ''taking a break from diabetes.'' Table 5 and Supplementary Table S4 presents the synthesis of qualitative studies, including the SoQF and the CERQual assessment of confidence in the evidence. These additional issues were not considered to define a relative importance, taking into account that there were no data that allowed us to determine it.

Relative importance of clinical efficacy and treatment burden

Clinical efficacy. Six quantitative studies[24–28,31] provided high-quality evidence that glycemic control is a very important outcome for patients (Tables 3 and 4). In qualitative studies, patients reported that the improved blood glucose control was the primary benefit of CSII and AP systems, and remarked positively about the importance of being able to carefully monitor their glucose control (high confidence in the evidence, Table 5).

Four quantitative studies[24,26–28] reported that hypoglycemia was of intermediate importance (Table 3) with a significant variability in the importance that patients gave to this outcome (moderate quality, Table 4). A number of patients highlighted a reduction in episodes or severity of hypoglycemia as a benefit of insulin pump therapy, and some experienced less fear of nocturnal hypoglycemia, while several reported increased hypoglycemic events associated with sports when using AP (Table 5), this last finding was not reported for patients on CSII. Two studies presented evidence that glycemic variability is of intermediate importance to patients treated with CSII[24,25] (low quality, Tables 3 and 4). Participants in multiple qualitative studies were particularly impressed by how stable they observed glucose values were while they were on AP[35–37,39] (Table 5).

Two studies[28,31] reported the prevention of complications as an outcome of intermediate importance (low quality, Tables 3 and 4). The estimates of importance differed between studies. In a similar way, three qualitative studies[32,38,39] superficially described diabetic complications as an issue for patients, noting patients' perception that potential reduction of long-term complications is related to improved glucose control (Table 5).

Treatment burden. Four studies[24,29–31] reported the intermediate importance of size and appearance of the devices (high quality, Tables 3 and 4). Seven qualitative studies[32,33,36,38,39,41,42] reported complementary findings for this theme (high confidence, Table 5). Women reported difficulties with the visibility of the pump and its concealment under the clothes, describing it as a ''fashion challenge'' that became especially salient in the summer. The importance of size and appearance was lower for men, and was similar for old or recent devices.

Four studies presented evidence that patients perceived the ease of use as intermediate importance[24–27] (high quality, Tables 3 and 4). In general, patients described that the management of pump was easy, especially if they had previous experience with similar devices; nevertheless, the majority of participants reported having experienced some

Table 1. Characteristics of Cross-Sectional Surveys Included

Reference	*Age, mean (SD) (unless otherwise noted)*	*Country of origin*	*Percent female*	*No. of participants*	*Duration of diabetes, mean (SD) (unless otherwise noted)*	*Treatment used*	*Method to elicit values and preferences*	*Funding source*
Barnard et al.[24,a]	34.2 (range 3–72)	United Kingdom	63	266	19.5 years (range 7 weeks to 68 years)	41% CSII + CGM, 35% CSII + SMGB	Multiple-choice and closed-ended questions	Nonindustry
Peyrot and Rubin[25]	46.4 (12.7)	United States	53	142[b]	22.6 (12.7)	71% CSII, 29% MDI	IDSRQ[c]	Industry
Bevier et al.[26]	46.6 (12.5)	United States	69	36	28.5 (15.5)	40% CSII + CGM, 41% CSII + SMGB	5-point Likert scale	Industry
Peyrot and Rubin[27]	41.9 (12.3)	United States, Canada	43	334	15.2 (12.5)	50% CSII + CGM, 50% MDI + SMGB	IDSRQ[c]	Industry
Puder et al.[28]	44 (14)	Switzerland	51	102	19 (13)	41% CSII, 59% MDI	Multiple-choice questions. Two responses were possible	Nonindustry
Tanenbaum et al.[29]	35.3 (14.8)	United States	61	1503, 72 discontinued pump therapy	20.4 (12.5)	38% CSII + SMBG, 32% CSII + CGM, 25% MDI + SMGB	Closed-ended multiple responses, questions	Nonindustry
Seereiner et al.[30]	21.5 (4.5)	Germany	44	42[d]	13.6 (6.5) 8.1 (5.9)	47% CSII + SMBG, former users, 53% MDI + SMGB	4-point Likert scale	Industry
Knight et al.[31]	34.7 (11.9)	United Kingdom	46	382	13.7 (9.0)	30% CSII, 42% intensified conventional therapy, 26% unintensified regimen	Unclear whether reasons for choices were open-ended or options offered by investigators	Nonindustry

[a]Included responses of adult patients and parents of children with type 1 diabetes.
[b]One hundred ninety-seven patients included, 142 with type 1 diabetes.
[c]The tool assessed the overall preference for the insulin delivery system and five additional domains, treatment satisfaction, treatment interference with daily activities, clinical efficacy, diabetes worries, and diabetes social burdens, using Likert scales.
[d]Included patients who never used CSII or former users of CSII, more than 80% of participants were older than 18 years.
CGM, continuous glucose monitoring; CSII, continuous subcutaneous insulin infusion; IDSRQ, insulin delivery system rating questionnaire; MDI, multiple daily injections of insulin; SMBG, self-monitoring of blood glucose.

Table 2. Characteristics of Qualitative Studies Included

Reference	*Age, mean (SD) (unless otherwise noted)*	*Country of origin*	*Percent female*	*No. of participants*	*Duration of diabetes, mean (SD) (unless otherwise noted)*	*Context*	*Treatment evaluated*	*Participants*	*Method to elicit values and preferences*	*Funding source*
Ritholz et al.[32]	47 (9.5)	United States	59	30	27.3 (13.1)	Adults receiving treatment at the Joslin Diabetes Center (Boston, Massachusetts).	CSII	CSII users; no additional details about the type of device	Focus group	NIH; Diabetes and Endocrinology Research Core NIH Grant; Animas Corporation
Barnard and Skinner[33]	Not reported	United Kingdom	Not reported	80	Not reported	Costumers of Roche Diagnostics, contacting helpline for pump supplies.	CSII	CSII users; no additional details about the type of device	Brief telephonic semistructured interviews	Roche Diagnostics
Saarinen et al.[34]	46 (range 25–74)	Sweden	45	11	Range 4–46 years	Adults receiving treatment at Karolinska University Hospital (Solna, Sweden)	CSII	CSII previously treated with MDI	Focus group	Not reported
Barnard et al.[36]	38.6 (9.6)	United Kingdom, Austria, Germany	45	32	22.3 (8.8)	Patients included in a crossover randomized clinical trial	AP	12 weeks of CSII + CGM vs. artificial pancreas	Semistructured interviews conducted at baseline, midpoint, and end of the study	JDRF and Seventh Framework Programme of the European Union; National Institute for Health Research, Cambridge.
Iturralde et al.[35]	28.2 (6.1)	United States	Not reported	17	18.3 (6.9)	Participants in multisite HCL clinical trial, of a prototype device.	HCL	4–5 days of HCL	Focus group	JDRF; Michael D. Ryan & Rosemary McNicholas Ryan Pediatric Diabetes Research Fund
Hendrieckx et al.[37]	42 (10)	Australia	56	16	27 (7)	Patients included in a crossover randomized clinical trial	HCL	4 nights. Overnight in home HCL vs. CSII + CGM + LGS	Semistructured interviews	JDRF International
Barnard et al.[38]	43 (12)	United Kingdom	46	24	29 (11)	Patients included in a crossover randomized clinical trial.	AP	4 weeks. Overnight in home AP vs. CSII + CGM	Semistructured interviews	Diabetes UK

(*continued*)

Table 2. (Continued)

Reference	*Age, mean (SD) (unless otherwise noted)*	*Country of origin*	*Percent female*	*No. of participants*	*Duration of diabetes, mean (SD) (unless otherwise noted)*	*Context*	*Treatment evaluated*	*Participants*	*Method to elicit values and preferences*	*Funding source*
Naranjo et al.[39]	39.5 (range 18–77)	United States; United Kingdom	71	113	Not reported	Four different sites in the United States (Joslin Diabetes Center, Lurie Children's Hospital, and Stanford Children's Health) and United Kingdom (Bournemouth University)	AP	CSII (75%). Participants with and without AP knowledge or experience.	Semistructured interviews or focus groups	The Leona M. and Harry B. Helmsley Charitable Trust.
Kropff et al.[40]	47.0 (11.2)	the Netherlands	Not reported	6	28.6 (10.8)	Patients included in a crossover randomized clinical trial.	AP	8 weeks of evening and night AP vs. CSII + CGM	Semistructured interviews	European Community Framework Programme 7
Hayes et al.[41]	Not reported	United Kingdom	60	5	Not reported	A single site in the South of England.	CSII	Patients who chose to discontinue CSII; no additional details about the type of device	Hermeneutic phenomenology using semistructured interviews	Not reported
Farrington et al.[42]	34.1 (4.6)	United Kingdom	100	16	23.6 (7.2)	Patients included in a crossover randomized clinical trial Patients included in a crossover randomized clinical trial	AP	Pregnant women 4 weeks in home AP vs. CSII + CGM	Semistructured interviews at baseline, and end of the study	Diabetes UK, National Institute for Health Research

AP, artificial pancreas; HCL, hybrid closed-loop system, meaning artificial pancreas that automates insulin delivery but requires user inputs; JDRF, Juvenile Diabetes Research Foundation; LGS, low-glucose suspend function; NIH, National Institutes of Health; SMBG, self-monitoring of blood glucose.

Table 3. Values and Preferences Regarding Glycemic Control and Treatment Burden

					Treatment burden					
Reference	*Glycemic control*	*Hypoglycemia*	*Glycemic variability*	*Complications*	*Size and appearance*	*Financial aspects*	*Ease of use*	*Confidence in technology*	*Pain or discomfort*	*Embarrassment*
Barnard et al.[24]	99.2% described the improved overall glucose control as a potential advantage of a new device.	98.5% described fewer low-glucose levels as a potential advantage of a new device.	98.1% described less day-to-day swings in blood glucose levels, as a potential advantage of a new device.		31.9% said that successful artificial pancreas should be small, and 20.7% said that should be easily concealed. 23.7% said that they would stop using the device for the size or appearance.	35% of patients would stop using the device for the cost.	14.3% described the minimal need for patient intervention as an important characteristic of device. 15.8% said that the device should be like a pancreas.	11.7% of patients would stop using the device for lack of reliability/ accuracy.		
Peyrot and Rubin[25]	Clinical efficacy (including glucose control), was identified as an important factor to predict preference for CSII.		Clinical efficacy (including glucose stability), was identified as an important factor to predict preference for CSII.				Treatment satisfaction (including ease of take insulin) was identified as an important factor to predict preference for CSII.	Treatment satisfaction (including uncertainty about getting the amount of insulin intended) was identified as an important factor to predict preference for CSII.	Treatment satisfaction (including pain) was identified as an important factor to predict preference for CSII.	Treatment satisfaction (including embarrassment) was identified as an important factor to predict preference for CSII.
Bevier et al.[26]	Usefulness (including improved blood glucose control), was identified as an important factor to predict AP technology adoption.	Usefulness (including fewer episodes of hypoglycemia), was identified as an important factor to predict AP technology adoption.					Construct of ease of use (including requires minimal effort) was identified as an important factor to predict AP adoption.		Construct of ease of use (including reduced discomfort) was identified as a nonimportant factor to predict AP adoption.	

(*continued*)

Table 3. (Continued)

					Treatment burden					
Reference	*Glycemic control*	*Hypoglycemia*	*Glycemic variability*	*Complications*	*Size and appearance*	*Financial aspects*	*Ease of use*	*Confidence in technology*	*Pain or discomfort*	*Embarrassment*
Peyrot and Rubin[27]	Perceived clinical efficacy at baseline and changes in perceived efficacy (including control of hyperglycemia) were identified as important factors to predict changes in preference in favor of CSII.	Perceived clinical efficacy at baseline and changes in perceived efficacy (including hypoglycemia) were identified as important factors to predict changes in preference in favor of CSII.					Perceived convenience at baseline and changes in perceived convenience (including ease of use to take insulin) were identified as important factors to predict changes in preference in favor of CSII.		Perceived convenience at baseline and changes in perceived convenience (including pain) were identified as important factors to predict changes in preference in favor of CSII.	Perceived convenience at baseline and changes in perceived convenience (including embarrassment) were identified as important factors to predict changes in preference in favor of CSII.
Puder et al.[28]	63% of patients selected good blood glucose control as the most important goal of treatment.	8% of patients selected avoidance of hypoglycemia as the most important goal of treatment.		27% of patients selected prevention of complications as the most important goal of treatment.					<5% of Patients selected avoidance of injections as the most important goal of treatment	
Tanenbaum et al.[29]					Patient felt appearance was a barrier for using CSII: 34.8% of patients do not like having diabetes devices on the body, and 26% do not like how it looked.	61.3% of patients thought that the cost of supplies is a barrier for using CSII. 57.4% of patients thought that the cost of device is a barrier for using CSII.		Patient felt this was a barrier for using CSII: 20% of patients were reportedly nervous that the device might not work, and 17% were nervous to rely on technology.		Patient felt this was a barrier for using CSII: 10.5% of patients reported concerns about what others will think and 10.4% did not like diabetes devices because people noticed them and asked questions.

(*continued*)

Table 3. (Continued)

					Treatment burden					
Reference	*Glycemic control*	*Hypoglycemia*	*Glycemic variability*	*Complications*	*Size and appearance*	*Financial aspects*	*Ease of use*	*Confidence in technology*	*Pain or discomfort*	*Embarrassment*
Seereiner et al.[30]					50% of patients strongly agreed that the pump is overly visible, and was a reason for not trying the CSII.				55% of patients strongly agreed that catheter insertion is more unpleasant than injecting and was a factor in ceasing CSII.	15% of patients strongly agreed that the use of pump in public being unpleasant was a factor in ceasing CSII.
Knight et al.[31]	58.9% of patients selected CSII because they wished to improve glycemic control.			4.2% of patients selected CSII because of the fear of complications.	6.2% of patients selected options different to CSII because of the size or appearance of the pump.				6.3% of patients selected CSII because of ''fewer injections.''	

Table 4. Evidence Profiles and Grading of Recommendations, Assessment Development, and Evaluation Assessment for the Quality of Evidence

Quality assessment								
Outcome	*Study design/measurement instrument*	*Risk of bias*	*Inconsistency*	*Indirectness*	*Imprecision*	*Other*	*Estimate of outcome importance*	*Quality*
Glycemic control	Six cross-sectional studies, 1264 participants	No serious risk of bias[a]	No serious inconsistency	No serious indirectness	No serious imprecision	None	Very important	High
Hypoglycemia	Four cross-sectional studies, 738 participants	No serious risk of bias	Serious inconsistency[b]	No serious indirectness	No serious imprecision	None	Intermediate importance	Moderate
Glycemic variability	Two cross-sectional studies, 408 participants	Serious risk of bias[c]	Serious inconsistency[b]	No serious indirectness	No serious imprecision	None	Intermediate importance	Low
Complications	Two cross-sectional studies, 492 participants	Serious risk of bias[d]	Serious inconsistency[b]	No serious indirectness	No serious imprecision	None	Intermediate importance	Low
Size and appearance	Four cross-sectional studies, 2188 participants	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	Intermediate importance	High
Financial aspects	Two cross-sectional studies, 1769 participants	Serious risk of bias[c,d]	Serious inconsistency[b]	No serious indirectness	No serious imprecision	None	Intermediate importance	Low
Ease of use	Four cross-sectional studies, 778 participants	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	Intermediate importance	High
Confidence in technology	Three cross-sectional studies, 1911 participants	Serious risk of bias[c,d]	No serious inconsistency	No serious indirectness	No serious imprecision	None	Intermediate importance	Moderate
Pain	Six cross-sectional studies, 1038 participants	No serious risk of bias	Serious inconsistency[b]	No serious indirectness	No serious imprecision	None	Limited importance	Moderate
Embarrassment	Four cross-sectional studies, 2021 participants	No serious risk of bias	Serious inconsistency[b]	No serious indirectness	No serious imprecision	None	Intermediate importance	Moderate

[a]In four studies the population could be biased toward CSII preference, or was self-selected, however, the estimates of importance were high, and so, we decided not to downgrade the quality of evidence because of risk of bias.
[b]Estimates of importance are different between studies without differences in populations or interventions used, suggesting methodological inconsistency.
[c]The population was self-selected.
[d]The instrument used to obtain the relative importance was created only for the study and the measurement properties were not evaluated.

Table 5. Summary of Qualitative Findings and Assessment of Confidence in Evidence from Qualitative Research

Summary of review finding	*Studies contributing to the review finding*	*CERQual assessment of confidence in the evidence*	*Explanation of CERQual assessment*
Glycemic control (1) Patients reported improved blood glucose control was the primary benefit of CSII and AP systems.[34] (2) Having greater control over diabetes in terms of being able to follow their glucose control in detail was perceived as important for AP and CSII + CGM users.[34] (3) In few patients, the pump failed to meet patients' expectations of improved glucose,[39] or time within a target glucose range,[33] and it was a reason to discontinue the pump.[39] (4) Some patients were disappointed by what they saw as the HCL system not managing hyperglycemia aggressively enough.[33]	Barnard et al.[36] Ritholz et al.[32] Barnard et al.[38] Naranjo et al.[39] Kropff et al.[40] Hayes et al.[41] Iturralde et al.[35] Farrington et al.[42]	High confidence	No or very minor concerns
Hypoglycemia (1) A number of participants highlighted a reduction in episodes or severity of hypoglycemia as a benefit of insulin pump therapy. Some experienced less fear of nocturnal hypoglycemia.[32] (2) When comparing AP with CSII, some patients reported the presence of increased hypoglycemic events with AP, particularly associated with sports-related activities.[34] These participants said that it ''knocked their confidence.''[36]	Barnard et al.[36] Saarinen et al.[34] Ritholz et al.[32] Barnard et al.[38]	High confidence	Minor methodological limitations (one with insufficient data analysis and two studies with purposive sample)
Glycemic variability (1) Patients were particularly impressed by how stable they observed glucose values to be while on AP.[33] (2) Few commented that there remained room for improvement in blood glucose stability.[34]	Iturralde et al.[35] Barnard et al.[36] Naranjo et al.[39] Hendrieckx et al.[37]	High confidence	No or very minor concerns
Complications Some patients reported potential reduction of long-term complications (via improved blood glucose control) as an important benefit.[36]	Barnard et al.[38] Naranjo et al.[39] Ritholz et al.[32]	Moderate confidence	Moderate concerns about coherence[a] (three studies with poor description of the importance for patients)
Size and appearance (1) The majority of participants worried about the size, weight, and appearance of devices.[37] (2) Mainly the women reported difficulties with the visibility of the pump and its concealment, describing it as a ''fashion challenge.''[30] (3) They described the difficulty of trying to hide the pump, particularly in the summer.[34] (4) Men reported less importance.[30] (5) Within this theme, responses varied greatly among participants.[31]	Barnard et al.[36] Barnard and Skinner[33] Barnard et al.,[38] Ritholz et al.[32] Hayes et al.[41] Farrington et al.[42] Naranjo et al.[39]	High confidence	No or very minor concerns

(*continued*)

TABLE 5. (CONTINUED)

Summary of review finding	*Studies contributing to the review finding*	*CERQual assessment of confidence in the evidence*	*Explanation of CERQual assessment*
Ease of use (1) Most participants felt that managing the pump was easy.[32] (2) Both a transition from MDI to CSII,[32] and from CSII were described as easy.[35] (3) AP users reported that previous experience with CGM was advantageous in preparing them for closed loop.[35]	Saarinen et al.[34] Hendrieckx et al.[37]	Moderate confidence	Moderate concerns about adequacy (two studies with a small sample size)
Technical problems The majority of participants reported having experienced some technical or usability difficulties with the equipment, such as frequent loss of connectivity, pump catheter problems, inability to calibrate the sensor, or the algorithm not responding as expected.[35,36]	Barnard et al.[36] Hayes et al.[41] Hendrieckx et al.[37] Kropff et al.[40] Barnard et al.[38] Farrington et al.[42]	High confidence	No or very minor concerns
Confidence in technology (1) Most participants said they trusted the AP device, but not fully or without double-checking its actions.[37] (2) Participants did not perceive themselves to be handing over control to the device,[38] and they wanted to be able to override decision-making functions of the systems.[37]	Hendrieckx et al.[37] Naranjo et al.[39] Kropff et al.[40] Farrington et al.[42]	High confidence	No or very minor concerns
Pain or discomfort (1) For some users of CSII, the needle was found to be thick, long, and hurt at insertion, with some participants continuing to be aware of the needle or cannula causing an intermittent feeling of discomfort.[39] (2) Some described this as one of the reasons for discontinuing the therapy.[39]	Hayes et al.[41] Saarinen et al.[34] Barnard and Skinner [33]	Moderate confidence	Moderate methodological limitations (one study with insufficiently rigorous data analysis providing most of the evidence), and minor concerns about adequacy (two studies with small sample size)
Unexpected tasks (1) Some participants expressed surprise that the AP system required user input for meals and exercise instead of using only sensor values to calculate insulin doses.[33] (2) Required tasks perceived as burdensome included responding to alarms, entering in meal information, confirming boluses, providing corrective insulin doses, calibrating CGM, and taking meter readings, sometimes in excess of what would happen in usual care.[33] (3) They expected the AP system to behave much like a ''real pancreas'' and were concerned that users would become disappointed.[33]	Iturralde et al.[35] Kropff et al.[40] Ritholz et al.[32]	High confidence	Minor concerns about methodological limitations (one study with purposive sample)
Sleep (1) Some patients reported improved sleep as a consequence of using the AP system when compared with CSII + CGM, because of fewer glucose values being out of range and thus fewer interruptions from alarms.[34] (2) Others reported sleep interrupted by the alarms and frequent buzzing of the insulin pump.[38]	Barnard et al.[36] Iturralde et al.[35] Hendrieckxe et al.[37] Barnard et al.[38] Kropff et al.[40] Farrington et al.[42]	High confidence	No or very minor concerns

(*continued*)

TABLE 5. (CONTINUED)

Summary of review finding	*Studies contributing to the review finding*	*CERQual assessment of confidence in the evidence*	*Explanation of CERQual assessment*
Exercise Participants who exercised regularly reported a negative effect of AP on their ability to exercise because of frequent alarms and the inability to elevate their glucose level before starting exercise.[38] It was difficult to balance food, exercise, and insulin. They felt that their blood sugar was frequently too low after exercise.[32]	Saarinen et al.[34] Kropff et al.[40]	Moderate confidence	Moderate concerns about adequacy (two studies with a small sample size)
Intimacy issues Some female participants said they had experienced reactions from those they lived with, who had initially shown fear and used a cautious approach in the context of intimate encounters.[32]	Saarinen et al.[34] Hayes et al.[41]	Moderate confidence	Minor methodological limitations (one study with purposive sample), and moderate concerns about adequacy (two studies with small sample size)
Flexibility CSII users reported greater meal flexibility compared with MDI. With MDI, the participants usually ate at fixed times, which lead to a loss in hunger sensation, while with the pump, they are more flexible and regained the feeling of hunger.[32] The AP system allowed participants to eat and exercise more freely, and they reported eating foods such as pizza that are ordinarily hard to manage.[33]	Iturralde et al.[35] Saarinen et al.[34]	Moderate confidence	Moderate concerns about adequacy (two studies with a small sample size)
A break from diabetes Participants expressed that using the system changed the role that diabetes played in their lives and made it less burdensome in profound ways.[33] Terms such as ''put diabetes in a box,'' ''taking a break,'' or that technology was ''taking over for a while'' were used.	Hendrieckx et al.[37] Iturralde et al.[35] Barnard et al.[38] Barnard and Skinner [33] Farrington et al.[42]	High confidence	Minor methodological limitations (one study with insufficiently rigorous data analysis)
Obsessiveness Most pregnant women reported increased time thinking about diabetes during closed loop. Prompted by the greatly increased quantity of data, some women described obsessive checking of system readouts.[40]	Farrington et al.[42]	Low confidence	Serious concerns about adequacy (one study with a small sample size)

CERQual, Confidence in Evidence from Reviews of Qualitative research.

technical or usability difficulties with the equipment, including loss of connectivity, pump catheter problems, or inability to calibrate the sensor (Table 5).

Three studies[24,25,29] reported that confidence in the technology is an issue of intermediate importance for patients (moderate quality, Tables 3 and 4). Ten to 20% of patients do not rely completely on the devices or would stop using the devices for lack of reliability. Patients did not perceive themselves to be handing over control to the device, and wanted to be able to override decision-making functions of the systems (Table 5).

Six studies[25–28,30,31] provided evidence that patients experience pain or discomfort as an outcome of limited importance (moderate quality, Tables 3 and 4). Less than 10% of patients selected the automated delivery systems because of ''fewer injections'' or considered avoidance of injections as the most important goal of treatment. For some patients, the needle was found to be thick, long, and hurt at insertion with some continuing to be aware of the needle or cannula, resulting in an intermittent feeling of discomfort (Table 5). One study[24] reported that 23.7% of patients would stop using the device for potential scarring.

A minority of patients (10% to 20%) reported embarrassment, defined as feeling uncomfortable with the use of the devices in public, which we judged as of intermediate importance. These patients found it unpleasant when others noticed the device and asked them questions (Tables 3 and 4). Two studies[24,29] reported financial aspects as of intermediate

importance and thus potential barriers for the use of the device (low quality, Tables 3 and 4).

Additional themes. Patients who compared CSII versus MDI and AP versus CSII reported greater flexibility to eat and exercise as advantages of the more sophisticated devices (moderate confidence, Table 5). One study[28] reported that flexibility or nutritional freedom was selected as the most important treatment goal in less than 5% of patients.

Qualitative studies reported additional findings that are considered important for patients, but the relative importance of these issues has not been evaluated quantitatively. Table 5 presents a complete description of the findings and the associated level of confidence.

Subgroup analysis

Two surveys[29,30] and one qualitative study[41] reported the findings in patients who discontinued CSII. In these patients, the burden of treatment was perceived as very important. They reported a greater frequency of inconveniences related to the visibility of the pump and the discomfort associated with the therapy (40% to 55%). In addition, they reported less confidence in the technology.

One study reported the outcomes in a group of pregnant patients[42] (low confidence). The findings were similar to those reported in the general population with respect to glycemic control, sleep, device size, technical problems, and confidence in technology. A finding particular to this group was the obsessiveness related to the greater amount of available data (Table 5). It was not possible to perform a subgroup analysis by age group because the primary studies did not present the information separately.

Discussion

In this systematic review, we identified glycemic control as a key attribute of diabetes management that drives patients' preference when faced with the decision to start with automated insulin delivery systems. Other outcomes, including reduction of glycemic variability and decreased incidence of hypoglycemia and chronic complications, were considered to be of intermediate importance and were ranked similarly to some components of the treatment burden, such as the size and appearance of devices, cost, ease of use, and the embarrassment of using them in public.

Other attributes related to the treatment, such as unexpected tasks for patients while using AP, difficulty exercising, advantages and disadvantages related to sleep, intimacy problems, and the feeling of ''taking a break from diabetes,'' were identified as important for some patients, but the information provided was insufficient to judge their relative importance.

The analysis performed in patients who discontinued the therapy suggests the existence of a subgroup that gives a greater relative importance to treatment problems than to possible improvements in glycemic control. For them, the perceptions of pain, discomfort, and inconvenience in concealing the device are more salient.

A major strength of this study is that we used an innovative approach to conduct a mixed-methods systematic review, allowing us to take full advantage of the complementary information provided by quantitative and qualitative studies. The quantitative studies allowed us to estimate the relative importance of each issue to the patients, and the qualitative studies provided a deeper understanding of each finding and identified additional issues that patients report as important, but that investigators have not fully evaluated.

Other strengths include, first, our comprehensive search of databases, using a validated filter,[15] allowing identification of studies with varying designs and strategies to elicit patients' views regarding the relative importance of benefits and the burden of treatment of automated insulin delivery systems. Second, we selected the studies, extracted the data, and performed the risk of bias assessment independently and in duplicate. Third, we used specific instruments for each study design to assess the risk of bias or methodological limitations (CASP for qualitative studies[17] and an instrument recently proposed by GRADE for quantitative studies[16]). Fourth, use of GRADE methodology allowed us to communicate not only the findings of the review but also an assessment of the quality of the evidence and the confidence in each finding, including a transparent presentation of the reasons for quality ratings.

An important limitation of this review is that our results cannot be applied to adolescents and children. We decided to limit the review to adults taking into account that Bergenstal[2] described two groups of patients treated with sensor-augmented insulin pump therapy, the most successful group (those older than 25 years) also had the highest frequency of sensor use (83% of patients used the device at least 6 days each week). On the contrary, worst outcomes were observed in patients from 15 to 24 years of age, where only 30% of the subjects used the device properly. These differences could be associated with the different relative importance given to some outcomes (e.g., glycemic control, prevention of complications, and some components of treatment burden) between adolescents and adults. This is also the reason why we planned to perform a subgroup analysis by age group considering the possible differences among adults younger than 25, but it was not possible to separate the data. A new systematic review will be needed to assess the values and preferences of children and adolescents.

Other limitations of our review are those related to the eligible studies. We found that most of the studies meeting our inclusion criteria reported outcomes at a single time point, so we could not evaluate patient preferences regarding treatment benefits or side effects over time. Studies informing about the perceptions of patients in the long term may yield important additional insights. In addition most of the studies excluded patients with a recent history of severe hypoglycemia. These patients may have a different preference profile that our review cannot detect.

Although this literature provided evidence on patient preferences using a wide variety of methods, differences between preference assessment methods may have influenced the relative values patients placed on treatment-related attributes, and could explain the variability found in estimates of importance for outcomes such as chronic complications and hypoglycemia. Three studies[25–27] reported regression analysis to predict preferences for CSII or technology adoption, allowing definition of important factors, but the authors reported coefficients that provided no insight into the magnitude of associations and thus the relative importance of each factor. Several studies reported low response rates or did

not report response rates at all. All these limitations result in low-quality evidence regarding the importance of a number of factors.

To date, no other systematic reviews have addressed values and preference regarding treatment in patients with type 1 diabetes. A previous systematic review evaluated patient preferences for oral or injected medications, other than insulin, in type 2 diabetes.[43] Similar to our findings, glycemic control was a key determinant of patient preferences. In addition, the authors reported that determinants of treatment burden (e.g., administration, frequency, and cost) and side effects (e.g., weight gain, gastrointestinal effects, and hypoglycemia) can be important attributes related to therapy.

One may question why patients place such high importance in glycemic control rather than, for example, prevention of diabetic complications or hypoglycemia. It is surprising if we consider that moderately high blood glucose levels do not produce symptoms. This is likely because physicians and other health care providers, in their discussions with patients and in the literature they offer to patients, have placed great emphasis on glucose control. In doing so, it is likely they implicitly or explicitly convey the message that glucose control is strongly linked to an important improvement in outcomes. Indeed, despite the high importance that patients place in glucose control, Puder et al. reported[28] that patients have the impression that blood glucose control is even more important for their physicians (main treatment goal for 86%) than for themselves. A similar situation could exist with other health professionals (including nurses and diabetes educators). In a similar way, the perception of importance that patients gave to glycemic variability is likely a consequence of physicians and other health care providers conveying the message that increased glycemic variability will result in more serious diabetic complication. Although there is some randomized trial evidence that tighter control reduces the incidence of serious complications, the impact is not large, and glucose control explains only a part of the variability in the incidence of complications.[44] Moreover, the proposition that less glycemic variability reduces important adverse outcomes remains to be established in long-term clinical trials.[45] One might argue that the evidence does not fully support the emphasis that clinicians—and thereafter the patients—place on glycemic control.

Our results have implications at different levels. Clinicians may use these findings to guide their discussion with patients considering the technologies evaluated here. For example, clinicians could elicit patients' feelings regarding the size and difficulty of concealing the device, or the embarrassment of using it in public. In addition, clinicians may make sure to discuss, before starting therapy, the tasks related to device management, benefits, and problems related to sleep and exercise, and potential issues related with intimate encounters. Finally, we have shown that a comprehensive and formal training program before the initial use of devices can improve clinical efficacy,[46] and our findings can provide additional information on the ideal content of this training to overcome the barriers perceived by some patients related to low confidence in technology and the technical issues frequently experienced by them.

In the development of guideline recommendations, panels are required to trade off desirable and undesirable consequences of alternative management strategies; patient values and preferences are key to such judgments. The goal of the current study was only to identify issues that patients consider most important, not to evaluate the relative performance of insulin delivery strategies on these outcomes. Guideline panels should, however, in their deliberations, look for evidence regarding the relative merit of the devices with regard to the issues that moderate- or high-quality evidence indicates patients consider most important.

Our results provide useful information for the development of newly validated psychosocial measures and tools to quantify the relative importance of results in the field of diabetes technology. The use of comparable and validated tools in new clinical trials by several device developers would be highly desirable.

Conclusions

Our systematic review of the evidence on patient values and preferences relevant to use of automated delivery systems in adults with type 1 diabetes reveals that glycemic control is the key attribute that drives patient preferences. Some components of treatment-related burden, such as the size and appearance of devices, cost, ease of use, and the embarrassment of using them in public, are of similar importance to hypoglycemia and chronic complications for patients. Clinicians should consider the preferences of patients identified in this study when caring for their patients, and guideline panels should consider the findings in the development of evidence-based guidelines.

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Author Disclosure Statement

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Supplementary Material

Supplementary Appendix SA1
Supplementary Table S1
Supplementary Table S2
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Supplementary Table S4

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